Textbook of Addiction Treatment

International Perspectives

Nady el-Guebaly
Giuseppe Carrà
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Alexander M. Baldacchino
Editors

Second Edition

ISAM International Society of Addiction Medicine

Springer

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Editors
Nady el-Guebaly
Division of Addiction
Department of Psychiatry
University of Calgary
Calgary, AB
Canada

Marc Galanter
Division of Alcoholism and Drug Abuse
Department of Psychiatry
NYU School of Medicine
New York, NY
USA

Giuseppe Carrà
Mental Health Department
University of Milano-Bicocca
Monza
Italy

Alexander M. Baldacchino
Population and Behavioural Science
Division (Psychiatry and Addictions)
University of St Andrews
St.Andrews
UK

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Preface: An International Perspective and Its Evolution

The International Society of Addiction Medicine (ISAM) was founded in Palm Springs, USA, in 1999. From the onset, the elements of its main mission were:

- *Advancement of the knowledge of addiction as a treatable disease*
- *Recognition that physicians worldwide have a major role to play in the management of addiction and associated disorders*
- *Enhancement of the credibility of the physician's role*
- *Emphasis of the importance of educational activities*
- *Establishment of consensus documents and practice guidelines*

To implement this mission, the Society organizes an annual global meeting and fundamental workshops. It also supports the International Certification in Addiction Medicine since 2005 with over 250 applicants from 17 countries sitting this internationally accredited exam.

In seeking reference texts to create the examination questions for the certification, it became evident that the two or three excellent multiauthored textbooks available in English are all originated from the USA, with an occasional contribution from an author from another country. These books are heavily centered on data arising from a US context and culture. ISAM decided that a textbook with a broader authorship representation was required as well as a search for data originating from across the world. We aimed to describe the multifaceted options available for culturally sensitive strategies prioritizing demand reduction.

The first edition in 2015 resulted from the collaborative efforts over 3 years of some 265 contributors from 30 countries. Based on the positive response of the first edition and also some constructive comments to make the second edition more accessible, it was decided to strive for more concise chapters aimed at highlighting the basics of the field and presented in an educationally sensitive format. Each chapter has key words and key points to anchor their main teaching insights. We endeavored to increase their clinical relevance and the authors provided sets of selective references.

The resulting second edition consists of ten sections, with some 222 contributors from 23 countries. It also presents an excellent opportunity to review the rapid evolution of our field over the course of a short 5 years.

Sociocultural, Neurological, and Genetic Foundations

The prevalence of drug intake is determined by not only individual stress factors but also regional and larger-scale cultural patterns of drug consumption, social role models, as well as legal requirements and prohibitions.

A common sequence is for the onset of substance abuse to be largely influenced by cultural factors; environmental and social factors are important in the transition to hazardous consumption, while neurobiological and other risk factors have become more salient in the transition to substance use disorder. The last 5 years have highlighted a number of new trends. While appropriate efforts were made since 2000 to legitimize addiction as a chronic disease, the public imagination has been captured by the acute aspects of the illness. Thousands upon thousands of overdoses with increasingly lethal compounds such as the opioid fentanyl have resulted in an unheard amount of media coverage and political discourse. Furthermore, a previously noted trend for the creation of laboratory manufactured chemicals just accelerated. Carfentanyl followed fentanyl in a matter of months. Traditional legal drugs such as nicotine, considered on the wane in western countries, made a resurgence using new delivery strategies, such as vaping. Medications are also benefitting from an expanding range of methods of delivery. A definite trend in basic sciences is the search for correlates between the prior scientific silos. Psychological symptoms have cerebral correlates. The genetic and now epigenetic components of the heritability of addiction also point to cross-population differences in risk susceptibility across large samples. This edition also includes a review of animal models of addictive behavior at the various stages of addiction. All these considerations consequently inform the spectrum of applied prevention strategies.

Differences in international perspectives and challenges in achieving a universal taxonomy remain. DSM-5 proposed the recent aggregation of the concept of dependence with that of substance use. This edition presents the nosology of the new ICD-11 (Diagnostic Definition, Criteria, and Classification of SUDs).

The Global Facets of Drug Use and the Current Trends in Biological Approaches

The differential availability of traditional drugs such as alcohol, tobacco, opioids, and cannabis along with newer drugs such as cocaine, amphetamines, hallucinogens, sedatives, and anabolic steroids is evident across the global stage and brings insights into the origins of abuse. Advances in neurosciences have so far yielded about a dozen drug-specific medications, and barriers to access to this small number by conservative national policies, economic constraints, and lack of clinicians' expertise are progressively eroding. A mounting evidence of efficacy arises from a number of diverse complementary options such as acupuncture, biologics, transcranial magnetic stimulation, nutrients, phytomedicines, and mind-body treatments. The evidence for these

approaches originates from around the globe, where some of these techniques derive from a long-standing acculturation.

Behavioral Approaches and the Balance of Fidelity and Adaptation

Globally, behavioral approaches are a major element of treatment. Over the last 50 years, these therapies have evolved from generic advice-giving and confrontational strategies to more sophisticated, evidence-based techniques aimed at improving retention in treatment and positive reinforcement of change. Behavioral approaches are either directed at the individual or at groups, couples, families, and communities. Not all such approaches have been evaluated to the same extent, with the major effort directed at the investigation of motivational interviewing, cognitive behavioral therapy, and contingency management. Recent trends include the increased empirical evidence for the combination of behavioral approaches along with medication. More recent developing approaches have included mindfulness strategies, a multimodal approach to chronic pain, and the expansion of exercise components. These approaches are also benefitting from the new world of technology for improved access.

Challenges in the international dissemination of these approaches include the significant effort required for the transfer of knowledge and skills as well as the need to balance the evidence-based principles and methods of the approach with the adaptation needed to incorporate new cultural contexts and values in a translated language.

Screening and Major Components of a Systems Approach

While there is consensus about the benefits of screening and brief intervention strategies, the selection of optimal screening instruments, laboratory detection methods, and brief intervention techniques is the subject of an international effort to assess cross-cultural validity as well as investigate cost-effective laboratory tests and intervention strategies to accommodate the world's range of financial and practice resources.

A community treatment system requires a comprehensive network of different approaches, services, and participants. A public health perspective stresses connections among services. These services share concepts of different indications and rules for patient pathways through treatment phases following a stepped care model.

The network, in addition to formal therapeutic regimes, includes low-threshold approaches through outreach activities and harm reduction interventions. The resources and priorities will of course differ between developing and developed countries. A comprehensive network remains a work in progress with continuous adaptations. An overall drug policy document should reflect political support to provide adequate and sustainable resources.

Faced with the difficulties in abating, if not ending, the disease of addiction, a diverse group of socially grounded therapies have sprung worldwide. Approaches have included peer-led movements with no formal affiliation such as the 12-step programs which are spanning most of the globe. Other peer-led programs have evolved as institutions regulated by governments such as therapeutic communities. These approaches are not identical worldwide but have nevertheless many similarities. A major advantage of these approaches has been their cost-effectiveness rendering them accessible to a range of economic capabilities.

The second advantage has been their adaptability to social institutions as diverse as the workplace, the justice system, or the residential treatment programs. These approaches have gained widespread acceptance particularly in developing countries.

A system must include continuous monitoring and evaluation. The education and training of staff must be informed by the results of the evaluation. Stakeholders are to be involved in the priority setting as well as ethical and legal considerations.

Policies and Training in Addiction

There is increased recognition of the interplay between policy, legal, quality, and other governance standards in our field. A major trend accelerating over the last 5 years has been the increased recognition of addiction problems as public health rather than legal problems. This has led to prioritization of demand reduction strategies over supply reduction approaches. The social experiment over the last 5 years of the various aspects of legalization of cannabis is under scrutiny. Benefits and challenges are being reported.

The education, training, and sustenance of an appropriate workforce are critical to the survival of our field. A range of pioneering efforts is available. They are based on an increasingly consensual framework of identified competencies recognized by specialty associations as well as a number of universities through a master's degree.

Recognition of these competencies is facilitated through diverse pathways such as an American Board Examination, an International Certification (ISAM), and a number of diploma degrees. The knowledge base is accessible through a number of open access literature repositories or other educational activities. Fellowships in research training are available through NIDA, and a number of travel fellowships to conferences are offered.

Concerning the recognition of a specialty status, there is no "one-size-fits-all" model. This journey must adapt to local educational and licensing requirements that govern the national practices of medicine; options for recognition of competency may include certification by examination or completion of a comprehensive portfolio.

Beyond training, the recruitment of an adequate workforce must take into consideration the provision of attractive career paths countering stigma as well as adequate remuneration and working conditions.

What Constitutes a Behavioral Addiction?

Over the last 40 years, an increasing range of behaviors have been recognized as susceptible to develop from excessive engagement to a habitual or compulsive pattern. In addition to the investigation of common biological and psychological underpinnings, an international perspective highlights sociocultural differences. The same applies to the meeting of basic needs such as food, sex, or exercise and their evolution into compulsive behaviors. Ever-increasing access to services, products, and credit may accelerate this course.

Other insights are arising from the study of behavioral addictions as windows into human nature without the effects of substances. A model of addiction is emerging, depending less on "harm-based" negative consequences which are subject to ever-changing cultural values and judgment calls and more on the presence of concepts such as craving, loss of control, impulsivity, compulsion, mood dysregulation, and/or cognitive distortions.

Differences in treatment seeking patterns, treatment approaches, and settings as well as goals of treatment are highlighted in the international comparative analysis.

The major new additions in this Section are the updates on problematic Internet use and Internet gaming disorder. The new ICD-11 criteria as well as the DSM-5 appendix perspectives are discussed. Challenges about this concept and implications for the expansion of the range of potential correlated behaviors are outlined.

The Recognition of Medical Consequences and Comorbidities

The principles of assessment and management of the medical consequences of drug use ought not to be different around the world, and yet morbidity and mortality rates of drug users vary markedly due to differences in the general health status of the population, access to health care, and rates of treatment uptake and dropout. Almost every system is involved, including psychiatric, neurocognitive, cardiovascular, metabolic, and hepatic complications. An estimated one-third of the global population is living with one or more bacterial or viral infections. Nutrition is important, and nutritional disorders impact on recovery from other co-occurring illnesses. A new chapter on Oral Health has been added. The availability and acceptability of simple preventive measures like the use of a condom significantly affect the rate of sexually transmitted infections. The medical consequences of drug use interact in each country with the general level of hygiene as well as availability of preventive and treatment resources. While the management of acute disorders is the main focus of health resources in developing countries, chronic disorders including chronic pain become the major concern in developed countries, and substance use plays an important role in the course of both these acute and chronic disorders.

The Co-occurring Care of Substance Use and Psychiatric Disorders and System Change

While the recognition of medical comorbidities has not resulted in an overall health system change, reorganization is occurring in the addiction and mental health fields. Since the 1950s, the recognition of the co-occurrence of substance use and psychiatric disorders and its impact on the delivery of services has evolved. In most developed countries, the addiction field struggled to establish its own system of delivery of care based on the need to treat otherwise unrecognized or marginalized individuals with addictive disorders. In the United States, NIDA and NIAAA as separate research institutes led the building of a scientific knowledge foundation for our field. Worldwide, various degrees of separation remained in existence with many countries maintaining the addiction services under the umbrella of mental health.

For the last 30 years, increased recognition of the high prevalence of individuals with co-occurring disorders has resulted in replanning the coordination between addiction and other mental health services and in some cases integration of both systems. Based on improved empirical evidence in both fields, this renewed coordination is leading to enhanced attention to the neurobiological interface as well as pharmacological and psychotherapeutic combined options. It is also recognized that ethnic, racial, and cultural groups manifest their medical illnesses including psychiatric within the context of their heritage. The redesign of optimal systems of care as well as related workforce training is ongoing. Diagnostic-based approaches now integrate the treatment of substance use and other psychiatric disorders.

The Dilemmas of Special Populations

The challenge of prioritizing special groups for further recognition is a daunting one, and there is no international consensus. Our own selection included women, addressing half of humanity as well as the elderly soon to become a quarter of humanity. Two chapters describe the interactions between individuals abusing substances and the criminal justice system as well as the developing drug court network. Much attention has been directed at the care of physicians and other health care providers as an example of evidenced excellent outcome when well-defined workplace strategies are in place. Our last group involves the "displaced" populations either through conflicts or disasters; internationally, these groups are in the millions!

Perhaps a common feature of these groups is a sense that their fit within the general system of care may not be optimal, and there is demonstrated evidence that some of their needs may be better met wholly or partly in distinct pathways of care.

Meeting the Needs of Our Youth

Contrary to the previously listed groups, there is international consensus that the youth of the world deserve their own care. Much is to be gained by a focused system for young people who use drugs. They face the higher risk of initiating substance use. This initiation is determined by a multitude of risk factors in different developmental contexts, some of it originating from parental chronic substance use.

Adolescence is also a critical period where protective factors can also modify the pathways to substance use. The earlier the intervention during that period, the more chance there may be of a successful outcome including the prevention of chronicity and the reduction of the risk of suicide. Knowledge of the impact of both risk and protective factors can also optimize preventive strategies.

The engagement of a young person who is often vulnerable and even marginalized may require the involvement of multiple systems along with repeated assessments. Greater specificity in treatment choice that is developmentally appropriate such as CBT and MET along with family-based interventions has been demonstrated to provide the most consistent gains. Barriers to involvement such as stigma, safety, transportation, and family commitment must also be addressed.

In conclusion, as no country has so far been able to eradicate the misuse of substances or control excessive behaviors, pooling the international experience is warranted. A global scanning of the options allows us to forecast potentially promising approaches. Considering the world experience, we are also reminded of the dictum "Absence of evidence may not necessarily mean evidence of absence." It may just be that the evidence has yet not been unearthed and our current investigations are still not sensitive enough. The second edition is a testimony to the rapid evolution of our field, its challenges, and also its progress.

The COVID-19 pandemic started as we were concluding the final preparation of this edition. This pandemic brought home the critical need for global interconnectedness and the importance of comprehensive public health approaches. This pandemic superimposes itself on top of the many concerns reviewed in the rest of the textbook. An additional chapter has been added to the Section on Medical Disorders highlighting the conceptualization of syndemics and related strategies addressing the challenges of concurrent epidemics.

Calgary, AB, Canada — Nady el-Guebaly
Monza, Italy — Giuseppe Carrà
New York, NY, USA — Marc Galanter
St Andrews, UK — Alexander M. Baldacchino

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Contents

Contributors

Robert Ali University of Adelaide, Adelaide, SA, Australia

Joseph Althaus The National Problem Gambling Clinic, London, UK

The Barberry National Centre for Mental Health, Birmingham, UK

Stephen Amadala Alberta Health Services, Calgary, AB, Canada

Pedro J. Amor Department of Personality, Assessment and Psychological Treatment, National Distance Education University (UNED), Madrid, Spain

Garima Arora Dental Health Services Research Unit, University of Dundee, Dundee, UK

Sawitri Assanangkornchai Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

N. Avena University of Florida College of Medicine, Gainesville, FL, USA

Thomas F. Babor Department of Public Health Sciences, University of Connecticut School of Medicine, Farmington, CT, USA

Sudie E. Back Medical University of South Carolina, Charleston, SC, USA

Alexander M. Baldacchino Population and Behavioural Science Division (Psychiatry and Addictions), University of St Andrews and NHS Fife, St Andrews, UK

St Andrews Medical School, University of St Andrews, Scotland, UK

Jane Ballantyne University of Washington, Seattle, WA, USA

Manuel Barrera Jr Department of Psychology, Arizona State University, Tempe, AZ, USA

Pablo Barrio Addictions Unit, Department of Psychiatry, University of Catalonia, Barcelona, Spain

Francesco Bartoli Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Department of Mental Health and Addiction, ASST Nord Milano, Milan, Italy

M. Teresa Bascarán INEUROPA-ISPA, Oviedo, Spain

CIBERSAM, Oviedo, Spain

David Best University of Derby, Derby, UK

Julio Bobes INEUROPA-ISPA, Oviedo, Spain

CIBERSAM, Oviedo, Spain

Department of Psychiatry, University of Oviedo, Oviedo, Spain

M. Teresa Bobes-Bascarán Servicio de Salud Del Principado de Asturias (SESPA), Oviedo, Spain

Department of Psychology, University of Oviedo, Oviedo, Spain

INEUROPA-ISPA, Oviedo, Spain

CIBERSAM, Oviedo, Spain

Kristopher Bough Division of Basic Neuroscience and Behavioral Research, National Institute on Drug Abuse, USA

Henrietta Bowden-Jones Honorary Professor, Division of Psychology and Language Science, University College London, London, UK

Honorary Senior Visiting Fellow, Cambridge University, London, UK

President of Psychiatry Section, Royal Society of Medicine, London, UK

The National Problem Gambling Clinic, London, UK

Kathleen T. Brady Department of Psychiatry and Behavioral Sciences, Clinical Neuroscience Division, Medical University of South Carolina, Charleston, SC, USA

Department of Psychiatry and Behavioral Sciences, Addiction Sciences Division, Medical University of South Carolina, Charleston, SC, USA

Distinguished University Professor, Vice President for Research, Medical University of South Carolina, Charleston, SC, USA

Jørgen G. Bramness Norwegian Competence Centre for Dual Diagnosis Innland Hospital Trust, Hamar, Norway

Norwegian Institute of Public Health, Oslo, Norway

Institute of Clinical Medicine, UiT, The Arctic University of Norway, Tromsø, Norway

María Dolores Braquehais Integral Care Program for Sick Health Professionals, Galatea Clinic, Galatea Foundation, Catalan Medical Association, Barcelona, Spain

Group of Psychiatry, Mental Health and Addictions, Vall Hebron Research Institute, Barcelona, Spain

Barbara Broers Unit for Dependencies, Division for Primary Care, Department for Community Medicine, Primary Care and Emergencies, Geneva University Hospitals, Geneva, Switzerland

Vivian B. Brown Prototypes: Centers for Innovation in Health, Mental Health, and Substance Use Disorders, Pittsboro, NC, USA

Eugeni Bruguera Integral Care Program for Sick Health Professionals, Galatea Clinic, Galatea Foundation, Catalan Medical Association, Barcelona, Spain

Group of Psychiatry, Mental Health and Addictions, Vall Hebron Research Institute, Barcelona, Spain

Department of Psychiatry and Legal Medicine, Hospital Universitari Vall d'Hebron, CIBERSAM, Universitat Autònoma de Barcelona, Barcelona, Spain

Alan J. Budney Center for Technology and Behavioral Health, Department of Psychiatry, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

Gregory Bunt Daytop Village, Inc., New York, NY, USA

Department of Psychiatry, NYU Langone Medical Center, New York, NY, USA

Gregor Burkhart EMCDDA, Lisbon, Portugal

Anja Busse United Nations Office on Drugs and Crime, Vienna, Austria

Giuseppe Carrà Mental Health Department, University of Milano-Bicocca, Milan, Italy

Department of Mental Health and Addiction, ASST Nord Milano, Milan, Italy

Division of Psychiatry, University College London, London, UK

Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Daniele Carretta Department of Mental Health and Addiction, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

Miquel Casas Department of Psychiatry and Legal Medicine, Hospital Universitari Vall d'Hebron, CIBERSAM, Universitat Autònoma de Barcelona, Barcelona, Spain

Richard Cash 360Edge, Melbourne, VIC, Australia

Felipe González Castro Edson College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ, USA

Kai Yeng Chan Consultation Liaison and Addictions Psychiatry Medicine, Townsville Hospital, Douglas, QLD, Australia

Katrin Charlet Department of Psychiatry and Psychotherapy, CCM, Charité - Universitätsmedizin Berlin, Berlin, Germany

Guang Chen Drug Health, Western Sydney Local Health District, Westmead, NSW, Australia

Brian Conway Vancouver Infectious Diseases Centre, Vancouver, BC, Canada

Ryan Cotter Division of Cardiology, University of Colorado, Aurora, CO, USA

David Crockford Department of Psychiatry, University of Calgary, Calgary, AB, Canada

Ilana B. Crome Keele University, Staffordshire, UK

St George's, University of London, London, UK

Silvia L. Cruz Department of Pharmacobiology, CINVESTAV, Mexico City, Mexico

Naomi Dambreville The City College of New York, CUNY, New York, NY, USA

The Graduate Center, CUNY, New York, NY, USA

Leigh Dickerson Davidson David E. Smith, MD & Associates, San Francisco, CA, USA

Cornelis A. J. De Jong Radboud University, Nijmegen, The Netherlands

George De Leon BST at the School of Nursing, NYU, New York, NY, USA

Department of Psychiatry, NYU School of Medicine, New York, NY, USA

Zsolt Demetrovics Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

John F. Dillon Gut Group, Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, UK

Fernando Dinamarca Institut de Neuropsiquiatria i Addiccions, Hospital del Mar, Barcelona, Spain

IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain

Michael Dinh Royal Prince Alfred Hospital, The University of Sydney, Discipline of Emergency Medicine, Sydney, NSW, Australia

Hannah M. Dix Gastroenterology Department, NHS Tayside, Dundee, UK

Nicole Durham Addictions Division, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Enrique Echeburúa Department of Clinical Psychology, University of the Basque Country UPV/EHU, San Sebastián, Spain

J. Guy Edwards Southampton University Hospitals, Southampton, UK

Department of Psychiatry and Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand

Hamed Ekhtiari Laureate Institute for Brain Research, Tulsa, OK, USA

Nady el-Guebaly Division of Addiction, Department of Psychiatry, University of Calgary, Calgary, AB, Canada

Ahmed Elkashef Division of Therapeutics and Medical Consequences, National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland, USA

Nadine Ezard St Vincent's Hospital Sydney / UNSW, Sydney, Australia

L. Llamosas Falcón Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Preventive Medicine and Public Health, Hospital Universitario 12 de Octubre, Madrid, Spain

Magi Farré Universitat Autònoma de Barcelona, Barcelona, Spain

Hospital Universitari Germans Trias i Pujol (IGTP), Badalona, Spain

Thierry Favrod-Coune Unit for Dependencies, Division for Primary Care, Department for Primary Care Medicine, Geneva University Hospitals, Geneva, Switzerland

Marica Ferri EMCDDA, Lisbon, Portugal

Tatiana Zambrano Filomensky Impulse Control Disorders Outpatient Unit, University of São Paulo, São Paulo, Brazil

Francina Fonseca Institut de Neuropsiquiatria i Addiccions, Hospital del Mar, Barcelona, Spain

IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain

Universitat Autònoma de Barcelona, Barcelona, Spain

Ronald Fraser McGill University, Montreal, QC, Canada

Ruth Freeman Dental Health Services Research Unit, University of Dundee, NHS Tayside, Dundee, UK

Eva Friedel Charite - Universitätsmedizin Berlin, Berlin, Germany

Marc Galanter Division of Alcoholism and Drug Abuse, Department of Psychiatry, NYU School of Medicine, New York, NY, USA

Department of Psychiatry, NYU School of Medicine, New York, NY, USA

Hugh Garavan Department of Psychiatry, University of Vermont, Burlington, VT, USA

Maria Garbusow Department of Psychiatry and Psychotherapy, CCM, Charité - Universitätsmedizin Berlin, Berlin, Germany

M. Paz García-Portilla INEUROPA-ISPA, Oviedo, Spain

CIBERSAM, Oviedo, Spain

Department of Psychiatry, University of Oviedo, Oviedo, Spain

Eliot L. Gardner Neuropsychopharmacology Section, Molecular Targets and Medications Discovery Research Branch, Intramural Research Program, National Institute on Drug Abuse, US National Institutes of Health, Baltimore, MD, USA

Tony P. George Addictions Division, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Stephen Gilbert Anaesthesia and Pain Medicine, Townsville Hospital, Douglas, QLD, Australia

North Queensland Persistent Pain Management Service, Townsville Hospital, Townsville, QLD, Australia

Thomas Gilbertson Department of Neurology, Ninewells Hospital and Medical School, Dundee, UK

Division of Imaging Science and Technology, Medical School, University of Dundee, Dundee, UK

M. Gold Washington University, St. Louis, MO, USA

Hugo González National Institute of Psychiatry Ramón de la Fuente Muiz, Mexico City, Mexico

Christine M. Goodair Population Health Research Institute, St George's, University of London, London, UK

David A. Gorelick Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

Linda Gowing University of Adelaide, Adelaide, SA, Australia

Kevin M. Gray Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Paul Griffiths EMCDDA, Lisbon, Portugal

Antoni Gual Addictions Unit, Department of Psychiatry, University of Catalonia, Barcelona, Spain

Neurosciences Institute, Hospital Clínic, IDIBAPS, Barcelona, Spain

Steven W. Gust International Program, National Institute on Drug Abuse, National Institutes of Health, US Department of Health and Human Services, Washington, DC, USA

Anna Haber Western Sydney University School of Medicine, Sydney, Australia

Paul S. Haber Drug Health Services, Sydney Local Health District, The University of Sydney Central Clinical School, Sydney, NSW, Australia

University of Sydney and Drug Health Service, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Richard Hallinan Drug Health Services, Liverpool Hospital, South Western Sydney Local Health District, Liverpool, NSW, Australia

The Byrne Surgery, Redfern, NSW, Australia

Rebecca Hamer Sheffield Hallam University, Sheffield, UK

Jennifer Harland University of Adelaide, Adelaide, SA, Australia

Richard Hartnoll European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal (retired)

Deborah S. Hasin Department of Epidemiology, Columbia University Mailman School of Public Health, New York State Psychiatric Institute, New York, NY, USA

Dagmar Hedrich European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal

Andreas Heinz Department of Psychiatry and Psychotherapy, CCM, Charité - Universitätsmedizin Berlin, Berlin, Germany

Annemarie Hennessy Western Sydney University School of Medicine, Sydney, Australia

Susan Henry-Edwards University of Adelaide, Adelaide, SA, Australia

Mariely Hernandez The City College of New York, CUNY, New York, NY, USA

The Graduate Center, CUNY, New York, NY, USA

Meyen Hertzsprung M Hertzsprung Psychological Services, Calgary, AB, Canada

David C. Hodgins Department of Psychology, University of Calgary, Calgary, AB, Canada

Ben Houghton St George's University of London, London, UK

Lori Isaif McGill University Health Centre, Montreal, QC, Canada

Shelly Iskandar Psychiatric Department, Hasan Sadikin Hospital, Padjajaran University, Bandung, Indonesia

Alexandra Ivanciu Department of Psychiatry, University of Vermont, Burlington, VT, USA

Lauren M. Jansson The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Chloe J. Jordan National Institute on Drug Abuse, Baltimore, MD, USA

Aloysius Joseph Daytop International, Inc., New York, NY, USA

Jakob Kaminski Charite - Universitätsmedizin Berlin, Berlin, Germany

Gen Kanayama Biological Psychiatry Laboratory, McLean Hospital, Belmont, MA, USA

Harvard Medical School, Boston, MA, USA

Linda K. Kaye Edge Hill University, Ormskirk, UK

Jag H. Khalsa Division of Therapeutics and Medical Consequences, National Institute on Drug Abuse, National Institutes of Health, Aldie, VA, USA

Division of Therapeutics and Medical Consequences, National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland, USA

E. J. Khantzian Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Jungjin Kim Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA

Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Hyoun S. Kim Department of Psychology, University of Calgary, Calgary, AB, Canada

Orsolya Király Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

Axel Klein Global Drug Policy Observatory, University of Swansea, Swansea, UK

Keith Klostermann Medaille College, Buffalo, NY, USA

Gail Koshorek Sleep Disorder & Research Center, Henry Ford Health System, Detroit, MI, USA

Christos Kouimtsidis Imperial College, London, UK

Mori J. Krantz Division of Cardiology, University of Colorado, Aurora, CO, USA

Denver Health Medical Center, Division of Cardiology, Denver, CO, USA

Daniel L. Krashin University of Washington, Seattle, WA, USA

Daria J. Kuss Nottingham Trent University, Nottingham, UK

Lise Laporte McGill University Health Centre, Montreal, QC, Canada

Noeline C. Latt Disciplines of Psychiatry and Addiction Medicine, Faculty of Medicine, University of Sydney, Camperdown, NSW, Australia

Formerly Northern Area Drug and Alcohol Service, Royal North Shore Hospital, St Leonards, NSW, Australia

Nicole K. Lee National Drug Research Institute (NDRI), Curtin University, Bentley, WA, Australia

360Edge, Melbourne, VIC, Australia

Robert F. Leeman Department of Health Education and Behavior, University of Florida, Gainesville, FL, USA

Department of Psychiatry, Yale University, New Haven, CT, USA

Bernard Le Foll Translational Addiction Research Laboratory, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

Alcohol Research and Treatment Clinic, Acute Care Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada

Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada

Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada

Division of Brain and Therapeutics, Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada

Shea M. Lemley Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

Frances Rudnick Levin Columbia University Medical Center, New York State Psychiatric Institute, New York, NY, USA

Luming Li Psychiatry, Yale University, New Haven, CT, USA

Jessica B. Lydiard University of Miami, Miami, FL, USA

Brian Mac Grory Brown University, Providence, RI, USA

Tianna Magel Vancouver Infectious Diseases Centre, Vancouver, BC, Canada

Hussein Manji United Nations Office on Drugs and Crime, Vienna, Austria

Marianne Marcus The University of Texas Health Science Center at Houston, Houston, TX, USA

Douglas B. Marlowe National Association of Drug Court Professionals, Chadds Ford, PA, USA

Lisa A. Marsch Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

Flavio F. Marsiglia School of Social Work, Arizona State University, Phoenix, AZ, USA

Lisa Marzilli Dominion Diagnostics Lab, Narragansett, RI, USA

Jenna L. McCauley Medical University of South Carolina, Charleston, SC, USA

Andrew S. McClintock University of Wisconsin-Madison, Madison, WI, USA

Michael G. McDonell Washington State University, Spokane, WA, USA

R. Kathryn McHugh Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA

Department of Psychiatry, Harvard Medical School, Boston, MA, USA

S. McNamara Department of Respiratory & Sleep Medicine, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Sterling M. McPherson Washington State University, Spokane, WA, USA

Tim McSweeney Department of Psychology, University of Hertfordshire, Hatfield, UK

María Elena Medina-Mora Mental Health Global Research Center, National Institute of Psychiatry Ramón de la Fuente Muiz/UNAM, Mexico City, Mexico

Robert Milin Adolescent Day Treatment Unit, Royal Ottawa Mental Health Centre, Ottawa, ON, Canada

Department of Psychiatry University of Ottawa, Ottawa, ON, Canada

Michael Miller Department of Psychiatry, University of Wisconsin, Madison, WI, USA

Larissa J. Mooney Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles (UCLA), Los Angeles, CA, USA

VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA

Christian A. Müller Department of Psychiatry and Psychotherapy, CCM, Charité - Universitätsmedizin Berlin, Berlin, Germany

Natalia Murinova University of Washington, Seattle, WA, USA

S. Murray Icahn School of Medicine, Mount Sinai, NY, USA

B. Nanayakkara Department of Respiratory & Sleep Medicine, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Edward V. Nunes Division on Substance Use Disorders, Department of Psychiatry, Columbia University Irving Medical Center, New York State Psychiatric Institute, New York, NY, USA

Michael Odenwald Department of Psychology, Konstanz University, Konstanz, Germany

Timothy J. O'Farrell Harvard Medical School, Brockton, NY, USA

Andrew T. Olagunju Department of Psychiatry and Behavioral Neurosciences McMaster University & St Joseph Healthcare Hamilton, Hamilton, ON, Canada

Department of Psychiatry, College of Medicine, University of Lagos, Lagos, Nigeria

Matthew Oliver Royal Prince Alfred Hospital, The University of Sydney, Discipline of Emergency Medicine, Sydney, NSW, Australia

Esther Papaseit Universitat Autònoma de Barcelona, Barcelona, Spain

Hospital Universitari Germans Trias i Pujol (IGTP), Badalona, Spain

Fernando B. Perfas Daytop International Training Academy, New York, NY, USA

Sara Park Perrins School of Environmental and Forest Sciences, University of Washington, Seattle, WA, USA

Harrison G. Pope Jr Biological Psychiatry Laboratory, McLean Hospital, Belmont, MA, USA

Harvard Medical School, Boston, MA, USA

Marc N. Potenza Department of Psychiatry, Yale University, New Haven, CT, USA

Departments of Child Study and Neurobiology, Yale University, New Haven, CT, USA

Ulrich W. Preuss Vitos Hospital for Psychiatry and Psychotherapy, Kassel, Germany

Department for Psychiatry, Psychotherapy and Psychosomatic Medicine, University of Halle, Halle, Germany

C. Probst Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Anna Quirk Department of Endocrinology, St Vincent's Hospital, Darlinghurst, NSW, Australia

Department of Endocrinology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Rahul Rao Institute of Psychiatry, Psychology and Neuroscience, London, UK

Richard A. Rawson Vermont Center for Behavior and Health, University of Vermont, Burlington, VT, USA

Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles (UCLA), Los Angeles, CA, USA

Tania Real National Institute of Psychiatry Ramón de la Fuente Muiz, Mexico City, Mexico

J. Rehm Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

Institute of Medical Science, University of Toronto, Toronto, ON, Canada

Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany

Department of International Health Projects, Institute for Leadership and Health Management, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation

Stephan Ripke Charite - Universitätsmedizin Berlin, Berlin, Germany

Emma M. Robinson Gut Group, Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, UK

Rebeca Robles National Institute of Psychiatry Ramón de la Fuente Muiz, Mexico City, Mexico

Timothy Roehrs Sleep Disorder & Research Center, Henry Ford Health System, Detroit, MI, USA

Department of Psychiatry and Behavioral Neuroscience, Wayne State University, SOM, Detroit, MI, USA

John M. Roll Washington State University, Spokane, WA, USA

Evelien Rooke Department of Neurology, Ninewells Hospital and Medical School, Dundee, UK

Robin Room Centre for Alcohol Policy Research, La Trobe University, Bundoora, VIC, Australia

Centre for Social Research on Alcohol & Drugs, Department of Public Health Sciences, Stockholm University, Stockholm, Sweden

Hendrik G. Roozen University of New Mexico, Albuquerque, NM, USA

Paula Ross 360Edge, Melbourne, VIC, Australia

Thomas Roth Sleep Disorder & Research Center, Henry Ford Health System, Detroit, MI, USA

Department of Psychiatry and Behavioral Neuroscience, Wayne State University, SOM, Detroit, MI, USA

Hans-Jürgen Rumpf University of Lübeck, Lübeck, Germany

Brian Rush Centre for Addiction and Mental Health, Toronto, ON, Canada

Claudia Salazar Central North West London NHS Foundation Trust, London, UK

Siddharth Sarkar Department of Psychiatry and National Drug Dependence Treatment Center, All India Institute of Medical Sciences, New Delhi, India

Julia Sasiadek Addictions Division, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

John B. Saunders Centre for Youth Substance Abuse Research, University of Queensland, St Lucia, QLD, Australia

Disciplines of Psychiatry and Addiction Medicine, Faculty of Medicine, University of Sydney, Camperdown, NSW, Australia

Miriam Sebold Department of Psychiatry and Psychotherapy, CCM, Charité - Universitätsmedizin Berlin, Berlin, Germany

Bhags Sharma Addiction Services, NHS Fife, Scotland, UK

K. D. Shield Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

Dan Shlosberg Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

Gal Shoval Geha Mental Health Center, Petah Tiqva, Israel

Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Matisyahu Shulman Division on Substance Use Disorders, Department of Psychiatry, Columbia University Irving Medical Center, New York State Psychiatric Institute, New York, NY, USA

Roland Simon IFT Institute for Therapy Research, Munich, Germany

Jane Ellen Smith Department of Psychology, University of New Mexico, Albuquerque, NM, USA

David E. Smith David E. Smith, MD & Associates, San Francisco, CA, USA

Brendan Smyth Department of Renal Medicine, St. George Hospital, Sydney, Australia

Michael J. Sofis Center for Technology and Behavioral Health, Department of Psychiatry, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

Philip A. Spechler Department of Psychiatry, University of Vermont, Burlington, VT, USA

Douglas Steele Division of Imaging Science and Technology, Medical School, University of Dundee, Dundee, UK

Frederike Stöth Institute of Legal Forensic Medicine, University of Bern, Bern, Switzerland

Hermano Tavares Impulse Control Disorders Outpatient Unit, University of São Paulo, São Paulo, Brazil

Joe Tay Wee Teck University of Glasgow, Scotland, Glasgow, UK

Debora Teles Personality Disorder Program, McGill University Health Centre, Montreal, QC, Canada

Natasha Thon IDIBAPS Neurosciences Institute, Barcelona, Spain

Marta Torrens Institut de Neuropsiquiatria i Addiccions, Hospital del Mar, Barcelona, Spain

IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain

Universitat Autònoma de Barcelona, Barcelona, Spain

Christopher Tremonti Sydney Local Health District, Camperdown, NSW, Australia

Leanne Trick Translational Addiction Research Laboratory, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

Stephen Twigg Department of Endocrinology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Sydney Medical School (Central), Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

Ambros Uchtenhagen Swiss Research Foundation for Public Health and Addiction, Zurich University, Zurich, Switzerland

Annie Umbricht The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Martha L. Velez The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Antonio Verdejo-Garcia Turner Institute for Brain and Mental Health, Monash University, Melbourne, VIC, Australia

Jelena Verkler Sleep Disorder & Research Center, Henry Ford Health System, Detroit, MI, USA

Claudio Violato University of Minnesota Medical School, Minneapolis, MN, USA

Jonathan M. Wai Division on Substance Use Disorders, Department of Psychiatry, Columbia University Irving Medical Center, New York State Psychiatric Institute, New York, NY, USA

Nasir Warfa Maltepe University, Maltepe/İstanbul, Turkey

Wolfgang Weinmann Institute of Legal Forensic Medicine, University of Bern, Bern, Switzerland

Roger D. Weiss Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA

Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Gabrielle Welle-Strand Norwegian Center of Addiction Research/Oslo University Hospital, Oslo, Norway

Blake Werner Yale University, New Haven, CT, USA

Jessica Wong Klinik am Homberg, Bad Wildungen, Germany

Kelli Wuerth Vancouver Infectious Diseases Centre, Vancouver, BC, Canada

Friedrich Martin Wurst Medical Faculty, University of Basel, Basel, Switzerland

Psychiatric University Hospital Basel, Basel, Switzerland

S. Yarnell-Mac Grory Yale School of Medicine – Department of Psychiatry, New Haven, CT, USA

Yvonne H. C. Yau Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada

Michel Yegles Laboratoire National de Santé, Forensic Toxicology, Dudelange, Luxemburg

Mehran Zare-Bidoky Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran

School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

David Zendle University of York, York, UK

Part I

Basic Sciences and Clinical Foundations

Andreas Heinz and Nady el-Guebaly

Basic Sciences and Clinical Foundations: An Introduction

1

Andreas Heinz and Nady el-Guebaly

Content

Abstract

We here introduce the section "Basic Sciences and Clinical Foundations." In this section, we address the social, cultural, and regional as well as the neurobiological and genetic aspects of addiction. The foundational section of this international textbook on addiction treatment aims to provide a prologue to the topic. This section starts with chapters on neurobiology including a review of the neurotoxic and neuroadaptive consequences of chronic drug intake with a focus on alcohol. A chapter on genetics presents the heritability of addiction and its genetic and epigenetic components. The next chapter complements the focus on neurobiological correlates of addictive behavior with a discussion of animal models of addiction. The next chapter presents the international epidemiological aspects of addiction with a focus on the findings of the Global Burden of Disease Study. The role of socio-environmental factors in diagnosis and treatment is addressed in the next chapter, which also describes their respective impact on the patient-clinician interpersonal dynamics as well as interactions in the family, intimate social networks, community at large, and policy makers. We thus emphasize how cultural factors, that is, shared beliefs, norms, and patterns of behavior, interact with drug consumption in different populations. The social patterning of psychoactive drug use differs as to whether it is medicinal, regular, intermittent, or addictive. The next chapter focuses on the prevention applications of the components discussed with a review of the international experience. These contributions underpin the evolution of diagnostic definitions and classifications reviewed in the subsequent chapter. In conclusion, this foundational section provides a focused scientific review of current knowledge. As this is the first section of this textbook, the aim is to demonstrate the basic sciences and clinical foundations and to reflect the commonalities and differences of broad global and international perspectives.

A. Heinz (✉)
Charité – Universitätsmedizin Berlin,
Berlin, Germany
e-mail: andreas.heinz@charite.de

N. el-Guebaly
Division of Addiction, Department of Psychiatry,
University of Calgary, Calgary, AB, Canada
e-mail: nady.el-guebaly@ahs.ca

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Diagnoses

Drug use and dependence are the leading causes of disability and suffering particularly among adolescence and younger adults [11]. Addictive disorders also contribute to a substantial percentage of interpersonal violence, partly due to the direct effect of drugs of abuse such as alcohol [13] and partly due to social consequences of illicit drug abuse [20, 21, 27]. In this section, we will discuss the social, cultural, and regional as well as the neurobiological and genetic aspects of addiction. The appreciation of this term has evolved. In 1976, Griffith Edwards suggested to focus on key aspects of drug dependence, namely, tolerance to drug effects developing with its chronic (ab)use and withdrawal symptoms appearing when chronic drug use is suddenly interrupted [4]. Edwards suggested replacing the term "addiction" as this more likely stigmatizes patients because it points to strong drug urges and the allegedly impaired ability to control such desires. He instead proposed to focus on the "somatic" aspects of the addictive disorders, most notably tolerance and withdrawal. However, tolerance also develops to nonaddictive drugs such as ß-blockers or antidepressive medication, and withdrawal symptoms emerge as a sign of impaired cerebral homoeostasis when drug consumption is suddenly stopped [15, 19]. Caffeine consumption can also cause withdrawal symptoms, which is relevant but not sufficient for diagnosing drug dependence. In accordance with these considerations, a "caffeine dependence" syndrome was described in ICD-10 but is no longer found in the current version of ICD-11, and DSM-5 lists "caffeine use disorder" only as a condition for further study [14]. Beyond tolerance development and withdrawal symptoms, current classification systems emphasize craving for the drug of abuse and the impaired ability to control the consumption of this drug in spite of its harmful effects as key aspects of addictive disorders [1].

Craving, loss of control, and consumption despite negative consequences have often been labeled as the "psychological" symptoms of an addictive disorder, while tolerance development and withdrawal symptoms have been called "somatic" signs of the disease; however, in our view, this distinction between psychological and somatic symptoms of addictive disorders should no longer be supported, as both withdrawal symptoms and craving for the drug of abuse have cerebral correlates. Tolerance development is associated with neuroadaptations within affected neurotransmitter systems, and withdrawal symptoms result from an imbalance between central excitatory and inhibitory neurotransmitters, causing an overshoot of autonomic nervous system responses [18]. Craving in turn might be attributable to dysfunctions of motivational systems including dopaminergic neurotransmission in the ventral striatum [8, 12]. Furthermore, current theories of addictive behavior emphasize a gradual shift from goal-directed, reward-seeking behavior toward automatic or even "compulsive" drug intake, a concept that has previously been promoted by Tiffany and Carter [26] with respect to nicotine dependence and that has currently gained a lot of behavioral as well as neurobiological support in animal experiments and human studies focusing on chronic drug intakes [6, 7]. These considerations show that far from being limited to either the psychological or somatic domain, all key aspects of addictive disorders such as tolerance development, withdrawal symptoms, drug craving, and impaired control of drug use are associated with central nervous system correlates and neuroadaptations.

Modern theories of psychiatric disorders integrate subjectively reported symptoms such as craving or urges to consume a drug with behavioral variables such as acute or habitual drug intake and their respective neurobiological correlates (e.g., activation of the ventral or dorsal striatum and the respectively associated frontocortical-striatal-thalamic loops [3, 10, 23]. Such neurobiological approaches are now

complemented by computational approaches that compare different models of behavior for best fit and identify decisive computational steps (including reward prediction errors); the neurobiological correlates of such computations can then be identified, for example, with neuroimaging [29].

Modern neurobiological research has often pointed to the intimate interaction between social stress effects and the development and maintenance of drug addiction [13, 17]. For example, exposure to developmentally early social isolation stress in nonhuman primates promotes excessive alcohol intake, and the degree to which such social effects impact on the neurobiological correlates of addiction is modulated by genetic variability [2, 9, 13, 16].

Beyond individual social stress factors, regional and large-scale cultural patterns of drug consumption, legal requirements, and prohibitions as well as complex social role models all contribute to the prevalence of drug intake [5, 24]. Also, modern cosmopolitan societies need to consider the effects of different explanatory models of addictive disorders. For example, we and others have observed that it may not suffice to translate information material to prevent the development of addictive disorders because the concept, the terms, and the general understanding of addictive behavior can vary substantially between persons and cultures, and misunderstandings can only be avoided if local and linguistic concepts of "normal" and "harmful" drug use are known [22, 28]. More recently, the stigmatizing effect of some of our current terminology has come under scrutiny [25].

Our textbook addresses all the above mentioned aspects of addiction. The foundational section of this international textbook on addiction treatment aims to provide an apt prologue to the topic. It consequently includes articles on the burden of disease, the cultural as well as genetic aspects of addictive disorders, and the neurobiology of addiction and also on the resulting strategies for prevention and treatment of drug use and dependence.

The second chapter on neurobiology by Dr. Sebold and coworkers is a review of the neurotoxic and neuroadaptive consequences of chronic drug intake with a focus on alcohol (Chap. 2). Dispositional factors are reviewed, and the neurobiological effects of alcohol consumption are outlined, followed by a discussion of some key animal and human studies underpinning the concept of a reward system and the important differentiation between the experiences of "liking" and "wanting." The chapter concludes with an analysis of the consequences for treatment options.

The third chapter on genetics by Dr. Friedel et al. presents a complementary perspective to the first one (Chap. 3). It reviews the heritability of addiction and its genetic and epigenetic components. It also highlights gene x environment interactions and explains how epigenetic mechanisms may mediate the impact of social stress factors on gene expression.

The fourth chapter by Dr. Gardner focuses on animal models of addictive behavior (Chap. 4). It shows how animal models of the various stages of addiction, from preexisting vulnerability to models of relapse, can be used to measure drug effects on the central nervous system and how these effects can modify drug-related behavior. It discusses key aspects of addictive behavior including the role of dopamine and further neurotransmitter systems on drug reinforcement.

The fifth chapter by Dr. Rehm et al. presents the international epidemiological aspects of addiction with a focus on the findings of the Global Burden of Disease Study (Chap. 5). Regional differences are compared. A sequence emerges whereby the onset of substance abuse is largely influenced by cultural factors; environmental and social factors are important in the transition to hazardous consumption, while neurobiological and other risk factors become more salient in the transition to substance use disorder. The public health impact of intravenous and polysubstance drug use and a resulting epidemic of infectious diseases are leading to a contemplation of much needed drug policy reforms.

An international textbook ought to pay particular attention to sociocultural dimensions. Consequently, the next chapter authored by Dr. Room focuses on the cultural factors, that is, the shared beliefs, norms, and patterns of behaviors (Chap. 6). The social pat-

terning of psychoactive drug use differs as to whether it is medicinal, regular, intermittent, or addictive. The handling of alcohol and drug problems often changes over time, for example, from a judicial to a health problem. It thus complements the chapters on gene x environment interactions and explains how cultural diversity modifies patterns of drug consumption and respective norms. The chapter concludes with Alcoholics Anonymous as an example of core practices worldwide but also local cultural adaptations.

The next chapter focuses on the prevention applications of the components previously discussed with review of the international experience. This seventh chapter is authored by Drs. Simon and Burkhart and describes prevention strategies in different regional settings (Chap. 7). Drs. Burkhart and Simon from the European Monitoring Centre for Drugs and Drug Addiction first describe a logical frame for prevention and assessment of its effectiveness. The basics of several prevention strategies are then described including mass media campaigns and environmental prevention. The benefits and limitations of different targets of the preventative efforts range from the population at large to vulnerable groups to family-based prevention and indicated prevention for individuals. The authors then discuss important regional and cultural aspects of prevention. Societal values influence student and adolescent behaviors as well as parenting practices. Again, an international perspective is presented as to recent developments and trends in preventative measures. Examples of the previously described strategies in different regions of the world and their relative acceptance are presented along with resulting lessons about successful transfer and adaptation of the experience between continents and countries.

The last chapter (Chap. 8) by Drs. Saunders and Latt reviews the diagnostic evolution in the ICD and DSM systems.

In conclusion, we hope this foundational section provides an informative basic science review of current knowledge. The first section of this textbook aims to reflect the commonalities and differences of broad global and international perspectives as salient determinants of management strategies.

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Neurobiology of Alcohol Dependence

2

Miriam Sebold, Christian A. Müller, Maria Garbusow, Katrin Charlet, and Andreas Heinz

Contents

Abstract

Chronic drug intake (including alcohol) has profound neurotoxic and neuroadaptive consequences on neurotransmitter systems and brain circuitries that are strongly involved in learning and memory. Neuroadaptive alterations within these systems can contribute to addiction development and maintenance. Current brain imaging studies identified neural correlates of behavioral processes that play a key role in addiction, such as cue-induced craving or automatic action tendencies. In this chapter, we describe neurobiological theories of addiction development and maintenance with a focus on motivational alterations and their neurobiological correlates as revealed by current neuroimaging studies in alcohol dependence. We discuss findings that assess alterations in reward anticipation and processing and their respective effects on learning mechanisms implicated in alcohol dependence. A better understanding of neural pro-

M. Sebold · C. A. Müller · M. Garbusow · K. Charlet · A. Heinz (✉)
Department of Psychiatry and Psychotherapy, CCM, Charité - Universitätsmedizin Berlin, Berlin, Germany
e-mail: andreas.heinz@charite.de

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cesses directly associated with the development and maintenance of addiction can help to improve prevention programs as well as therapeutic and pharmacological interventions in the treatment of addicted patients.

2.1 Introduction

The dependence syndrome is characterized by cognitive and physiological phenomena after repeated substance intake including continuous drug intake despite the knowledge of its negative consequences. Further symptoms are drug craving and a high priority given to drug use, the development of tolerance towards the specific drug effects, and the inability to control drug intake (International Classification of Diseases, tenth Revision (ICD-10)). Alcohol is legal in most countries and therefore socially accepted and highly available, contributing to high consumption patterns worldwide. According to *the Global status report on alcohol and health*, the World Health Organization (WHO) described a prevalence of 4% of alcohol use disorders worldwide with more than 2.5 million people dying annually due to the consequences of hazardous alcohol intake, which as a causal factor exceeds global death rates caused by HIV/AIDS or tuberculosis. However, beyond somatic effects, alcohol dependence has profound social, economic, and psychological consequences. Since up to 85% of the patients with alcohol dependence relapse after detoxification, strong effort has been made to investigate the underlying pathophysiological mechanisms in the development and maintenance of substance use disorders. By using brain imaging techniques, neural correlates of processes have been identified that are assumed to be involved in relapse, such as cue-induced craving or dysfunctional decision-making. The goal of such studies is to shed light on the neurobiology of drug addiction as well as to provide new options for specific behavioral and pharmacological interventions. Neuroimaging studies that predict relapses in detoxified patients have clinical implications, as programs treating addiction could use this information to assess patients with high risk of relapse and to refer them to higher levels of care. In this chapter, we will illustrate neurobiological theories of addiction development and maintenance. We focus on the neurobiology of alcohol dependence to illustrate key mechanisms of drug addiction and mostly refer to human studies. For other drugs of abuse and more reference to animal studies, please also see Koob and Volkow [28]. We will describe neuroadaptive effects of excessive chronic alcohol consumption and present studies that discovered alterations in neurotransmitter systems and neural activity.

2.2 Dispositional Factors for the Development of Alcohol Dependence

Several risk factors for the development of alcohol dependence have been reported in the literature including the influence of genes and environment. We will focus on key mechanisms identified in animal experiments and human studies.

2.2.1 Level of Response to Alcohol

One dispositional factor that has been discussed in the literature is the individual response to alcohol: individuals with a low level of response to alcohol, that is, those who need high amounts of alcohol to experience stimulating or sedative effects, tend to use alcohol excessively and seem therefore to be at a higher risk of developing alcohol dependence. Thus, low sensitivity toward the effects of ethanol predicts future heavy alcohol consumption and alcohol-related problems. This phenotype represents a genetically influenced trait with a heritability rate of 40–60% and can be observed more often in subjects with a positive versus negative family history of alcoholism, pointing to a close gene-environment

association [43]. Concerning the neurobiological correlates of this trait, studies using functional magnetic resonance imaging (fMRI) reported that the neural processing of affective and cognitive stimuli [38] is affected by this trait. Subjects with low responses to alcohol show decreased activation towards these stimuli, which might contribute to their impaired ability to recognize modest levels of alcohol intoxication.

Early Social Deprivation

Another dispositional factor for the development of alcohol dependence is stress. Stress factors that can increase the risk to develop an addictive disorder include traumatic childhood experiences such as social deprivation early in life, isolation, or abandonment [32]. Experiencing social stress activates effector systems such as the hypothalamic-pituitary-adrenal (HPA) axis. As a result, this might alter the mesolimbic dopamine system, which is critically involved in the development of drug dependence (Chap. 3). In line with this, Morgan et al. [33] observed in a positron emission tomography (PET) study in nonhuman primates that low social status (which potentially induces stress) is associated with lower dopamine receptor availability (which has been associated with increased dopamine concentrations in the extracellular space [21] and increased cocaine intake).

Furthermore, primates experiencing early social deprivation showed serotonergic dysfunction associated with high levels of aggression and low levels of response to acute alcohol intoxication [16]. In accordance, young primates who were separated from their mother in early infancy displayed a lower level of serotonin turnover, a higher availability of serotonin transporters (5-HTT), and higher levels of alcohol intake [17]. Hinckers et al. [23] observed that subjects with a genetic disposition for a high availability of 5-HTT displayed lower levels of response to alcohol and higher alcohol consumption during adolescence. These findings suggest an important genetic role in the interaction between stress, serotonergic neurotransmission, and alcohol response.

2.3 Addiction and the Reward System

2.3.1 Disentangling "Liking" from "Wanting"

The above-described dispositional factors contribute to the development of substance dependence. However, it is not known in detail why some substances (e.g., alcohol, cocaine, nicotine) make individuals addicted whereas others (more natural and healthy substances) do not. There is accumulating evidence that this "addictive feature" critically relies on the dopaminergic transmission the substance induces.

All drugs of abuse have in common that their intake leads to increased dopaminergic neurotransmission in the ventral striatum and the nucleus accumbens (NAcc) [11]. As alternative reinforcers (like food, sex, money) also elicit dopaminergic release, it was initially suggested that dopamine mediates reward and causes hedonic feelings. Dopaminergic innervated regions of the mesocorticolimbic circuit have therefore commonly been termed as the "reward system." This system includes ascending dopaminergic pathways from the ventral tegmental area (VTA) and substantia nigra via the ventral (including the NAcc) and the dorsal striatum and the amygdala to frontal and limbic circuits (Fig. 2.1). However, the assumption that dopamine primarily causes hedonic feelings was challenged by studies demonstrating increased dopaminergic neurotransmission when reward occurs unexpectedly or when it is greater than expected (Sect. 3.2). Thus, instead of mediating pleasure, dopamine might play a crucial role in signaling salience and consequently motivating an individual to strive toward a certain reward. Further evidence for a role of dopamine in motivation comes from studies demonstrating symptoms of apathy instead of anhedonia in subjects who received pharmacological blockage of dopaminergic neurotransmission (e.g., via neuroleptics). Apathy is defined as the lack of interest, enthusiasm, or concern and can therefore be seen as the endpoint on a motivational continuum [40].

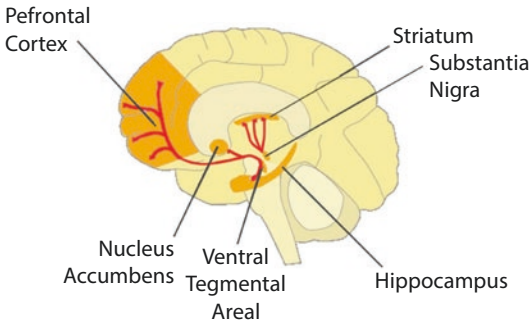

Fig. 2.1 The dopaminergic mesocorticolimbic circuit: the VTA; ventral striatum, including the nucleus accumbens (NAcc); dorsal striatum; amygdala; and frontal and limbic circuits. Key regions of the so-called neural reward system include the VTA and nucleus accumbens

Therefore, wanting (experience of desire and urge to strive for something) was suggested to be disentangled from liking (experience of pleasure, causes feelings of positive emotions and hedonism). Whereas the dopaminergic system is most commonly associated with "wanting" [4], the opioidergic is related to "liking." Evidence for the role of the opioidergic system in mediating hedonic effects of reward comes from animal studies using μ-opioid receptor (MOR) knockout mice, which show insensitivity toward the hedonic effects of morphine [31]. In accordance, nalmefene – a compound with antagonistic activity at MORs – decreases subjective pleasantness of palatable foods in humans [55]. Besides food reward, the opioid system further seems to mediate the affective value of drug reward, including alcohol consumption. Indeed, in vivo availability of MORs was elevated in alcohol-dependent patients [20], and naltrexone, a MOR antagonist that is administered for craving reduction in addiction treatment, is assumed to block the hedonic effects of alcohol, thus reducing relapse rates and alcohol intake in alcohol-dependent patients.

Beyond opioids, other neurotransmitters have been implicated in the mediation of "liking." For instance, stimulation of endocannabinoid and GABA-benzodiazepine sites in limbic structures increased pleasure of food rewards. Therefore, hedonic liking of the consumption of a fully predicted reward can be mediated through a variety of neurotransmitter systems.

2.3.2 Dopamine in Mediating Learning Effects

As described above, dopamine plays a major role in motivation. Schultz [44] was the first to demonstrate a shift in phasic dopaminergic activity from received reward to the reward-predicting cue, when subjects had learned the contingency between the reward and the stimulus. Moreover, Schultz and his colleagues observed a dip of dopaminergic transmission when the outcome was worse than expected, for instance, when the reward suddenly was omitted ([44]; see Fig. 2.2). These phasic dopaminergic signals serve as a teaching signal to adapt subsequent expectations and are then translated into actions. In other words, a dopaminergic signal makes us recognize that something important is about to happen; thus, it triggers motivation and encourages us to act either to achieve a reward or to avoid a punishment. It is important to bear in mind that there is a multifaceted role for dopamine in addiction. Beyond tonic dopamine release, phasic increases encode the magnitude of unexpected rewards and are also elicited by reward-associated cues, unless they are themselves predicted by preceding stimuli. Phasic dopamine release elicited by drugs of abuse is usually stronger than release evoked by natural reinforcers, thus biasing behavior toward drug intake [10].

2.3.3 Incentive Salience Theory of Addiction

The adaptation of phasic dopaminergic signals over the course of learning appears to reflect the assignment of value to cues (Fig. 2.2b). Thus, in addiction, environmental stimuli, which have repeatedly been paired with drugs, acquire incentive salience as a result of Pavlovian learning [40]. The attribution of incentive salience to drug-associated stimuli is closely linked to the observation that addicted subjects show significant responses to drug-related stimuli, a phenomenon referred to as cue reactivity [7]. In alcohol dependence, external stimuli of visual or olfac-

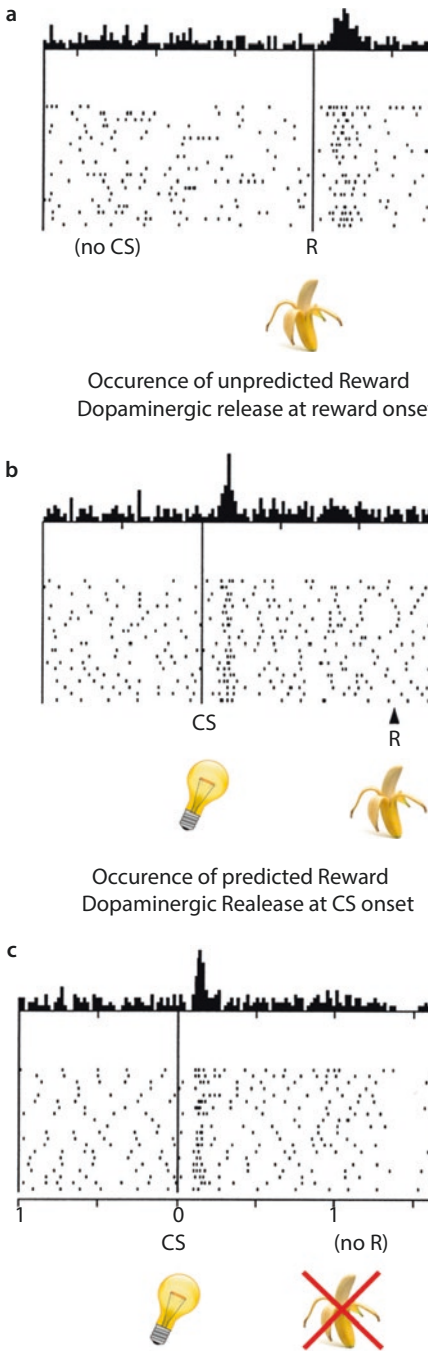

Fig. 2.2 (**a**) Burst of dopaminergic firing in occurrence of an unpredicted reward (R) at reward onset (positive prediction error). (**b**) After Pavlovian conditioning: burst of dopaminergic firing not at reward but at conditioned stimulus (CS) onset. (**c**) No reward: dip of dopaminergic firing at expected reward onset (negative prediction error). (Adapted from Schultz [44])

tory modality, such as the sight of an alcohol bottle in the supermarket or the smell of a beer in a pub, might serve as such cues. Cue-induced responses in substance dependence exist on a variety of physiological levels including changes in heart rate, sweat gland activity, skin temperature, and functional brain activity [7]. Moreover, alcohol-dependent patients report increased craving whenever they are confronted with alcohol cues, which may help to explain the cue-reactivity phenomenon.

Experimentally, cue reactivity is most commonly operationalized by confronting subjects with substance-related cues (e.g., images) and neutral control images. fMRI studies have shown that substance-dependent subjects display increased activation of several core regions of the mesolimbic pathway, when confronted with substance-related stimuli. This finding has been reported in various substance dependencies, including heroin, cocaine, alcohol, cannabis, and nicotine dependence. Brain regions which have reliably been identified in different cue-reactivity fMRI studies include the anterior cingulate cortex (ACC), the medial prefrontal cortex (mPFC), the ventral and dorsal striatum and the orbitofrontal cortex (OFC), the dorsolateral prefrontal cortex (dlPFC), and the amygdala [42]. Crucially, physiological responses to substance-related cues supposedly reflect automatic conditioned responses that are not under conscious control (Sect. 3.4), as demonstrated by studies using drug cues that are presented below the threshold of consciousness.

Increased cue reactivity was also reported in relation to consciously experienced cues, as indicated by self-reported measurements that assess craving or the desire for a particular substance of abuse [45]. Importantly, subjective and physiological cue reactivity are sometimes dissociated. Indeed, physiological cue reactivity resembles responses elicited by positive stimuli, although these subjects deny conscious feelings of pleasure or even report aversive feelings to these drug cues [35]. Thus, one can conclude that physiological indicators of cue reactivity are more proximal to implicit associations compared to explicit self-reports and therefore may provide higher predictive validity.

One of the most important features about cue reactivity is that these stimuli can modulate behavior. Thus, cues that have acquired incentive salience attract attention and guide approach behavior and therefore act as "motivational magnets" [4]. Indeed, when drug administration is repeatedly paired with an external cue, rats approach the cue more likely and with increasing rapidity even when it no longer predicts drug administration. Likewise, alcohol-associated stimuli increase alcohol consumption in rats [8]. Besides alcohol cues, other reward-associated cues also play a role in substance dependence. For instance, cues that have been associated with monetary reward modulate subsequent behavior in alcohol dependence [14]. Thus, the extent to which reward-predicting cues acquire incentive salience can modulate subsequent behavior, and the resulting impact on neural responses may reflect the severity of substance dependence.

2.3.4 Habitual Drug Seeking

Whereas the incentive salience theory suggests that in addiction, drug-associated cues become motivationally highly attractive and therefore "wanted," Tiffany's theory of addiction suggests that drug consumption reflects a habitual responding that is controlled by automatically initiated action schemata [49]. Thus, in addiction, drug-associated stimuli might not elicit a positive affective or motivational state that results in drug-seeking behavior. Rather, according to Tiffany's theory, in addiction, drug consumption happens to occur in a habitual fashion. Theoretical arguments for habits were based on the observation that drug consumption in addiction seems to be initiated and completed without intention, difficult to impede in the presence of triggering stimuli, and conducted in the absence of awareness. Further evidence for habitual drug consumption comes from clinical observations of addicted patients: many relapses happen to occur without any preceding urges to consume drugs or conscious craving. According to their "transition to habit" theory, Everitt and Robbins [13] suggested that addiction reflects the endpoint of a series of transitions: from initial drug intake that causes hedonic feelings (liking) to a stage when substance use becomes habitual (wanting) and ultimately to loss of control, where drug consumption is compulsive and therefore disentangled from anticipatory drug effects. Evidence for this comes from animal studies: rats that have learned a specific response in order to self-administer drugs continue to perform this response even when drug delivery is suppressed [26]. Thus, actions of these rats were no longer guided by outcome expectancy (*lever press results in drug delivery and hedonic feelings*), but rather by external cues that elicit conditioned responses (*lever press whenever a cue is available*). This experiment manipulates the value of the cue-induced lever press, and such manipulations are typically used to test whether actions are goal-directed or habitual. In this procedure (devaluation design), the value of an action is suddenly decreased (by detaching it from the positive outcome or by associating it with a negative outcome). When actions are habitual, this devaluation does not alter choice behavior on that stimulus. Contrary to this, when actions are goal-directed, the devaluation of a stimulus decreases choice behavior of that stimulus. Studies demonstrated that unlimited access to alcohol fosters ethanol consumption in rats even when the alcohol is altered by bitter-tasting quinine [24]. Interestingly, responding for ethanol becomes insensitive to devaluation at a stage when responding for food reward still is sensitive to devaluation, indicating that the shift from goal- to stimulus-directed consumption is more rapid for alcohol than natural rewards [12].

On the neural level, "wanting" is probably mediated by the ventral striatum, while the state of habitual drug intake is modulated by the dorsal striatum. Thus, the development of an addiction is promoted by a transformation from goal-directed to stimulus-driven, automatic behavior, which is assumed to be accompanied by a shift of ventral to dorsal striatal activity. Animal studies seem to confirm this contention: once substance use becomes habitual, drug-associated stimuli foster release of dopamine in the dorsal striatum [9]. However, the translation of observations in animals excessively trained to perform lever

presses for food or drugs to human behavior is controversial. In humans, studies investigating a shift from goal-directed to habitual control often use multistep paradigms. These tasks bear two important differences to the procedures commonly used in animals. First, they use non-drug-related rewards (e.g., monetary rewards). Secondly, they are rather complex and rely on cognitive abilities such as working memory. These limitations might have caused the inconsistent picture regarding habit formation in substance-dependent humans. Whereas some studies have demonstrated such a shift [47], others have shown no such link in alcohol dependence [46]. Based on these studies, the role of habitual versus goal-directed decision-making in human substance dependence remains to be further explored.

2.4 Consequences of Chronic Alcohol Consumption

2.4.1 Neuroadaptive Dopaminergic Changes

Chronic alcohol intake is associated with profound neuroadaptive and neurotoxic effects on dopaminergic, GABAergic, serotonergic, and glutamatergic neurotransmission. For instance, alcohol-dependent patients display low levels of dopamine synthesis and release as well as an decreased availability of D2 receptors (DRD2) in the ventral striatum [52]. The reduction of DRD2 is positively associated with lifetime alcohol intake, suggesting that excessive alcohol consumption causes DRD2 decreases. These dopaminergic changes can recover with prolonged abstinence. In early phases of abstinence, however, they can cause the individual to strive for particularly strong activators of the downregulated dopaminergic system (such as drugs or drug-associated stimuli). This is in line with the finding that the degree of striatal downregulation of DRD2 in alcohol dependence is associated with the extent of cue-induced neural activation and with the severity of alcohol craving [18]. The bias towards high dopaminergic stimulatory drugs can influence choices against weaker primary and secondary reinforcers such as food, money, or social interactions. Thus, dopaminergic dysfunction may primarily interfere with learning of new conditional stimuli and contexts that predict non-drug reward. A study demonstrated impairments in learning from non-drug-related rewards in alcohol dependence [37], which correlated with craving for (well-learned non-explicit) alcohol intake. The shift of natural reward processing to preferential drug-related reward processing has been metaphorically described as a "hijacking of the reward system." In line with this, alcohol-dependent patients displayed a decrease in ventral striatum activity when confronted with monetary cues but an increased activation in the same region when confronted with drug cues [3], which further suggests an essential role for the ventral striatum in relapse prediction. In accordance with the assumption of a hijacked reward system, it was suggested that strong neural responses to rewarding and non-drug-related stimuli might serve as a potential protective brain mechanism against relapse. Indeed, increased ventral striatal responses to affectively positive pictures were related to more subsequent abstinent days and less prospective alcohol intake [22].

2.4.2 Neuroanatomical Alterations

Alcohol as a neurotoxic substance causes widespread neural alterations when chronically consumed: up to 70% of alcohol-dependent patients show alcohol-associated brain atrophy, that is, tissue loss of gray and white matter, ventricular enlargement, and sulci widening [6]. Morphometric studies investigating brain volume changes in alcohol dependence found that this atrophy mainly affects frontal, temporal, and parieto-occipital regions but also the hippocampus, the corpora mammillaria, and the cerebellum, with the most marked atrophic changes within the white and gray matter of the frontal lobe [34]. In particular, volume deficits of frontal and parieto-occipital regions appear to be clinically relevant, since these changes were reported to be predictive of higher risk of relapse [39].

These atrophic changes might lead to impairments of working memory and executive functioning, thus possibly reducing long-term action planning and inhibition of short-term reward-directed behavior (e.g., alcohol intake) [54]. However, the precise pathophysiological mechanism of alcohol-associated brain atrophy is not fully understood; possibly, a hyperglutamatergic state during alcohol withdrawal leads to a calcium influx via activation of glutamatergic NMDA receptors and thereby initiates cytotoxic cascades [50]. Furthermore, alcohol withdrawal was reported to activate the HPA axis, resulting in elevated cortisol concentrations. Cortisol concentrations in turn were associated with altered serotonergic neurotransmission, which also contributed to increased severity of depression in early abstinence [19]. Interestingly, these neuropathological changes seem to be partially reversible, because regenerations of brain volume during short-term and long-term alcohol abstinence were described in alcohol-dependent patients [56]

2.4.3 Alcohol Tolerance and Withdrawal

Chronic substance use results in different neuroadaptive changes in the brain, leading to tolerance towards the acute effects of the substance and causing withdrawal symptoms when substance use is reduced or stopped. Alcohol-related withdrawal symptoms are of psychological (e.g., anhedonia and anxiety) and physical (e.g., tachycardia, nausea, sweating, headaches, tremors) nature. Tolerance-related neuroadaptation seems to be essential for the maintenance of homeostasis between excitatory and inhibitory functions in the brain and counteracts the acute effects of the drug of abuse [27]. As a consequence of these alterations, a reduction or cessation of substance use may lead to a severe disturbance of homeostasis, which can clinically manifest as psychovegetative withdrawal symptoms, potentially including severe complications such as epileptic seizures or delirium. Both development of tolerance and withdrawal symptoms seem to be related to alcohol's activation of GABAergic as well as inhibition of glutamatergic neurotransmission [29]. GABA represents the main inhibitory neurotransmitter in the human brain and is involved in rapid information processing in cortical and subcortical areas. While acute alcohol consumption induces activation of inhibitory GABA-A receptors, leading to sedation after intake of large amounts of ethanol, chronic alcohol consumption seems to result in an increased tolerance for acute alcohol effects due to a systematic downregulation of GABA-A receptors. Long-lasting GABA-A receptor changes have been found in alcohol-dependent patients after several weeks of alcohol abstinence and even may persist long during further abstinence [1]. Regarding psychovegetative withdrawal symptoms, neuroadaptive changes within the glutamatergic system appear to result from chronic alcohol-induced antagonism at glutamatergic NMDA receptors. Indeed, a compensatory upregulation of glutamatergic NMDA receptors as a consequence of chronic alcohol intake has been observed [53]. In case of reduction or cessation of alcohol consumption, the excitatory neurotransmitter glutamate then can activate an elevated number of NMDA receptors [15]. This process can also cause imbalances between inhibitory and excitatory functioning with a predominance of excitation, clinically resulting in withdrawal symptoms.

2.5 Pharmaco-fMRI: New Insights of Pharmacological Treatment

Albeit treatment of drug-associated harm with drug substitution has been proven to be a useful option in opioid addiction, in alcohol dependence, treatment with putative partially substitutive psychoactive compounds (such as γ-hydroxybutyric acid, GHB) is uncommon and can induce GHB dependence [51]. Instead, so-called anti-craving substances such as naltrexone, nalmefene, or acamprosate are temporarily applied for relapse prevention or reduction of alcohol consumption, respectively. Meta-analyses have demonstrated moderate effective-

ness of naltrexone and acamprosate with regard to reduction of alcohol consumption or maintenance of abstinence, respectively [25]. The application of neuroimaging techniques in pharmacologically treated alcohol-dependent patients might potentially be useful in predicting which medication helps to prevent relapse. For example, elevated levels of MORs have been observed in the ventral striatum of some alcohol-dependent patients after withdrawal and are targeted by naltrexone, which blocks MORs [20].

A combination of fMRI and pharmacological treatment (pharmaco-fMRI) might allow to further elucidate how and where a specific compound acts on the central nervous system. For example, naltrexone treatment produced a significant reduction of cue-induced activity in the ventral striatum in alcohol-dependent subjects [36]. Notably, these changes in neural activity were additionally related to decreases in cue-induced craving, indicating a close link between pharmacological effects of naltrexone, striatal activation, and pharmacological craving modulation. Further studies were conducted to assess the effectiveness of acamprosate. Acamprosate is assumed to reduce neuronal hyperexcitability, which may be responsible for acute alcohol withdrawal on the level of both excitatory glutamate and inhibitory GABA neurotransmitter pathways. Findings of a preclinical study suggest a calcium-related mechanism in alcohol dependence [48], and acamprosate treatment resulted in a significant reduction of cue-induced activity in the striatum and the posterior cingulate in alcohol dependence [30].

Besides naltrexone and acamprosate, alternative pharmacological treatments have been suggested to reduce craving and relapse rates in alcohol-dependent patients. One example for a pharmacological treatment is baclofen, a GABA-B receptor agonist, which has raised attention since first clinical studies suggested its effectiveness in the treatment of alcohol-dependent patients. Recent meta-analyses reported inconsistent results with regard to its efficacy in alcohol dependence [5, 41]. In alcohol-dependent patients, a pharmaco-fMRI study found that patients receiving baclofen showed a stronger decrease, in cue-elicited brain activation in left orbitofrontal cortex, bilateral amygdala and left VTA than patients receiving a placebo treatment. Thus, baclofen might decrease cue-elicited brain activation in areas known to be involved in the processing of salient stimuli [2].

2.6 Conclusion

Altogether, neurochemical effects of acute alcohol intake can be experienced as rewarding and therefore reinforce drug intake via Pavlovian conditioning. These learning mechanisms appear to underlie a shift from occasional alcohol consumption to habitual intake. Neuroadaptive alterations (particularly regarding dopaminergic neurotransmission within the so-called reward system) are related to craving and increased processing of alcohol cues. Thus, neurobiological consequences of excessive alcohol intake are in accordance with the clinical observation that many alcohol-dependent patients find it particularly difficult to abstain from habitual consumption patterns and relapse after drug withdrawal, despite high individual motivation to remain abstinent. Neuroimaging studies might help to gain a better understanding of the neurobiological correlates of craving and motivation for alcohol intake. Furthermore, longitudinal and multimodal imaging studies might help to identify patients with a high relapse risk who could benefit from a higher intensity of treatment.

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Glossary

Devaluation A psychological design for the assessment of stimulus-triggered (habitual) responding. Animals are trained to perform two responses, one for each of two different rewards. One reward is then devalued by associating it with bad taste (via quinine), sickness (lithium chloride), or satiety (via pre-feeding).

When given the opportunity to perform the instrumental responses again in extinction, the responses for the devalued reward should be selectively diminished, in case actions are controlled by outcome expectancy. Instead, when actions are stimulus-driven (thus habitual), actions for the devalued reward should not be altered.

Goal-directed actions Instrumental responses that are acquired through response-outcome associations. Goal-directed actions are performed with the intention of obtaining the goal. Goal-directed actions are sensitive to devaluation.

Habitual actions Instrumental responses that reflect the execution of stimulus-response associations. Habitual actions are enabled by particular stimulus configurations and thus insensitive to devaluation. Habitual behavior comprises features of automaticity such as speed, autonomy, lack of control, and absence of conscious awareness.

Incentive A stimulus that promotes approach to a reward as a result of predictive associations with this reward. Incentives serve as motivational devices, as they facilitate and energize behavior that has been associated with the reward. Incentives may acquire activational properties, which amplify the incentive properties of other stimuli that occur concurrently, but are not necessarily related to the reward.

Liking Emotional affective value of reward that has hedonic impact and causes feelings of pleasure. In addiction research, self-reported measure of hedonia has been used as a proxy for liking.

Pavlovian conditioning Associative learning, in which the conditioned stimulus (CS) comes to signal the occurrence of a second stimulus and the unconditioned stimulus (US) thus elicits conditioned responses following CS presentation.

Reinforcer A stimulus that increases the probability of a desired response. In contrast to incentives, reinforcers elicit responding on the basis of their contingency with actions (instrumental conditioning).

Reward A class of unconditioned motivational stimuli, which elicit pleasure and hedonic feelings that can act as positive reinforcers.

Wanting Motivational value of reward that has decision utility. In addiction research, craving for the positive effects of drugs has been used as a proxy for wanting.

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3 Heritability of Alcohol Use Disorder: Evidence from Twin Studies and Genome-Wide Association Studies

Eva Friedel, Jakob Kaminski, and Stephan Ripke

Contents

Abstract

The genetics of addictions including alcohol dependence have been the focus of extensive research, albeit with variable and often conflicting results. Heritability estimations suggest that about 50% of the variance of addictive behavior is due to (epi)genetic effects, while associations between addictive behavior (such as amount of drinking and relapse) and specific genetic combinations are generally in a modest range. This chapter introduces the methods used to estimate heritability and specific genetic influences, such as twin and adoption studies, polygenic risk scores, and genome-wide association studies. Environmental influences on gene expression and possible pathways of epigenetic modifications will be addressed.

Keywords

Heritability · Single-nucleotide polymorphism (SNP) · Polygenetic risk score (PRS) Epigenome · Genome-wide association studies (GWAS) · Linkage disequilibrium (LD)

E. Friedel (✉) · J. Kaminski · S. Ripke
Charite - Universitätsmedizin Berlin, Berlin, Germany
e-mail: eva.friedel@charite.de; jakob.kaminski@charite.de; stephan.ripke@charite.de

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3.1 Introduction

Clinical observations indicate that alcohol use disorder (AUD) is more frequent among relatives. Discussion arises around the question whether alcohol use is genetically determined or rather a product of a shared environment. Although patients might experience alcohol use in their parents, there is no unavoidable road toward addiction when children of alcohol-dependent parents drink their first alcoholic beverage. This suggests that environmental factors interact with biological factors in a complex way. Moreover, in an adoption study, genetic and environmental factors were of similar magnitude [26].

3.2 What Is Heritability in Addiction?

In general, heritability is understood as a proportion of a given phenotypic variance that is due to genetic variability. There are different ways in order to estimate this genetic variability (see Box 3.1). Twin and adoption studies were the mainstay of investigations of how traits are inherited from parents to their offspring for decades. The fact that dizygotic twins share about half of their genes and monozygotic twins share all their genes allows to statistically model how much of a trait might be linked to additive genetic effects. Landmark studies investigating heritability of AUD include work by Heath et al. [17], who used tetrachoric correlation (a statistical test that exploits the abovementioned assumption of additive genetic effects) and found that 64% of the variance is explained by genetic risk factors. More recent estimates for heritability from meta-analysis of twin and adoption studies result in an approximation of 50% of the variance explained by genetic factors [47]. Interestingly, this study also found moderate shared environmental effects (e.g., 10% of the variance). The authors interpret that environmental factors contribute to the familial aggregation of AUD. As compared to the high estimates from twin studies, a smaller proportion has been attributed to additive effects from common genetic variation, the so-called single-nucleotide polymorphism (SNP) heritability: 33% for AUD [34] and 18% [48] or 13% for average alcohol consumption [9]. Exploiting the aggregation of weighted counts of risk genes (single-nucleotide polymorphisms, SNPs) resulting in an individual polygenic risk score, up to 1% of the variance in AUD symptom scores has been explained [40]. Estimates from large genome-wide association studies (GWAS) and online surveys, treating alcohol use as continuous marker, find point estimates for heritability of 12% of the variance explained [39]. Interestingly, in their cohort, recruited via the online ancestry and health info service 23andMe, Inc., there was a positive association between educational attainment and AUDIT scores, suggesting a possible confound based on a selection bias.

In summary, there is a wide range in heritability estimates resulting from different kinds of methodological approaches (see Fig. 3.1). This phenomenon is frequently referred to as the case of the missing heritability. It is important to note that there is no easy answer when talking to patients about heritability of a complex trait that is highly polygenic and implies environmental factors. As a clinician, the best way to communicate disease risk is to underline the high probability of not passing on a genetic liability to the patients' offspring and to emphasize on environmental factors that are malleable in order to destigmatize and give hope for possible interventions.

3.3 Genome-Wide Association Studies

In the past 15 years, major advances in the field of human disease genetics have provided the path for novel research strategies such as GWAS to identify the genetic factors involved in various psychiatric traits and other genetically complex disorders. This progress started with the completion of the Human Genome Project in 2003. There, it became evident that the majority of

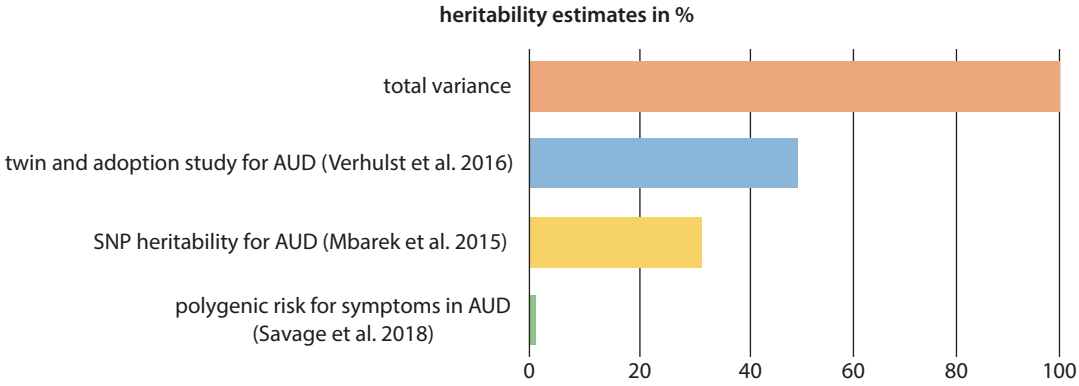

Fig. 3.1 Different heritability estimates from different methodologies. Heritability can be expressed as proportion of variance accounted for a certain phenotypic trait. Depending on the methodology, different estimates are obtained. Twin and adoption studies imply the whole genome; however, they might be biased toward an overestimation due to shared environment. SNP heritability evaluates the contribution of common variants by calculating the relatedness between apparently unrelated individuals and associating that measure to a certain phenotype. The explained variance with polygenic risk scores is expected to converge with the estimated SNP heritability with vastly increased sample size

bases do not differ, or are invariant, between two randomly chosen individuals in the world. Still, more than nine million unique SNPs exist in the genome of European individuals [45] with a minor allele frequency (MAF) of at least 1%. One important feature of the SNP genome was the haplotype block structure. This phenomenon is also called linkage disequilibrium (LD) and has important consequences for analysis methods like imputation and the development of SNP arrays that play a key role in GWAS.

Companies started to develop microarrays as SNP genotyping platforms to allow the simultaneous, rapid genotyping of hundreds of thousands of SNPs in an individual at affordable costs. The most commonly used approaches are allele discrimination by hybridization, as used by Affymetrix and the Infinium Assay of Illumina.

In a GWAS, a genome-wide set of SNPs is measured in a large number of cases (with disease) and controls (without disease) using commercially available high-throughput genotyping platforms (SNP microarrays). Currently, such genotyping platforms typically measure between 300,000 and 800,000 unique SNPs in each sample. Because many SNPs located in the same haplotype block are correlated via LD, it is computationally feasible to estimate the genotypes of the remaining (not genotyped) ~8,500,000 SNPs with MAF >1% across the genome using a reference data set, such as that provided by the 1000 Genomes Project [45] or the Haplotype Reference Consortium. This method of estimating missing genotypes is called imputation and enables a more comprehensive analysis of the SNP variation present in the human genome as well as meta-analyses across multiple data sets that have used different genotyping platforms. This is an important step combining GWAS data from distinct sources, which is necessary to increase statistical power to detect novel genetic associations.

Since there is no requirement for prior biological knowledge of the trait undergoing investigation, a GWAS is an unbiased, genome-wide search for SNPs that are involved in the development of a disease. The costs of SNP microarrays have decreased substantially over time, so that it is now feasible to analyze tens of thousands of individuals. This is a crucial requirement to achieve the statistical power to detect the small genetic effects mediated by common risk variants. One limitation of GWAS is the large number of tested SNPs, posing a massive multiple testing problem. This is addressed by correction methods, and an SNP allele is assumed to be

associated with the disease when the allele frequency difference between patients and controls produces $p < 5 \times 10^{-08}$.

This significance threshold, also named genome-wide significance threshold, accounts for testing one million independent SNPs, assuming a type 1 error rate of 5%.

Significant SNPs will point to regions of the genome that harbor potential causal variants. After the often inconsistent and frustrating results of the linkage and candidate gene era, the GWAS approach has led to a breakthrough and has discovered several thousands of genetic loci reliably associated with a range of complex phenotypes and diseases.[1] These findings not only provide novel biological insight into diseases but also have the potential to guide therapeutic development.

One limitation of GWAS is that it cannot identify the functionally causal variant(s) in an associated region. As a consequence of the LD between many variants within a haplotype block, the association signal typically covers a broad chromosomal region, sometimes spanning 500 kb or more and containing numerous genes. In practice, however, at least half of the associated regions encompass only one or two genes.

In other regions, pathway or gene set analyses or functional annotations may help prioritize candidate genes, but the identification of the responsible gene/functionally relevant variant remains a challenge.

3.4 Genome-Wide Association Studies in Psychiatric Disease

In 2006, the first GWAS of schizophrenia was published [33]. It comprised 320 patients and 325 controls, genotyped on 25,000 gene-based SNPs. No SNP was meeting today's threshold for genome-wide significance. The following published GWAS used the Affymetrix 500 K genotyping chip with much more comprehensive genomic coverage. However, by today's standards, sample sizes were still small: 178 cases and 144 controls in a study by Lencz et al. [30] and 738 cases and 733 controls in a sample by Sullivan et al. [44]. Again, none of the top hits met the criteria for genome-wide significance. The fourth published GWAS by O'Donovan et al. [10] could report the first reliable and consistent findings. Although the initial GWAS with 479 cases and 2937 controls did not yield genome-wide significant associations, there were a few findings that were very close to meet this significance threshold. A follow-up cohort with a sample size of 6666 cases and 9897 controls could confirm a lead SNP located in the transcription factor ZNF804A, considered by many in the field as the first, replicating finding in GWAS for schizophrenia. It became clear that the effect size of common risk genes for schizophrenia is generally lower than expected and that several hundreds of patients and controls did not suffice to detect genome-wide significant associations when appropriately correcting for multiple testing. Following this observation, researchers began to intensify collaborations and jointly analyzed GWAS data sets to substantiate the power of their analyses to trace variants with small genetic effects contributing to schizophrenia across the genome.

Large-scale collaborations like International Schizophrenia Consortium (ISC), SGENE, Molecular Genetics of Schizophrenia (MGS), the Bonn–Mannheim (BoMa) consortium, and, last but not the least, the Psychiatric Genomics Consortium (PGC) were founded and have substantially contributed to the success of GWAS for psychiatric traits in the past few years [43, 45]. A landmark paper from the ISC consortium could not only identify a handful of validated SNPs but also introduced the meanwhile widely applied polygenic risk score method into the field of psychiatric GWAS [24]. Since then, it has been shown in many different data sets that the polygenic risk score derived with an SNP set from an initial GWAS is capable of distinguishing schizophrenia patients from controls in independent data sets, albeit with low sensitivity and specificity. Notably, the predictive power of

[1] https://www.ebi.ac.uk/gwas/docs/diagram-downloads

the polygenic test improves (in terms of phenotypic variance explained) when SNPs with non-significant p-values are also included. This means that many schizophrenia-associated SNPs with small but true genetic effects still must be contained in this p-value range. The most important implication of that work was that further sample size increase would uncover many more yet unknown schizophrenia hits, while power of the polygenic risk score would become more powerful.

In 2011, Schizophrenia Working Group of the PGC published a GWAS study comprising 21,856 individuals (cases and controls) in combination with 29,939 individuals in a follow-up replication step, yielding to five novel gene loci [24]. This laid the foundation for a strongly accelerated collaboration. In 2014, the PGC published a second meta-analysis, including almost 37,000 individuals with schizophrenia, 302 investigators, 35 countries, and 4 continents [1]. One hundred twenty-eight statistically independent associations, implicating at least 108 schizophrenia-associated loci, were reported (Fig. 3.2).

Not only 83 of these loci were novel, but 25 previous findings could be confirmed supporting the use of large GWAS to create reproducible findings.

Genes from the reported 108 schizophrenia-associated loci were involved in the following functional categories: glutamatergic (and possibly dopaminergic) neurotransmission, neuronal calcium signaling, synaptic function and plasticity, neurodevelopment, and immune processes.

In the following years, GWAS of other psychiatric traits followed with a similar trajectory, most notably in major depression, identifying 102 independent variants.

This GWAS required a vastly increased sample size of 246,363 cases and 561,190 controls due to much smaller effect sizes of the underlying causal common variants.

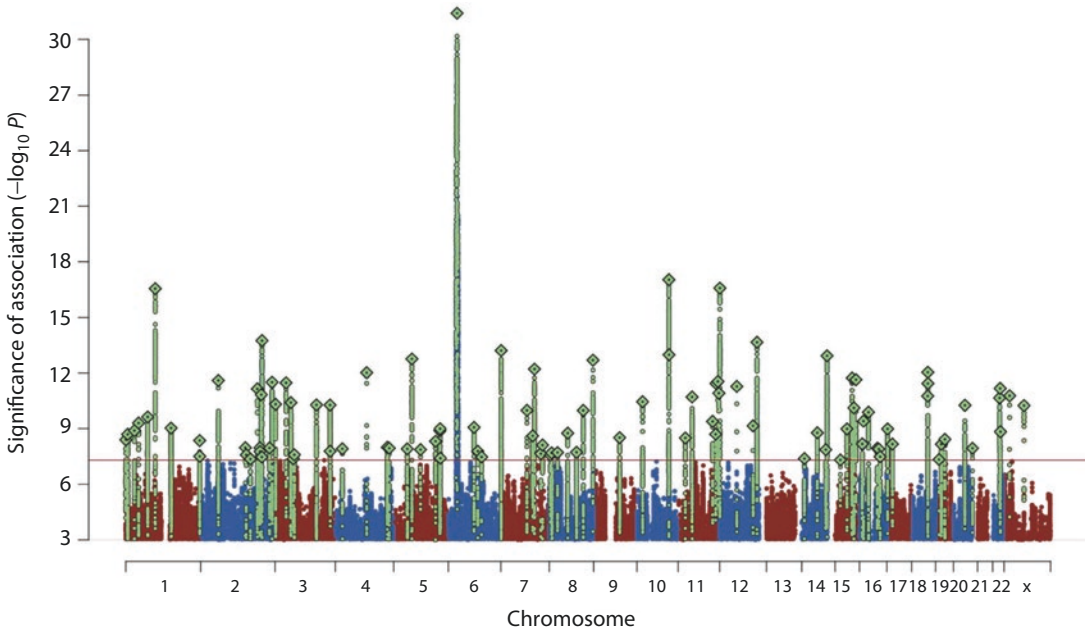

Fig. 3.2 Manhattan plot showing the results of the latest meta-analysis of the Schizophrenia Working Group of the PGC, implicating 108 independent schizophrenia-associated loci [1]

3.5 Future Directions of Psychiatric Genome-Wide Association Studies

When we illustrate number of schizophrenia-associated SNPs as a function of case sample size and compare them to two other genetically complex diseases/phenotypes, which showed great success in GWAS analyses (namely, Crohn's disease and human height), findings regarding schizophrenia are comparable to those for human height (Fig. 3.3).

It is apparent that, after a collective case number of roughly 15,000, we can observe an almost linear relationship between case number and the number of significantly associated genetic variants (~4 new hits per 1000 added cases). It is therefore reasonable to aim for further sample size increase to achieve a more sophisticated picture of the biology involved in psychiatric traits.

Two unpublished studies have been presented at various conferences: a GWAS of bipolar disorder, identifying more than 30 loci with 20,352 cases and 31,358 controls [42], and a GWAS of schizophrenia, with 65,205 cases and 87,919 controls, identifying 248 genome-wide significant regions (personal communication). These confirm the undamped effect of additional associations with further sample size increase.

GWAS in psychiatry is certainly a successful method for identifying common risk variants. Even though these diagnoses harbor presumed high heterogeneity, the field succeeded in identifying far more than a handful genetic loci for various psychiatric traits.

Despite these successes, it is important to continue recruitment of new cohorts to further increase power and discover more risk variants to get a more distinguished picture of the biological processes involved in these disorders. Improved bioinformatics techniques, such as refined biological gene set analyses, and more comprehensive references of pre-annotated pathways will be helpful to even better exploit GWAS results. It should also be emphasized that psychiatric GWAS hits are characterized by a broad frequency spectrum of disease alleles.

In the future, extended analysis of polygenic risk scores will likely be useful in clinical settings, e.g., for improved phenotypic classifications or for guiding medication and therapy. It should be noted though that, to date, the field has not arrived at a broad clinical integration of polygenic risk scores.

Pathophysiological consequences of the many risk variants identified need to be investigated further. For example, it is unclear whether the schizophrenia-risk SNPs are the functionally relevant SNPs or just "proxies" in LD. Experimental approaches (molecular and cellular investigations) will be the key to understand the functional

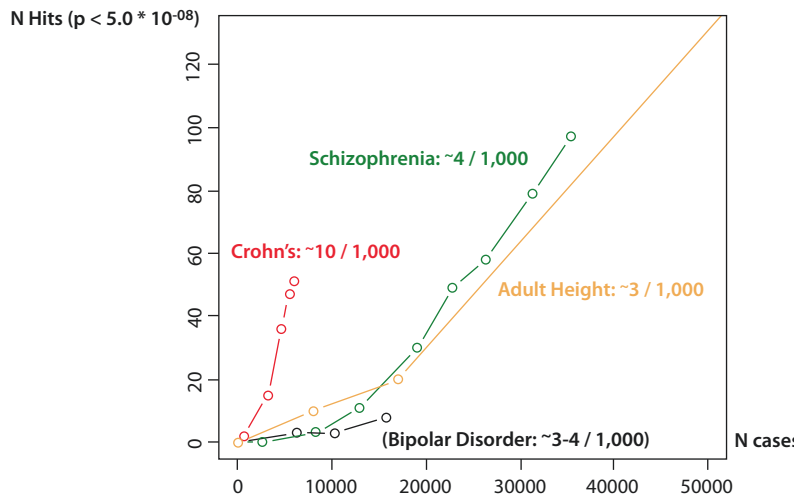

Fig. 3.3 Number of genome-wide significant findings as a function of sample size, reflected as number of cases. Red, Crohn's disease; yellow, schizophrenia; black, bipolar disorder; green, adult height

consequences of risk alleles and the underlying pathophysiological processes.

Some of the identified associations might already point to actionable therapeutic targets. Furthermore, we hope that with deeper insights into the biology of psychiatric disease, pharmacologic and non-pharmacologic therapy will become more beneficial to patients.

3.6 Potential Markers

The genetics of alcohol dependence is summarized in a comprehensive review by Rietschel and Treutlein [38]. Findings include 30 GWAS on AUD, alcohol consumption, and AUD-related traits. A more recent large GWAS for alcohol dependence of 16,087 subjects [13] report associations with genes relating to alcohol metabolism such as alcohol dehydrogenase and aldehyde dehydrogenase. Other studies identified several interesting candidate genes, for example, in the GATA4 gene that encodes a transcription factor of atrial natriuretic peptide [46] and XRCC5, which is involved in sensitivity to alcohol in humans and animals [25]. Furthermore, Val66Met polymorphism might contribute to alcohol dependence vulnerability via lower executive function performance [3], and brain-derived neurotrophic factor (BDNF) serum levels have been linked to AUD [29]. Moreover, genotype of serotonin transporter has been shown to be correlated with alcohol intake in nonhuman primates [20] and response to alcohol in adolescents [23] pointing toward the importance of alcohol sensitivity as a possible trait variable associated with the development of AUD [41].

In summary, the abovementioned findings underline the polygenic character of inheritance involving several genetic variants. One has to consider that genetic risk factors for AUD may be part of a broad genetic burden for a range of disorders, including vulnerability to social isolation, stress, and adverse environments [19, 21, 27]. It has been discussed that genetic factors related to AUD may exert their influences on alcohol use via processes of reward learning and habituation [14].

Box 3.1 How Can We Estimate Heritability

Twin Studies

The fact that monozygotic twins share twice as many genes compared to monozygotic twins makes it rather straightforward to calculated heritability estimates using Falconer's formula $H^2 = 2(r_{(MZ)}\text{-}r_{(DZ)})$. H^2 signifies the heritability, which is calculated as the difference in correlation coefficients r for phenotypic variance in monozygotic and dizygotic twins. There are several relevant limitations in twin studies. Firstly, Falconer's formula assumes that all genetic effects are additive; however, most likely and biologically plausible, there are gene x gene interactions, which can create nonlinear effects. Moreover, genes in related subjects do not occur randomly but are inherited together, which may render the estimate of heritability too strong. Assortative mating (the tendency that similar people have children together) might inflate heritability estimates from twin studies; eventually, it may overestimate dominant variance. And even in twin studies where the twins are raised apart, shared environment before separation and selective placement has to be considered [6].

Single-Nucleotide Polymorphism Heritability

An almost reverse approach to twin studies is the estimation of SNP heritability. It makes use of tiny differences in the proportions of genome shared among seemingly unrelated individuals. Here, the heritability is derived from an estimate of relatedness between apparently unrelated individuals derived from SNP variation. That means it is calculated from the extent to which phenotypic variance for a trait can be explained by SNPs across the genome. A kinship matrix is calculated, which

represents the similarities between individuals that are unrelated. This matrix is then fitted to a vector of the phenotype in a mixed model in order to estimate heritability.

The unrelatedness of the subjects studied helps to disentangle possible effects of SNPs that are inherited together. In other words, SNP mutations that are associated with a phenotype are likely representing causal effects of this SNP, rather than being due to a different source of genetic variation, which is associated with a SNP that is inherited alongside with other SNPs.

However, SNP heritability is limited to additive effects from only a subset of common genetic variants that are investigated (sometimes referred to as the "chip heritability"), and SNP heritability does not identify specific SNP associations, meaning it is not made for the discovery of the underlying genetic variants.

Polygenic Scores

A polygenic score comprises thousands of SNPs that are associated with a specific trait. The aggregation of many associated SNPs provides a score that can be used as an individual estimate for individual differences. The SNPs are weighted by their correlation with the trait. Thus, polygenic scores give an estimate of the subjects genetic risk for a specific trait. One has to bear in mind that polygenic scores provide a probabilistic estimate for a certain trait. For research purposes, polygenic scores are a useful tool to investigate the extent to which a genetic estimate of a trait mediates effects on other variables of interest.

3.7 Environmental Influences on Heritability

3.7.1 Epigenetic Mechanisms

Epigenetics refer to molecular processes that alter gene expression without altering the deoxyribonucleic acid (DNA) sequence itself [35]. The most commonly accepted mechanisms coded as epigenetic mechanisms are DNA methylation, histone modifications, and noncoding RNAs (see Fig. 3.4). *DNA methylation* refers to the addition of a methyl group to DNA base pairs, primarily the cytosine base in cytosine-guanine (CG) dinucleotides. When CG dinucleotides occur in a high frequency (at least 200 base pairs), they form so-called CG islands. These islands play an important role in gene regulation, as they typically occur at or near the transcription start site (or the promoter region) of genes. *Histone modification* refers to the physical organization of DNA as part of the chromatin, as the DNA is wrapped around histones. This physical interaction (between DNA and histones) directly modifies the accessibility of the genome to transcription factors. There are numerous processes affecting this interaction, e.g., methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation. Also, *noncoding RNAs* (microRNAs (miRNAs)) bind to mRNA, thus interfering with gene expression on a posttranslational level [50].

These mechanisms interact with chromatin, the protein complex that organizes DNA and thus can alter the extent to which genes are accessible to transcription factors. This chapter will focus on DNA methylation as the most commonly studied epigenetic mechanism in addiction.

Initial studies of aberrant DNA methylation patterns in AUD suggest that the "epigenetic" properties of ethanol may play an important role in the maintenance of alcohol consumption in AUD. Animal studies show that already before conception exposure to alcohol can cause alterations in DNA methylation in the brain of the offspring [15]. Ethanol induces methylation patterns in brain areas known to be involved in the development and maintenance of addictive behaviors are within the limbic system such as the ventral

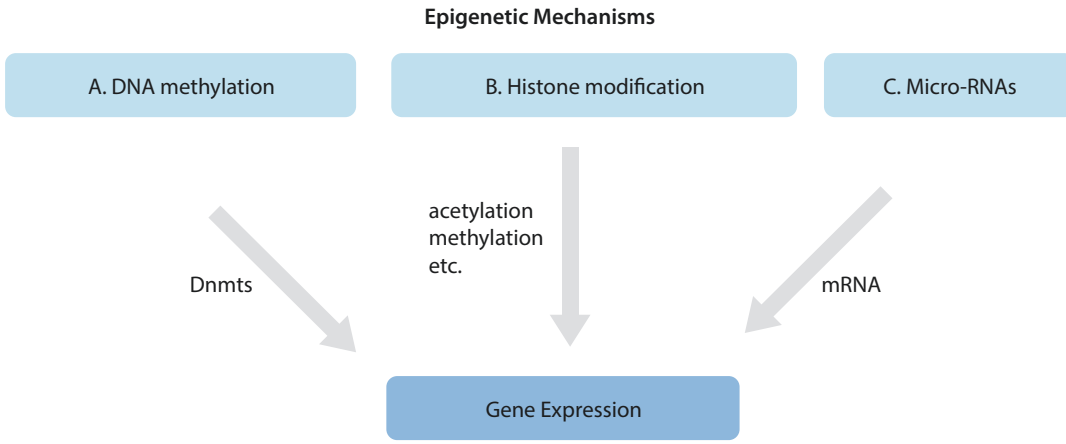

Fig. 3.4 Epigenetic mechanisms: A. DNA methylation is catalyzed by a family of DNA methyltransferases (Dnmts) that transfer a methyl group from *S*-adenyl methionine (SAM) to the fifth carbon of a cytosine residue to form 5mC. B. DNA is wrapped around histone proteins, which can be manipulated, e.g., through acetylation, methylation, phosphorylation and hence change accessibility to transcription factors without changing the DNA itself. C. MicroRNAs (miRNAs) are noncoding, single-stranded RNAs of 18–25 nucleotides. miRNAs affect gene expression through binding to mRNA. All processes are interrelated and affect gene expression (e.g., silencing or activation of target genes)

tegmental area (VTA), which is associated with reward dependent learning and memory and the hypothalamus, which contributes to stress and fear management [12]. Differences in methylations patterns induced by alcohol consumption have been shown to persist over generations [11] and can be reversed via specific chemical interventions [2].

Human postmortem brains show an overall decrease of methylation level after high alcohol exposure over life compared to healthy control brains [37]. In humans, the amount of alcohol exposure was directly linked to methylation patterns in genes highly relevant for addiction, including the γ-aminobutyric acid-A receptor (GABA) A and B gene [31]. Their differential methylation was associated with expression levels of a number of genes involved in immune function. Specifically, DNA methylation levels in promoter regions of genes implicated in addiction can be associated with AUD. These pathways include the dopaminergic system [5], the hypothalamus-pituitary-adrenal (HPA) stress axis [22], cell proliferation [18], and signaling pathways [4]. Furthermore, changes in methylation level have been associated with behavioral patterns such as craving for alcohol and withdrawal symptoms [5, 22].

Assessing epigenetic modifications is an important step forward in closing the gap between high estimates of heritability in AUD on the one hand and moderate to low associations between gene expression and behavioral indicators of AUD (such as amount of drinking, time to relapse, and withdrawal symptoms) on the other hand.

Besides the epigenetic properties of alcohol itself, there are numerous other variables that have been identified as highly relevant in the induction of epigenetic modification, including, for example, (mal)nutrition, consumption of other drugs, and exposure to stressful life experience as early as preconception [15]. With respect to the development and maintenance of AUD, stress exposure has been identified as one of key mechanisms mediating environmental and epigenetic influences and will thus be discussed in further detail within this chapter [7, 28, 32].

3.8 Aversive or Stressful Life Experience

So far, the exact mechanisms causing changes in DNA methylation patterns have only been insufficiently understood. Environmental influences during critical periods of development can lead to changes in learning, perception, and behavior via epigenetic mechanisms and may increase the risk of AUD and other psychiatric disorders. Such environmental stressors can be chemical influences, malnutrition, lack of maternal care, and adverse life experiences [28].

Animal models give further insight into the molecular mechanisms by which environmental factors influence gene transcription and behavior regulation. Maternal (caring via licking and grooming) behavior in the first week after birth altered the offsprings' epigenome at a glucocorticoid receptor (GR) gene promoter in the hippocampus [49], a region highly relevant for learning and habitization processes. Animals with caring mothers showed higher glucocorticoid receptor levels and reduced corticosterone and were less anxious compared to the offspring of less-caring mothers. These changes in epigenetic programming can persist over generations; thus, heritability turns into a dynamic and time-sensitive process.

In humans, aversive and stressful life changes such as loss of a friend, change in occupation, or problems in love relationship have been identified as potential modulators of (epi)genetic processes with relevance for alcohol-related behavior. Peng et al. [36] recently identified two new gene loci for alcohol-related life events in humans performing genome-wide analyses. They report two rare variants: the potassium channel subfamily K member 2 (K2P channel gene KCNK2) and missense and splice-site variants in pro-inflammatory mediator gene phosphodiesterase 4C (PDE4C). These genes play an important role in cell signaling and immune modulation and have been identified as relevant for serotonergic neurotransmission and depressive symptoms [36]. In agreement with animal studies, stress exposure during pregnancy in humans leads to changes in the individuals' response to stress after birth at different ages and has been linked to behavioral changes such as inconsiderate behavior, sleep disturbance, and attention deficits [32]. In turn, mechanisms reducing high levels of stress experience such as environmental enrichment and physical exercise can partially reverse DNA methylation differences associated with drinking in human subjects at high risk for developing AUD [8].

Summing up, epigenetic mechanisms are numerous and can be caused by multiple factors, only a few of which have been directly linked to addictive behavior. The interplay between genetic, epigenetic, and environmental factors has an ongoing influence on brain development and the associated behavioral changes, thus causing resilience or vulnerability to mental disorders such as AUD.

A key challenge for future research in the field of epigenetics will be to disentangle how changes in gene transcription contribute to the development and maintenance of addictive behaviors. At present, to name only a few of the challenges, we have to rely on new technologies and a poor knowledge of the methylome. By focusing on the CPG-rich islands near promoter regions, relevant sites for addictive behavior might be missed. Methylation patterns change over time and tissue type; thus, it remains speculative to relate methylation patterns retrieved from peripheral blood cells to brain-based processes. Many studies have small sample sizes, and different tissues and cells are being used to identify molecular changes. Up to now, there is no validated and commonly accepted framework for the analysis of genome-wide epigenetic data, which makes it extremely difficult to replicate new findings [16]. Nevertheless, epigenetic changes are an interface between environmental and genetic factors and may help to close the "heritability gap."

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Animal Models of Addiction

4

Eliot L. Gardner

Contents

Abstract

Addiction is a vastly complex disorder – with biological, psychological, social, and spiritual determinants. To a degree, the psychological, social, and spiritual determinants can be studied at the human level. This is highly problematic for the biological determinants, as it would almost certainly involve probing and manipulating the living human brain – with its many neural circuits and systems subserving choice, impulsivity, compulsive behavior, positive affect, negative affect, drug-seeking, drug-taking, drug craving, and relapse. Therefore, animal models have been developed to model the various biological and, in parallel, behavioral aspects of drug-seeking, drug-taking, and relapse. These models possess both face validity and a significant degree

E. L. Gardner (✉)
Neuropsychopharmacology Section, Molecular Targets and Medications Discovery Research Branch, Intramural Research Program, National Institute on Drug Abuse, US National Institutes of Health, Baltimore, MD, USA
e-mail: egardner@intra.nida.nih.gov

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of construct validity and predictive validity. Such models have yielded significant insights into the neurobiological substrates of addiction and have proven useful in the search for potentially effective anti-addiction, anti-craving, and anti-relapse medications to be used as adjuncts to other (e.g., cognitive, behavioral, psychosocial, group support) therapeutic modalities.

4.1 Introduction

Addiction is a complex disorder [44] involving dysfunction within vast regions of the central nervous system [49]. Given addiction's complexity, no single preclinical animal model can hope to satisfactorily capture the totality of its fundamental elements [62]. Rather, each animal model is an approximation that captures some but not all of the characteristics of the human condition. A major stumbling block in the development of animal models is that there is no generally accepted definition of addiction. Addiction is a term usually used to describe a self-administration habit involving an "addictive" substance, but there is no single criterion that distinguishes habits that qualify as addictions from habits that do not. People often talk glibly about being a "chocolate addict," but in the absence of a medical condition that makes sugar-rich chocolate consumption harmful to health (e.g., diabetes), it is hard to support the claim that indulging (even overindulging) in chocolate consumption qualifies as an addiction. Thus, there are many animal models, each of which reflects some real or presumed aspect of the habit-forming properties of addictive drugs. Although the models differ quite considerably, they each tend to identify the same major drugs, the same dose ranges, the same sites of action in the brain, and the same routes of administration as being associated with addiction liability [97]. The most strongly addictive substances are effective in each of the several models. Because each model seems, at least in terms of face validity, to reflect a different aspect of the habit-forming actions of addictive drugs, the most balanced picture of the addictive liability of a given drug comes from an integrated consideration of the drug's actions across a full range of models. Nevertheless, preclinical laboratory models have made enormous contributions to our understanding of addiction, as animal models have the advantage of possessing both face validity and a significant degree of construct validity and predictive validity (vid., [18]). In addition, animal models can be used to probe the underlying neurobiology and neurocircuitry of addiction – to a far greater degree of precision than is currently allowed by human neuroimaging techniques (vid., [30]).

4.2 The Cycle of Addiction

Drug addiction can be conceptualized as a cyclical process [93]. It often begins with factors (biological, psychological, social) that predispose to initial drug use. This is then followed by actual first drug use – and the intoxication and drug-induced "high" that accompanies such initial use. This often progresses to moderate or relatively infrequent use ("chipping"). Although moderate and/or infrequent, even "chipping" of addictive substances can have serious legal, health, psychological, and/or social consequences (e.g., [36, 78]). Alternatively, addictive drug use can progress to extended, escalating, and/or "binge" use (e.g., [92]) – obviously more serious conditions with obviously more serious sequelae (e.g., compromised family, occupational, social, and/or recreational activities). Binge use is also problematic in that it often predicts subsequent severe drug addiction [11]. Drug use can then progress to "compulsive" use – often defined as continued addictive drug use in the face of obvious and serious drug-induced harmful consequences to the drug user. As addictive drug use continues, an "opponent process" trap [31, 61] opens, during which the drug-induced "high" diminishes and drug-induced dysphoria increases – leaving the addictive drug user with a net loss of subjective drug-induced positive affect. Another "opponent process" situation arises in the context of drug withdrawal and its concomitant negative affect

[47]. In both situations, the resultant negative affect or dysphoria can lead to stress and to preoccupation with further drug use [93]. This, in turn, often leads to relapse to drug-seeking and drug-taking behavior. Since the founding of the Alcoholics Anonymous organization in the 1930s and the publication of its so-called Big Book [2], it has been well recognized that relapse is *the* major problem in the successful clinical management of drug addiction. Further, it has been recognized that there are three primary triggers to drug craving and relapse to drug-seeking behavior in recovering drug addicts – re-exposure to drug, exposure to stress, and re-exposure to environmental cues and contexts previously associated with drinking or drugging. An especially pernicious clinical problem is "incubation of craving," in which – counterintuitively – vulnerability to relapse actually increases with the mere passage of time since cessation of drug use and initiation of abstinence [81, 82].

4.3 Animal Models of the Various Stages in the Cycle of Addiction

4.3.1 Preexisting Vulnerability to Addiction

A major preexisting vulnerability to addiction revolves around the concept of "reward deficiency" – decreased ability to derive pleasure and satisfaction from the normal events of daily life [7]. This concept has been amplified (e.g., [9]) and accepted into mainstream theory on the nature and underlying substrates of addiction (e.g., [26, 44, 90]). Importantly, it can be modeled at the preclinical laboratory animal level [29]. Just as excess reward (such as produced by addictive drugs) has been amply and unambiguously tied to excess levels of the neurotransmitter dopamine in the nucleus accumbens (vid., [30, 31, 92, 97]), "reward deficiency" has been tied to deficiencies of nucleus accumbens dopamine [31, 44]. Such deficiencies can be measured. One measurement technique that has been widely used is that of positron emission tomography (PET) scanning [87]. PET is a nuclear medicine imaging technique that detects pairs of gamma rays emitted by a positron-emitting radioligand that has been introduced into the body. Three-dimensional images of ligand concentration within the body are then constructed by computer analysis. Ligands specific for dopamine include [^{11}C]raclopride and [^{18}F]fallypride. Another widely used animal model for assessing nucleus accumbens dopamine levels is in vivo brain microdialysis (vid., [25]). In this procedure, a very small dialysis probe is constructed from stainless steel tubing and microdialysis tubing and then surgically implanted into the desired chemical sampling site in the brain (e.g., nucleus accumbens). Typically, the stainless steel tubing is concentric, with an exceedingly small piece of dialysis tubing connecting the tips of the two concentric stainless steel tubes deep in the brain. Artificial cerebral spinal fluid is perfused through the apparatus – the input tubing connected to a fluid pump and the output tubing connected to a chemical sampling device such as high-pressure liquid chromatography (HPLC). Within the chemical sampling site in the brain, molecules of neurotransmitters (or other chemicals) dialyze across the membrane and are carried to the chemical sampling device. In vivo brain microdialysis is a robust and reliable technique for measuring neurotransmitter levels within a small (1–2 mm) sampling domain within the brain and has proven itself very useful in studying the neurobiology of addiction, craving, and relapse (e.g., [51, 70]). Hypodopaminergic states within the nucleus accumbens have been tied to enhanced vulnerability to self-administer cocaine in laboratory rodents and in nonhuman laboratory primates [14, 60].

Another preexisting condition that confers vulnerability to addiction is impulsivity [71]. Impulsivity confers vulnerability to initial drug use, continued drug use, and relapse to drug use after periods of abstinence. Two types of impulsivity relevant to drug addiction have been identified – impulsive action and impulsive choice. Impulsive action refers to an inability to withhold a prepotent response. Impulsive choice refers to an inability to tolerate delayed rewards. These two types of impulsivity are likely modulated by different neural substrates [16]. Impulsive choice is most commonly measured

using a reward delay discounting task in which the animal (or human) subject has a choice between an immediate small reward or a delayed large reward [1]. By altering the size of the reward and/or the delay for the larger reward, "reward delay discount" functions (i.e., the degree to which the test subject devalues a delayed reward) can be computed. Drug-abusing/dependent humans have high discount rates (i.e., they strongly prefer immediate rewards). This has been demonstrated for patients addicted to/dependent upon nicotine, ethanol, opioids, cocaine, and methamphetamine. Prior to becoming addicted to or dependent upon addictive substances, ordinary laboratory rats self-assort themselves into low-impulsive versus high-impulsive animals. For most laboratory rat strains, this self-assortment yields approximately 50% low-impulsive and 50% high-impulsive animals. High-impulsive laboratory rats are *extremely averse* to intermediate-to-long reward delays [33]. In low-impulsive rats, acute cocaine does not alter preexisting impulsivity. In high-impulsive rats, acute or chronic cocaine decreases impulsivity (arguably, a methylphenidate-like effect). In low-impulsive rats, chronic cocaine *dramatically increases* impulsivity [33]. Thus, in low-impulsive animals (less prone to drug-taking because of their preexisting low trait impulsivity), chronic cocaine increases impulsivity and therefore increases the tendency to drug-taking behavior [14]. One may therefore conclude that preexisting levels of trait impulsivity are of relevance to initial tendency to drug-taking behavior and also to the degree to which chronic drug exposure may alter a preexisting tendency to drug-taking behavior [33].

4.3.2 Addictive Drug Self-Administration

If one equates addiction with drug self-administration (an inaccurate homology, as the above-noted mention of "chipping" illustrates), the self-administration paradigm offers the most obvious animal model of addiction. Laboratory animals will self-administer several classes of addictive drugs by a wide variety of routes – oral, intragastric, intraperitoneal, intravenous, or intracranial. This is often done to the point of physiological dependence. Oral self-administration of ethanol and intravenous self-administration of heroin represent obvious analogues of human drug-seeking. In the strongest version of the model, the animal is required to work for access to the drug and not merely to ingest it. This is an instrumental conditioning paradigm, reflecting response learning, inasmuch as the drug is given in a response-contingent manner. In the case where the animal lever-presses for presentation of the drug, the lever-pressing is termed the instrumental response, and ingestion of the drug is termed the consummatory response.

Although the drug self-administration model is most often used with fixed-ratio reinforcement contingencies, an important variant is one in which progressive-ratio reinforcement is used [74]. In progressive-ratio drug self-administration, a progressively increasing workload is imposed upon the animal to receive a drug injection. For example, the workload may increase in a steeply incremental fashion: one lever press required for the first injection, two for the second injection, four for the third, eight for the fourth, and so on. Although typically the workload is not incremented so steeply, in every progressive-ratio drug self-administration session, a point is reached at which the animal's responding falls below some criterion level (often, an abrupt cessation of responding) – the progressive-ratio "break point." This "break point" is taken as a measure of reinforcing efficacy and "reward strength" of the self-administered substance [40]. Alternatively, some experts consider the progressive-ratio break point to reflect the degree of incentive motivation to self-administer drugs. Interestingly, psychostimulants yield different estimates of reward efficacy than do opioids in this animal model. Psychostimulants respond preferentially to incremental increases in response cost immediately following reinforcement, whereas opioids respond preferentially to incremental increases in response cost at the beginning of a discrete trial or daily test session. This has been taken to

mean that motivation to self-administer psychostimulants versus opiates is qualitatively different [4]. Provocatively, progressive-ratio break point estimates of the rewarding efficacy of different classes of addictive drugs in animals parallel quite closely the verbal rank orderings of appetitiveness for different classes of addictive drugs given by experienced polydrug-abusing humans [28].

4.3.3 Intoxication and the Drug-Induced "High"

A striking feature of drug addiction is how few chemicals are subject to abuse. If all congeners of all chemicals are included, approximately 30,000,000 chemical substances are known [30]. Yet, only approximately 300 (including nicotine, ethanol, psychostimulants, opiates, barbiturates, benzodiazepines, and cannabinoids) are addictive, and this figure is likely an overestimate. Obviously, 300 is a stunningly small subset of 30,000,000. It poses the question: what makes those 300 chemicals addictive while the remaining 30,000,000 are not? There are, after all, few pharmacological similarities among addictive drugs. Some – including barbiturates, ethanol, opioids, and benzodiazepines – are sedatives, while others, including nicotine, cocaine, and the amphetamines, are stimulants. Some – including opiates and cannabinoids – are analgesic, while others, in the proper laboratory or clinical situation, augment pain perception. Some – such as ethanol and opioids – produce physical dependence, while others, such as cocaine, produce little if any physical dependence. However, a few commonalities are apparent and instructive. All addictive drugs are subjectively rewarding, reinforcing, and pleasurable [30]. Laboratory animals volitionally self-administer them [28], just as humans do. Furthermore, the rank order of appetitiveness in animals parallels the rank order of appetitiveness in humans [28, 62]. Most importantly, all addictive drugs (with the exception of the LSD-like and mescaline-like hallucinogens) activate the reward circuitry of the brain [27, 30], thereby producing the subjective "high" that the drug abuser seeks. Furthermore, the degree of such activation of the brain's reward circuitry correlates well with the degree of the subjective "high."

4.3.3.1 The Brain's Reward Circuitry

The brain's reward circuitry was first discovered by Olds and Milner [63] at McGill University in Montreal. They found that animals would repeatedly return to an area of the laboratory in which they had received mild electrical stimulation of subcortical structures anatomically associated with the medial forebrain bundle. Subsequently, they found that animals would avidly perform tasks (e.g., depressing wall-mounted levers in their test chambers) in order to receive such brain stimulation. James Olds [64, 65] and his wife Marianne Olds [66, 67] subsequently extensively mapped the rodent brain, confirming that a large majority of the brain sites supporting brain stimulation reward are associated with the nuclei of origin, tracts, and terminal loci of the medial forebrain bundle. Other researchers (e.g., [77]) studied electrical brain stimulation reward in nonhuman primates and confirmed that the anatomic brain substrates supporting brain reward are homologous to those in rodents. Using sophisticated electrophysiological techniques, Gallistel et al. [23] determined that the primary neural substrate supporting electrical brain stimulation reward is the moderately fast-conducting, myelinated descending neural fiber system of the medial forebrain bundle. This system originates in the anterior bed nuclei of the medial forebrain bundle (an array of deep subcortical limbic loci anterior to the hypothalamus and preoptic area), descends to the ventral tegmental area of the midbrain via the medial forebrain bundle, and then ascends via the medial forebrain bundle to a select group of forebrain limbic loci including the nucleus accumbens, olfactory tubercle, and frontal cortex. Wise and Bozarth [98] were the first to realize that this assortment of brain loci and tracts constitutes a neural circuit containing three synaptically connected, in-series neuronal elements – a descending link running from the anterior bed nuclei of the medial forebrain bundle to the ventral tegmental area, an ascending

link running from the ventral tegmental area to the nucleus accumbens, and a further link running from the nucleus accumbens to the ventral pallidum. The first link is a descending myelinated fiber tract of unknown neurotransmitter type. The second link is an ascending fiber tract from the ventral tegmental area to the nucleus accumbens, with dopamine as its neurotransmitter (see below). The third link is a projection from the nucleus accumbens to the ventral pallidum, using γ-aminobutyric acid (GABA), substance P, and enkephalin as conjoint neurotransmitters. This three-neuron, in-series circuit receives synaptic inputs from, and is functionally modulated by, a wide variety of other neural circuits using a wide variety of neurotransmitters.

Addictive drugs of different classes act on this three-neuron, in-series brain reward neural circuit at different points to activate the circuit and produce the euphoric drug-induced "high."

Importantly, this brain reward circuitry evolved over eons of evolution to subserve biologically essential normal rewarding behaviors such as feeding, drinking, sexual behavior, maternal and paternal behaviors, and social interactions. From an appreciation of the natural and biologically essential nature of these reward circuits comes the notion that addictive drugs "hijack" the brain's reward circuits, activating them more strongly than natural rewards and diverting the drug addict's life to pursuit of drug-induced pleasure at the expense of "getting off" on life's normal pleasures and rewards [34, 76].

4.3.3.2 The Intense Nature of Brain Stimulation Reward

Electrical brain stimulation reward is remarkable for the intensity of the reward and reinforcement produced [30]. When the stimulating electrode is properly on target within the ventral tegmental area, medial forebrain bundle, or nucleus accumbens, laboratory animals will volitionally self-stimulate those areas at maximal rates. They will, tellingly, ignore readily available food, water, toys, and sexually receptive animals of the opposite sex in order to self-deliver the brain stimulation reward. They will also volitionally accept aversive and painful consequences in order to self-deliver the brain stimulation reward (also see below under "Compulsive Use"). In awake humans, such electrical stimulation can evoke intense subjective feelings of pleasure [6, 38, 80], in some instances similar to descriptions of intense medieval religious ecstasies (Ward A.A. Jr., personal communication, 1967). As the most addictive drugs (e.g., cocaine, methamphetamine) evoke comparable levels of subjective reward, it is easy to understand their intensely addictive nature.

4.3.3.3 Dopamine: The Crucial Reward Neurotransmitter

Soon after the discovery of the electrical brain stimulation reward phenomenon (Olds and Milner, 1956) and subsequent mapping of the rodent and nonhuman primate brain for brain reward loci and neuronal tracts (e.g., [23, 65–67, 77]), many attempts were made to determine the neurotransmitter underlying the brain reward phenomenon. The first suggestion that dopamine was the crucial neurotransmitter was made in 1969 by Gardner, who selectively depleted neurotransmitters in the brains of rhesus monkeys working a complex operant task to receive electrical brain stimulation reward and then – crucially – repleted (in sequence) each neurotransmitter believed to have been pharmacologically depleted [24]. Working independently, and using a different research approach, Wise and colleagues in Montreal confirmed this suggestion in a brilliant series of published articles (e.g., [20, 96, 103]). By selective anatomic placement of intracerebral micro-catheters and intracranial micro-electrodes, both the Gardner group and the Wise group suggested that dopamine was the crucial brain reward neurotransmitter activated by addictive drugs, specifically in the "second-stage" ventral tegmental area to nucleus accumbens link in the brain's reward circuitry that had been anatomically identified by Wise and Bozarth [98, 99] and by Gallistel et al. [23]. That dopamine is indeed the crucial "reward"

neurotransmitter in the brain has subsequently been confirmed by many investigators in laboratories worldwide and is based on many congruent findings. First, virtually all addictive drugs are functional dopamine agonists – some direct, some indirect, and some even transsynaptic (vid., [27, 30, 102]). With the exception of the LSD- and mescaline-like hallucinogens, functional dopamine agonism is the single pharmacological property that all addictive drugs share. Second, intracerebral microinjections of dopamine agonists produce conditioned place preference [86] and support volitional intracerebral self-administration [102]. Third, dopamine antagonists are negative reinforcers in animals (animals will work to avoid or escape their administration) and produce subjectively aversive effects in humans [30, 62]. Fourth, when dopamine antagonists are administered to animals volitionally self-administering addictive drugs, a compensatory increase in addictive drug intake occurs (to compensate for the decreased rewarding potency of the addictive drug), followed by extinction and cessation of the self-administration behavior (when the dopamine antagonism reaches a sufficient intensity so as to totally block the rewarding properties of the self-administered addictive drug) [62, 103]. Fifth, measures of real-time synaptic neurochemistry in the nucleus accumbens of test animals volitionally engaged in intravenous self-administration of addictive drugs show that following the first volitional self-administration of the test session, extracellular dopamine overflow in the nucleus accumbens displays a tonic increase of approximately 200%; thereafter, extracellular dopamine levels in the nucleus accumbens fluctuate phasically between approximately 200% and 100% over baseline; and the low point of each phasic dip in extracellular nucleus accumbens dopamine accurately predicts the next volitional intake of addictive drug by the test animal [100, 101]. Such data are extremely compelling, as they show that when animals self-administer heroin or cocaine (or other addictive drugs), they do so in order to, in turn, titrate blood levels of addictive drug, brain levels of addictive drug, and – most importantly – nucleus accumbens levels of dopamine.

4.3.4 Moderate Addictive Drug Use Versus Extended Access, Augmented Incentive Motivation for Drug Use, and Enhanced Reward Value of Addictive Drugs

For purposes of economy in the use of animals, time, laboratory personnel, and laboratory budgets, most self-administration studies in laboratory animals have historically been limited to 2 or 3 hours of addictive drug access. This, of course, does not accurately model clinical reality. And, further, it raises the question: is addictive drug self-administration fundamentally different if animals (and, presumably, humans) are allowed extended drug access as opposed to limited drug access? This question has been systemically addressed in a series of elegant published articles by, among others, George Koob and colleagues (e.g., [46]). These researchers – and others – have found that giving laboratory animals extended access to addictive drug self-administration produces radically different behavioral and neurobiological sequelae. For example, Koob and colleagues have reported a series of findings in laboratory rats that are extremely provocative with respect to their analogy, and probably homology, to human opioid addiction [95]. First, under extended access conditions (as compared to limited access conditions), intravenous self-administration was maintained *and escalated* for heroin, oxycodone, and fentanyl, but not for buprenorphine. Rats that were allowed limited drug access showed low and stable lever-pressing for each of the four opioids, but not an escalation in drug intake. Following escalation of drug intake, a classic inverted U-shaped dose-effect function was demonstrated in the heroin, oxycodone, and fentanyl self-administering rats, suggesting that the animals were titrating their doses. These findings indicate that extended access to heroin, oxycodone,

and fentanyl – but not buprenorphine – results in escalation of drug self-administration. Could this be an insight into buprenorphine's clinical efficacy but relative lack of addictive liability? This is an interesting question.

Second, extended access to drug self-administration was compared to limited access with respect to effects on self-administration break point under progressive-ratio reinforcement conditions. As noted above, shifts in progressive-ratio break points are believed to represent shifts in reward efficacy or motivational properties of the drug [40, 74]. Wade et al. [95] found increases in progressive-ratio break point (i.e., enhanced reward efficacy) for heroin, oxycodone, and fentanyl – but not for buprenorphine – under extended drug access conditions as compared to limited drug access conditions. Extended access rats showed increased motivation for intermediate doses of heroin, oxycodone, and fentanyl compared with limited access rats. No group differences for buprenorphine were found.

Additionally, it has been known for some time that increasing the dose of opioid, even in limited access conditions, can alter the reinforcing efficacy of the drug [48, 75]. The reason(s) for this may relate to differential binding affinities, efficacy, and opioid subtype preference. Heroin, oxycodone, fentanyl, and buprenorphine have few differences in time to onset when administered intravenously. However, each of these drugs shows differential binding affinities, efficacy, and opioid subtype preference. A comparison of the binding affinity for the mu opioid receptor may be an important factor in the reward value of these opioids. While heroin, oxycodone, and fentanyl have similar binding affinities [21, 94], buprenorphine has a much higher mu opioid receptor binding affinity – suggesting that time to offset from the receptor for buprenorphine may be longer than that for the other opioids [94]. Action at other receptors may also be relevant. Buprenorphine acts as a partial agonist at the mu opioid receptor, the nociceptin receptor (also known as the nociceptin/orphanin FQ receptor), and the kappa opioid receptor but also as an antagonist at the kappa opioid receptor [41]. Nociceptin receptor activation produces opposite effects on mesolimbic dopamine receptors than does mu opioid receptor activation – by decreasing extracellular nucleus accumbens dopamine levels [54, 59]. Also, activation of kappa receptors directly inhibits dopaminergic neurons [54] – reducing brain reward. Thus, buprenorphine's relative lack of addictive liability may result from multiple actions at multiple brain sites – with the extended access animal drug self-administration model yielding important insights into some of these actions, as well as yielding insights into mechanisms underlying the increased drug reward and increased incentive motivation for drug self-administration observed with chronic opioid use.

4.3.5 Compulsive Drug Use

Loss of control over harmful drug-seeking and drug-taking is one of the most intractable aspects of addiction, as human substance abusers continue to pursue and use addictive drugs despite incurring massively negative consequences to themselves, their families, their jobs, and their health [3]. Many have made the cogent argument that drug-seeking and drug-taking do not adequately define addiction (see comments above relating to "chipping"). Therefore, considerable attention has been paid to developing animal models that incorporate harmful consequences to the animal either concomitant with or consequent to drug-seeking and drug-taking (e.g., [5, 15, 69, 88]).

Although there are many variants of this general approach, one will be sufficiently illustrative [15]. Deroche-Gamonet and colleagues measured persistence of responding for drug when drug delivery was associated with punishment. During these sessions with laboratory rats, nose-pokes under fixed-ratio 5 reinforcement (one drug infusion for every fifth nose-poke) resulted in delivery of both the drug and an electrical foot shock. The shock punishment was signaled by a new cue light that illuminated at the time of the first nose-poke and turned off after the delivery of the shock.

They then went on to analyze the relationship between drug-seeking in the face of harmful conse-

quences and propensity to relapse to drug-seeking behavior. To study propensity to relapse, they used an animal relapse model ([73, 89]; see also discussion below) in which drug-seeking behavior is triggered – after a drug withdrawal period – by re-exposure to drug or re-exposure to conditioned cues (light, sound) previously associated with drug-taking. A 5-day and 30-day period of withdrawal following 3 months of drug self-administration were both studied. Responding during the relapse test was taken to measure vulnerability to relapse.

In the first experiment, rats were assigned to two groups on the basis of their relapse behavior. The high-relapse-prone animals differed profoundly from the low-relapse-prone animals. High-relapse-prone animals progressively increased their drug-seeking behavior during no-drug periods and also after punishment. They also had higher break points for drug self-administration under progressive-ratio reinforcement (i.e., displayed higher incentive motivation to self-administer; found the addictive drug to be more rewarding). Correlation analyses revealed that each addiction-like behavior (persistence of drug-seeking, resistance to punishment, motivation for drug) strongly predicted propensity to relapse.

In a second experiment, these researchers assessed whether addiction-like behaviors were also related to propensity to relapse after a longer period of withdrawal (30 days). Again, high propensity to relapse was positively correlated with persistence of drug-seeking, resistance to punishment, and motivation for drug.

These experiments show that after prolonged drug self-administration, addiction-like behaviors are found in rats. Importantly, addiction-like behaviors are not present after a short period of drug self-administration, but develop, as does addiction in humans, only after prolonged exposure to the drug. Furthermore, as do human addicts, rats showing an addiction-like behavior have a high propensity to relapse even after a long period of withdrawal. Finally, these findings indicate that the three addiction-like behaviors are measures of a single factor that reflects compulsive drug use.

4.3.6 The "Opponent Process" Trap

As noted, electrical brain stimulation reward is a powerful preclinical technique for measuring the reward value of addictive drugs (vid., [30]). In 1981, Gardner and colleagues decided to examine whether there were differences in morphine-enhanced brain reward depending upon the exact anatomic placement of the stimulating electrode in the ascending dopaminergic tract running from the ventral mesencephalon to the neostriatal forebrain [61]. These researchers found that when the brain stimulation reward electrode was in the medial portion of the tract, a single injection of morphine produced an *enhancement of brain reward* which waned as the morphine metabolized and dissipated during the hours following the injection. On subsequent days, the same pattern held, but *the degree of brain reward enhancement underwent tolerance (decreased) with each subsequent day*. When the brain stimulation reward electrode was in the lateral portion of the tract, a single injection of morphine produced *inhibition of brain reward* which waned as the morphine metabolized and dissipated during the hours following the injection. On subsequent days, *the degree of brain reward inhibition grew progressively on each subsequent day*. Further experiments, using in vivo voltammetry microelectrodes [25] to measure dopamine levels in different anatomic domains of the neostriatum revealed a similar picture [8]. Thus, the initial drug-enhanced reward dissipates, while the initial drug-induced inhibition of brain reward grows progressively stronger. It will be readily appreciated that this places the drug user in a nasty "trap" – the drug-induced euphoria undergoes tolerance, while the drug-induced dysphoria progressively grows. The opioid addict eventually comes to use opioids not to "get high," but rather to "get straight" (i.e., to try to push his/her diminished brain reward and, hence, subjective dysphoria back toward something approximating normal affect).

4.3.7 Drug Withdrawal and Negative Affect: Additional Drivers of Relapse to Drug-Seeking and Drug-Taking

George Koob, the director of the US National Institute on Alcohol Abuse and Alcoholism and one of the most creative and original thinkers in the field of addiction medicine, has pointed out that the negative affect and dysphoria produced by drug withdrawal are powerful drivers of relapse to drug-seeking and drug-taking behaviors [46–48]. As noted above, in addiction, healthful rewards lose their former motivational power. In a person with addiction, the reward and motivational systems become reoriented through conditioning to focus on the stronger release of dopamine produced by the drug and its cues. This is the concept behind the notion that addictive drugs "hijack" the normal reward mechanisms and processes of the brain.

For many years, it was believed that over time, persons with addiction would become more sensitive to the rewarding effects of drugs and that this increased sensitivity would be reflected in higher levels of dopamine in the circuits of their brains that process reward (including the nucleus accumbens and the dorsal striatum). However, we now know that this is incorrect. As noted above, in the presence of addiction, addictive drug consumption triggers *smaller* increases in dopamine levels [90, 91, 104]. This diminished dopamine release renders the brain's reward system much less sensitive to stimulation by both drug-related and non-drug-related rewards. Consequently, persons with addiction no longer experience the same degree of euphoria from a drug as they did when they first started using it. Thus, persons with addiction often become less motivated by everyday stimuli (e.g., relationships and activities) that they had previously found to be motivating and rewarding. It must be understood that these changes become deeply ingrained neurobiologically and cannot be quickly reversed through simple termination of drug use (e.g., detoxification). In fact, simple termination of drug use is so contraindicated by the underlying neurobiology of withdrawal and withdrawal-induced dysphoria that short-term detoxification programs can be considered to constitute medical malpractice. In addition to decreased nucleus accumbens dopamine tone, withdrawal actually recruits enhanced reactivity to stress and emergence of negative emotions – resulting in what has been termed a rebound "anti-reward" state [47]. This is different from the "opponent process trap" described above, in that the anti-reward state of Koob and Le Moal is a rebound phenomenon while the "opponent process trap" is the summation of opponent processes occurring simultaneously in anatomically different regions of the brain's reward circuitry. In Koob and Le Moal's "anti-reward" process, there is intense motivation to escape the discomfort associated with addictive drug withdrawal. As a result, the patient with addiction transitions from taking drugs simply to feel pleasure (to "get high") to taking them to obtain transient relief from dysphoria. In addition, stress responses in the brain are recruited [44, 45, 50, 85].

Persons with addiction frequently cannot understand why they continue to take the drug when it no longer yields pleasure. Many state that they continue to take the drug to escape the distress they feel when they are not intoxicated. Unfortunately, although the short-acting effects of increased dopamine levels triggered by drug administration temporarily relieve this distress, the result of repeated bingeing is to deepen the dysphoria during withdrawal, thus producing a vicious cycle.

4.3.8 Animal Models of Relapse

Relapse to drug-seeking and drug-taking is common and so pathognomonic of addiction that it is often used as a diagnostic criterion [3, 42]. As a result, many animal models of relapse have been developed and have added greatly to our knowledge of addiction and its underlying neurobiology (e.g., [12, 13, 73]). Fundamentally, animal models of relapse fall into two categories – those

in which abstinence is achieved by experimenter-imposed behavioral extinction of the drug-taking habit and those in which drug relapse is assessed after either forced or voluntary abstinence. Arguably, it is the latter set of animal models that most closely resemble the human situation, as human abstinence is typically either forced (e.g., by incarceration or inpatient treatment in hospital or clinic settings) or voluntary due to either the negative consequences of chronic drug use or the availability of strong nondrug rewards in the drug user's environment [17, 43, 55].

4.3.8.1 Extinction-Based Relapse Models

There are two fundamental variants of this model – relapse based on extinction of an operant response (e.g., lever-pressing, nose-poking, running from a start box to a goal box) for drug self-administration and relapse based on extinction of a Pavlovian association of addictive drug intake and drug-receipt-associated unique environmental cues and/or contexts (e.g., conditioned place preference). Thus, the fundamental distinction is between models based on Skinner's [83] or Thorndike's [39] work and models based on Pavlov's work [57].

Relapse Based on Operant Response Extinction

In the operant self-administration variant of the model, laboratory animals are trained to self-administer a drug by emitting an operant response (e.g., lever-pressing, nose-poking, running from a start box to a goal box) to receive drug. During the extinction phase, the operant response is extinguished by omitting the drug reward. During the reinstatement (relapse) test, the ability of various acute stimuli (or "triggers") to reinstate the previous drug-seeking behavior is measured under extinction conditions. The amount of previous operant responding (now nonreinforced) is the operational measure of drug-seeking behavior [19, 56, 84]. The three classical relapse triggers in this model are the same as observed in human relapse – re-exposure to drug, stress, or re-exposure to conditioned cues or contexts previously associated with drug intake [2].

Relapse Based on Pavlovian Response Extinction

In the conditioned place preference variant of the model, laboratory animals are placed in an experimental device with two environmental cue-distinct chambers and allowed to freely explore. The distinct cues that identify the chambers are typically visual, tactile, and/or olfactory. The cues are arranged such that they are initially motivationally neutral (i.e., the animal prefers neither chamber over the other). A barrier is then placed between the two cue-distinct chambers. By placing the animal alternatively in one chamber and the other (usually a 3-hour exposure, with daily alternation between chambers), the animals are trained to associate one distinct set of environmental cues/contexts with drug injections and the second compartment with injections of vehicle. If the drug is appetitive, the animals develop a very distinct preference for the drug-associated chamber. Subsequently, rats are subjected to extinction training during which they are exposed – alternatingly – to both contexts in the absence of drug. Reinstatement of the preference for the drug-paired compartment is then determined after noncontingent exposure to such relapse "triggers" as re-exposure to drug or exposure to stress [58, 79].

4.3.8.2 Abstinence-Based Relapse Models

Forced Abstinence by Removal from the Drug-Taking Environment

This is essentially a withdrawal-based model analogous (perhaps even homologous) to human incarceration or placement in a secure hospital or treatment center. A typical forced abstinence study includes three phases: training, forced withdrawal from drug, and testing. During the training phase, laboratory animals are allowed to self-administer a drug by emitting standard operant responses (e.g., lever-pressing, nose-poking). This is typically paired with presentation of discrete environmental cue(s). During the withdrawal phase, the animals are housed in the animal facility for different periods of abstinence. During the test phase, the animals are returned to the drug

self-administration environment/context, and the previous drug-yielding operant responses result in contingent presentation of the discrete cue(s) previously paired with drug infusions but not the drug itself [22, 72]. Nonreinforced lever-pressing in this single extinction session is the operational measure of "relapse to drug-seeking" and the main dependent measure.

Incubation of Craving

An exceptionally important variant of this model is the so-called "incubation of craving" model. In this model – otherwise identical to the "forced abstinence by removal from the drug-taking environment" model noted immediately above – groups of animals are subjected to different lengths of drug withdrawal before being tested for relapse [37]. Somewhat counterintuitively, it was found that (within limits) longer periods of drug withdrawal produced more intense relapse [37]. However, astute clinicians pointed out that this "counterintuitive" finding actually comported with clinical reality – Gawin and Kleber [35] having reported that cue-induced cocaine craving in human patients progressively increases over the first weeks of abstinence and remains high for a remarkably extended period. This "incubation of craving" model has been used extensively over the past 15 years in a large number of studies relating to the underlying neurobiology of drug reward, drug addiction, craving, and relapse.

Voluntary Abstinence Induced by Adverse Consequences of Drug Use

This, of course, comports nicely with observed clinical reality. In the preclinical model, laboratory animals are trained to self-administer a drug (usually paired with a discrete environmental cue). Then, drug-taking behavior is suppressed by aversive foot shock – either after the animal performs the operant response [68] or by introducing an electrical barrier in front of the drug-associated lever such as to deter the animal from making the operant response in the first place [10]. During the test phase, relapse to drug-seeking is precipitated by exposure to drug-priming injections or environmental cues. These models have recently been used to exceptional effect in identifying specific brain loci underlying relapse to drug-seeking behavior in the face of adverse consequences (e.g., [52, 53]).

4.4 Conclusion

Drug addiction at the human level is a biopsychosocial-spiritual disorder and is well-accepted in the field of addiction medicine. To a considerable extent, the psychological, social, and spiritual dimensions of this disorder can be studied – and even experimentally probed – at the human level. However, probing and manipulating the biological aspects of addiction are problematic, as they would – perforce – require probing and manipulating the living human brain. For this reason, animal models of addiction have been developed (and continue to be). The use of these models has yielded important insights into the biological aspects of addiction; has proven useful in identifying and testing potential anti-addiction, anti-craving, and anti-relapse medications that may prove useful at the human level; and has shed useful knowledge to inform the current debate on the possible medical utility of cannabis [28, 32].

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5 Burden of Disease: The Epidemiological Aspects of Addiction

J. Rehm, C. Probst, L. Llamosas Falcón, and K. D. Shield

Contents

Abstract

This chapter describes epidemiological aspects of substance use disorders. It begins with a narrative review of the transition from substance use to a substance use disorder. A methodological introduction into global burden of disease estimates for substance use disorders follows, and finally, this chapter reports on regional differences on burden of disease.

J. Rehm (✉)
Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

Institute of Medical Science, University of Toronto, Toronto, ON, Canada

Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany

Department of International Health Projects, Institute for Leadership and Health Management, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation

C. Probst
Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

L. L. Falcón
Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Preventive Medicine and Public Health, Hospital Universitario 12 de Octubre, Madrid, Spain

K. D. Shield
Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

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The investigation of what influences the course of substance use from initiation to the development of a substance use disorder reveals a multiplicity of factors. The overall picture suggests that extra-individual, social factors such as the cultural background, or peer behavior, predominantly influence use initiation and the transition to hazardous patterns of use, whereas intraindividual factors such as personality traits and genes are more prominent in the development and potential chronification of substance use disorders.

1.4% and 0.9% of the global population were affected by alcohol use and by drug use disorders, respectively, according to estimates from the Global Burden of Disease (GBD) study, which only includes the more severe cases. For all substances, prevalence is higher in men than in women. These disorders cause substantial burden of disease: alcohol use disorders account for 0.7% of the global burden of disease, while drug use disorders account for 1.1%. While tobacco use disorders are defined in psychiatric classification systems, their prevalence and associated burden are not estimated by the GBD.

The burden of disease attributable to different substance use disorders varies strongly across countries and regions. Burden due to alcohol use disorders is highest in upper-middle-income countries, while burden due to drug use disorders is highest in high-income countries.

Keywords

Substance use disorders · Epidemiology
Global burden of disease · Regional differences · Life course · Comorbidity

Addictions (substance use disorders), as currently defined in major classification systems, are highly prevalent and account for a considerable degree of the global burden of disease. This burden is typically defined as a summary health indicator, measured in disability-adjusted life years (DALYs) lost [45], which is composed of years of life lost due to premature mortality plus years of life lost to disability [18]. However, the burden of disease is not homogenous across substances, countries, and time. Furthermore, the transition from substance use to a substance use disorder is dependent on numerous factors. Accordingly, this chapter outlines these factors and describes the burden caused by substance use disorders as obtained from the [20].

5.1 The Transition into a Substance Use Disorder

There is a history of use initiation, and often an observable pattern of hazardous use, which precedes substance addiction. Generally, these observable trajectories can be approached from either a drug-centered or an individual-centered perspective [37]; we will focus on the main individual-centered aspects and will not deal with the differences between specific substances.

The initiation of substance use depends largely on social and environmental factors, such as the cultural context, advertising, or peer influence [19]. Worldwide per capita consumption and rates of abstention differ greatly between countries [14, 41, 49, 69]. For instance, lower abstention rates for alcohol consumption are observed in high-income countries, and higher abstention rates are observed in North African, Eastern Mediterranean, and South Asian countries [81, 82]; higher abstention rates are often associated with religion and with low economic wealth [41, 53, 68]. Substance use is often initiated in adolescence, but there are some economic, cultural, and substance-specific variations [13]; for instance, in India and in Thailand, the age of initiation has long been in or around the twenties [24, 46]. However, with economic and cultural changes, the age of initiation is dropping in some traditionally "dry" cultures. For example, in some states of India, the age of initiation has dropped by5 years or more in recent years [26, 50].

Across substances and cultures, women are less likely to initiate substance use [12, 13]. Substance availability [39, 52, 67] and advertising [10, 25, 70] have been shown to influence the

age of initiation. Beyond these influential cultural factors, the initiation of use is influenced by the individual's social network and immediate environment. Several studies have shown that social motives, peer or familial substance use, and normative beliefs of close peers influence the initiation of substance use across different substances [6, 17, 34, 48].

While most users maintain a low-risk pattern of use, some individuals will develop hazardous patterns of substance use [15, 73]. In particular, early onset of substance use has been shown to increase the risk of later hazardous substance use across substances [1, 2, 51, 55]. With respect to alcohol, research indicates that repeated intoxication at a young age is especially associated with later-in-life hazardous patterns of alcohol consumption [5, 36]. A review identifying the characteristics of people with hazardous alcohol consumption patterns in Europe [35] observed that hazardous drinking patterns were more prevalent in males, adolescents, and young adults. Furthermore, the review identified other social and environmental factors, such as the predominant drinking culture, peer influences [7, 42], parental monitoring [9], and concurrent use of other substances. Finally, the motivation for alcohol consumption seems to evolve from social motives and curiosity (predominantly controlled use) to hazardous consumption patterns motivated by self-enhancement and coping [32, 33].

The factors which influence the transition from hazardous use patterns to substance use disorders are less evident. Impulsivity-related personality traits, such as sensation seeking or the desire to be uninhibited, influence the transition from controlled use to hazardous use and from hazardous use to the development of a substance use disorder [31, 65, 71]. Intraindividual vulnerabilities, such as genetic factors [27, 37] and comorbid psychiatric or mental disorders [73], can be identified as characteristics of individuals who transition from substance use to a substance use disorder. In particular, high rates of incident substance use disorders have been observed, particularly for people with prior mood, anxiety, and personality disorders [72].

Almost three decades ago, Khantzian [30] developed the "self-medication hypothesis" in order to explain the development of addictive disorders where there was a prior background of mental illness or pain; this hypothesis is still discussed (e.g., [38]). Stress and stressful and traumatic life events are also important contributors to the development of substance use disorders [40]. Adolescents and young adults show an elevated prevalence of substance use disorders in several countries, with higher rates in males [29, 43, 44]. There are regions of the world, however, where middle-aged men (as opposed to adolescents and young adults) have the highest prevalence of substance use disorders (e.g., some countries in the European Union [59] and in Russia [47].

In summary, the onset of substance use is largely influenced by cultural factors and often begins at a young age. It may be assumed that hazardous use precedes the transition to a substance use disorder, but scientific evidence is limited in this regard. The majority of studies do not investigate the respective transitions separately, and longitudinal study designs risk missing the phase of hazardous use due to long study intervals. Furthermore, a large number of risk factors influence the transitions to hazardous use and then to substance use disorders. Environmental and social factors appear to be more important in the transition to hazardous consumption, whereas genetic risk factors and individual vulnerabilities appear to be more important in the transition from hazardous consumption to a substance use disorder [16, 28, 75]. Social factors also play a role in the transition from hazardous consumption to a substance use disorder. For example, during the Vietnam War, many American soldiers became dependent on heroin. After returning to the United States, the majority of these heroin addictions ceased [62, 63], but in the minority of cases where the addiction persisted, family history and genetically driven vulnerabilities are now considered to have played a major role. The risk factors and their differential influence on initiation and the hazardous progression of substance use are summarized in Fig. 5.1.

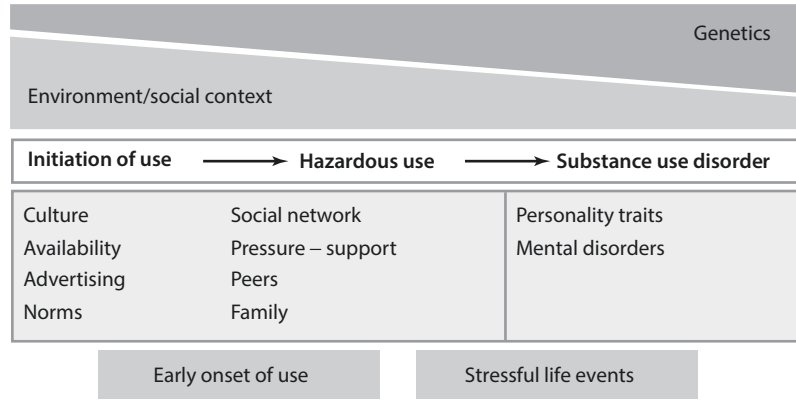

Fig. 5.1 Heuristic model of risk factors for the initiation of substance use, the transition to hazardous patterns of use, and then the transition to a substance use disorder

5.2 The Global Burden of Disease Associated with Substance Use Disorders

5.2.1 Methodology and Limitations of the Burden of Disease Estimations

To understand the burden of disease estimates and their potential limitations, it is necessary to understand how they are estimated. The definition of "substance use disorders" used in the GBD study [18] includes "substance dependence" as defined in the International Classification of Diseases Version 10 (ICD-10) [80] and "severe substance use disorders" as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [4] . Thus, the GBD studies do not include the burden of disease caused by "harmful use" as defined by the ICD-10 or "abuse" as defined in the DSM-IV [3]. As a result, the main burden reported in the GBD studies stems from alcohol dependence. In addition to dependence, the GBD category of alcohol use disorders includes alcohol poisonings and fetal alcohol spectrum disorder (FASD); however, the burden due to FASD is negligible in GBD study calculations.

The exclusion of "harmful use" or "abuse" (or the restriction to severe dependence) leads to an underestimation of the burden of substance use disorders, and the exclusion of these disorders impacts the relative burden of disease caused by alcohol versus drug use disorders; for alcohol, contrary to drug use disorders, a large part of the disease burden is actually due to harmful use/abuse. While disability outcomes stemming from the abuse/harmful use of alcohol are lower than disability outcomes resulting from dependence [66], the rates of the former outcomes are not zero [22]. Further, the prevalence of harmful use/abuse globally is almost as high as the prevalence of dependence globally [82] and is markedly higher in some countries (such as the United States [22] and in regions such as Africa [82].

Thus, when comparing current estimates of the burden of disease attributable to alcohol use disorders to estimates from previous GBD studies [57, 58], where harmful use/abuse of alcohol was not excluded, or to estimates for the same year published in the World Health Organization's (WHO) Global Status Report on Alcohol and Health [82], we can conclude that the current GBD study substantially underestimates the global burden of alcohol use disorders.

On the other hand, for drug use disorders, other than cannabis use disorders, the difference between the burden of drug use disorders as a disease condition and as a risk factor is not nearly as large as it is for alcohol use disorders (see Table 5.1); 66% of the burden from illegal drugs as a risk factor for drug use disorders stems from drug dependence (compared to 16% for alcohol).

Tobacco use disorders are a late addition to the category of substance use disorders. Only 50 years ago the WHO still clearly separated the

Table 5.1 Burden of disease associated with substance use disorders and with substance consumption as a risk factor (GBD 2017)

	DALYs lost (1000s)						
Cause	1990	95% CI	2010	95% CI	2017	95% CI	Percentage (%) change (1990 to 2017)
Use disorders							
Tobacco							
Alcohol	11,588	(9305–14,376)	16,663	(13,470–20,561)	17,463	(14,084–21,627)	51.0
Drug	15,937	(12,268–19,835)	22,716	(17,521–28,355)	27,187	(21,120–33,583)	70.6
Opioid	11,609	(8590–14,841)	17,535	(13,230–22,288)	21,485	(16,256–27,143)	85.1
Cocaine	587	(411–804)	871	(649–1142)	992	(747–1291)	69.0
Amphetamine	1073	(633–1600)	1145	(723–1695)	1184	(757–1744)	10.3
Cannabis	400	(252–601)	501	(318–737)	518	(329–766)	29.5
Other drugs	2266	(1797–2887)	2663	(2223–3208)	3008	(2553–3537)	32.7
Risk factor							
Tobacco	198,928	(184,735–215,168)	202,534	(190,633–214,512)	213,385	(201,156–226,659)	7.3
Alcohol	74,493	(65,887–84,150)	105,425	(94,784–117,365)	107,971	(96,195–120,117)	44.9
Drug	22,984	(19,048–27,276)	36,358	(30,828–42,153)	41,658	(35,318–48,195)	81.2
All DALYs lost	2,562,010	(2,417,539-2,722,707)	2,543,062	(2,346,588–2,763,048)	2,499,292	(2,285,525–2,737,391)	−2.4

Source: Global Burden of Disease Collaborative Network [20]
CI Confidence Interval

legal, "habit-forming" drugs of alcohol and tobacco from the "addictive illegal drugs" [79]. It is now accepted that both alcohol and tobacco are addictive substances, as evidenced for tobacco by all the current classifications: in the ICD-10 as "Mental and behavioral disorders due to use of tobacco" [80], in the ICD-11 as "Disorders due to use of nicotine" [83], and in the DSM-5 as "Tobacco Use Disorders" [4].

However, in the case of tobacco, the psychiatric classification of tobacco use disorders has never entered mainstream epidemiology and burden of disease research. Thus, "tobacco use disorders" was not a disease category in the latest GBD study report [20], nor for other burden of disease calculations (e.g., [78]). While part of the burden of tobacco as a risk factor shown in Table 5.1 is due to tobacco use disorders, the exact proportion is unclear, but it is likely higher than for either illegal drugs or alcohol (see also Table 5.1).

Another important aspect of the interpretation of the GBD study numbers concerns the underlying epidemiology. The methodology underlying the estimates of the prevalence of drug use disorders has been described in detail by Degenhardt and Hall [14]. With respect to alcohol use disorders, prevalence was based exclusively on a systematic review of high-quality general population surveys which measured alcohol dependence using standardized measures such as the Composite International Diagnostic Interview (CIDI; first version [64]; several versions are currently in use, most importantly the CIDI of the World Mental Health Survey [84], the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; [77]), or the Alcohol Use Disorder and Associated Disabilities Interview Schedule

(AUDADIS) [23]. Studies in several countries under the aegis of the WHO have claimed that for alcohol dependence, as well as for illegal drug dependence, standardized instruments yield similar diagnoses; however, for the prevalence of "harmful use" and "abuse" and subsequently for alcohol use disorders within the DSM-5, marked differences in diagnoses have been reported [11, 54, 74].

Even when standardized instruments are used, prevalence may differ. For example, in the early years of the abovementioned CIDI being used for the World Mental Health Surveys, dependence-item questions were asked only if the respondent had at least one abuse symptom, thereby leading to a large underestimation of dependence prevalence [21]. Similarly, small changes in wording of these items seem to have been responsible for substantial changes in Dutch prevalence figures over the past decade (see [56] for comparisons and further considerations).

Finally, while the burden of substance use disorders is high (Table 5.1), the specific GBD framework hides the fact that the majority of the burden from substance use occurs in people with substance use disorders [60, 61]. For example, on average, individuals with alcohol use disorders in treatment in Nordic countries lost on average 24–28 years of their life [76]; however, alcohol use disorders or alcohol poisoning were not listed as underlying causes of death on death certificates, and thus, in burden of disease studies, these deaths were attributed to comorbidities such as injuries and other chronic diseases [8]. This approach provides similar results for other substance use disorders, and therefore, the overall impact of substance use disorders on global health tends to be underestimated.

5.2.2 Global Burden of Substance Use Disorders and Regional Differences

According to the GBD study in 2017, more than 107 million people in 2017 were classified as having an alcohol use disorder (107.4 million; 95% confidence interval (CI): 95.9–119.7 million); all prevalence data were obtained from [20]; about 75.1 million of these people were men (95% CI: 67.3–83.3 million), and 32.3 million were women (95% CI: 28.3–36.5 million). These numbers correspond to 1.4% of the world's population in that year (95% CI: 1.2%–1.6%), 2.0% of all men (95% CI: 1.8%–2.2%), and 0.8% of all women (95% CI: 0.7%–0.9%). All percentages and rates are age-standardized to be comparable across countries, regions, and time. For drug use disorders, the following prevalence estimates were provided: 71.2 million people (95% CI: 64.0–79.8 million), approximately 47 million men (47.4 million; 95% CI: 42.4–53.1 million), and 24 million women (23.8 million; 95% CI: 21.4–26.9 million). Thus, 0.9% of the world's population in that year suffered from a drug use disorder (95% CI: 0.8%–1.1%), 1.3% of all men (95% CI: 1.1%–1.4%), and 0.6% of all women (95% CI: 0.6%–0.7%).

In the 2017 GBD study, alcohol use disorders resulted in 17,463,000 DALYs lost, accounting for 0.7% of the global burden of disease (see Table 5.1). In addition to the global burden of disease from alcohol use disorders, there is a larger burden of disease from illegal drug use disorders (27,187,000 DALYs lost, accounting for 1.1% of the global burden of disease). Temporal trends from 1990 to 2017 indicate an increasing age-standardized burden of alcohol use disorders (an increase of 51.0%) and drug use disorders (an increase of 70.6%). The increase in the age-standardized burden of drug use disorders was greatest for opioids (85.1%), followed by cocaine (69.0%), other drugs (32.7%), cannabis (29.5%), and amphetamines (10.3%) (Table 5.2).

Globally, the burden of disease due to alcohol use disorders and drug use disorders varied greatly by geography. In 2017, alcohol use disorders were highest in Eastern Europe and in tropical Latin America, with 1016 (95% CI: 875–1201) and 424 (95% CI: 341–522) DALYs lost per 100,000 people, respectively (see Fig. 5.2). The lowest burden of alcohol use disorders was experienced in North Africa and the Middle East, with 74 (95% CI: 54–97) DALYs lost in 2017; clearly, religious beliefs (Islam is the main religion in most countries of this region) played an important role. The country that experienced the greatest burden of alcohol use disorders in 2017 was Belarus, with 1153 (95% CI: 959–1384) DALYs lost per 100,000 people. By comparison, the

Table 5.2 Age-standardized burden of disease associated with substance use disorders and with substance consumption as a risk factor (GBD 2017)

	Age-standardized DALYs lost per 100,000						
Cause	1990	95% CI	2010	95% CI	2017	95% CI	Percentage (%) change (1990 to 2017)
Use disorders							
Tobacco							
Alcohol	232	(187–285)	229	(186–282)	216	(174–268)	−6.6
Drug	296	(228–366)	310	(240–387)	343	(266–424)	15.9
Opioid	217	(161–277)	240	(181–305)	270	(204–342)	24.8
Cocaine	11	(8–15)	12	(9–16)	12	(9–16)	13.2
Amphetamine	19	(11–27)	15	(10–23)	15	(10–23)	−17.7
Cannabis	7	(4–11)	7	(4–10)	7	(4–10)	−5.8
Other drugs	43	(34–54)	37	(31–44)	38	(32–45)	−11
Risk factor							
Tobacco	4502	(4218–4803)	2996	(2821–3172)	2646	(2493–2811)	−41.2
Alcohol	1574	(1383–1785)	1482	(1330–1653)	1329	(1185–1482)	−15.6
Drug	441	(368–519)	501	(425–579)	521	(441–604)	18
All DALYs lost	48,595	(45,720–51,787)	37,379	(34,572–40,490)	32,797	(30,042–35,849)	−32.5

Source: Global Burden of Disease Collaborative Network [20]
CI Confidence Interval

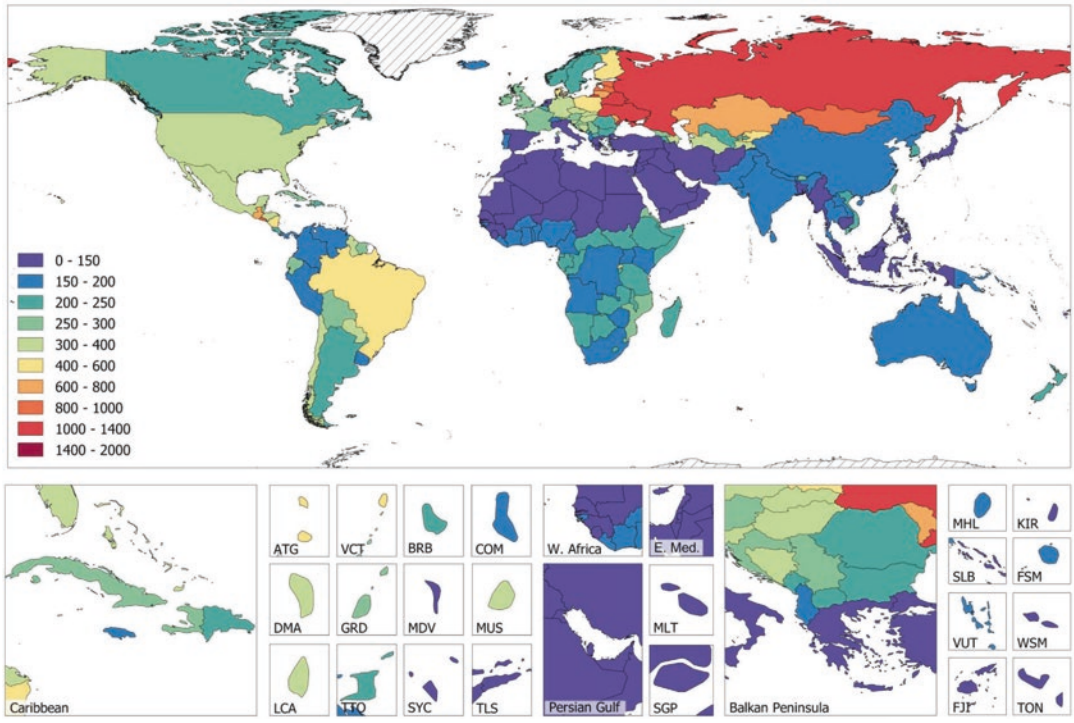

Fig. 5.2 Burden of disease in 2017 per 100,000 people resulting from alcohol use disorders (age-standardized, both sexes combined). (Source: https://vizhub.healthdata.org/gbd-compare/)

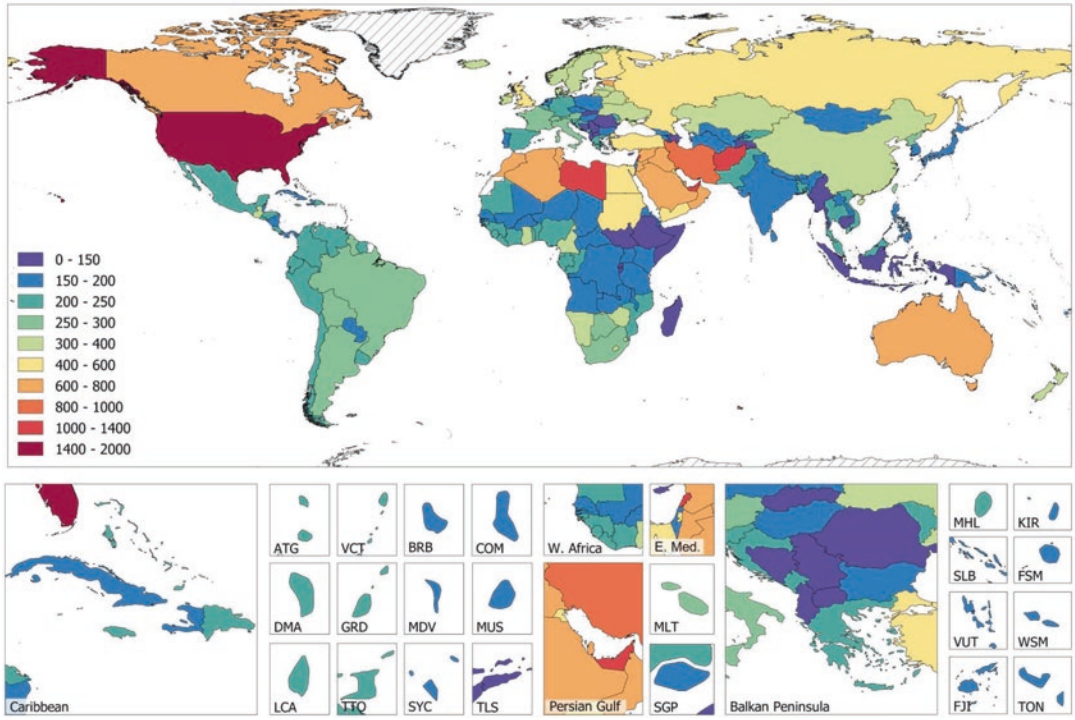

Fig. 5.3 Burden of disease in 2017 per 100,000 people resulting from drug use disorders (age-standardized, both sexes combined). (Source: https://vizhub.healthdata.org/gbd-compare/)

global burden of alcohol use disorders in 2017 was 216 (95% CI: 174–268) DALYs lost per 100,000 people.

In 2017, drug use disorders were highest in high-income North America, North Africa and the Middle East, and Australasia, with 1602 (95% CI: 1367–1843), 701 (95% CI: 514–902), and 566 (95% CI: 452–686) DALYs lost per 100,000 people, respectively (see Fig. 5.3). The largest country-level burden of drug use disorders was observed in the United States and the United Arab Emirates, with 1696 (95% CI: 1451–1947) and 1338 (95% CI: 1000–1706) DALYs lost per 100,000 people, respectively.

With respect to the burden of different categories of drug use disorders, opioid use disorders were highest in high-income North America, with 1155 (95% CI: 982–1340) DALYs lost per 100,000 people; cocaine use disorders were also highest in the same region, with 120 (95% CI: 93–154) DALYs lost per 100,000 people. Further, amphetamine use disorders were highest in Australasia, with 91 (95% CI: 60–131) DALYs lost per 100,000 people, and cannabis use disorders were highest in high-income North America, with 24 (95% CI: 15–36) DALYs lost per 100,000 people. For comparison, the global burden of drug use disorders in 2017 was 343 (95% CI: 266–424) DALYs lost per 100,000 people: opioid use disorders were responsible for 270 (95% CI: 204–342) DALYs lost per 100,000 people, cocaine use disorders were responsible for 12 (95% CI: 9–16) DALYs lost per 100,000 people, amphetamine use disorders were responsible for 15 (95% CI: 10–23) DALYs lost per 100,000 people, cannabis use disorders were responsible for 7 (95% CI: 4–10) DALYs lost per 100,000 people, and other drug use disorders were responsible for 38 (95% CI: 32–45) DALYs lost per 100,000 people.

The age-standardized burden of alcohol use disorders was greatest in upper-middle-income countries (285 DALYs lost per 100,000 people), followed by high-income countries (272 DALYs lost per 100,000 people), lower-middle-income countries (181.7 DALYs lost per 100,000 people), and low-income countries (150.4 DALYs lost per 100,000 people) (see Table 5.3). The burden caused by drug use disorders in 2017 was

Table 5.3 Age-standardized burden of disease associated with substance use disorders and with substance consumption as a risk factor by World Bank region (GBD 2017)

	Age-standardized DALYs lost per 100,000							
Cause	Low-income countries	95% CI	Lower-middle-income countries	95% CI	Upper-middle-income countries	95% CI	High-income countries	95% CI
Use disorders								
Tobacco								
Alcohol	150	(112–198)	182	(145–225)	285	(230–351)	271.8	(224–331)
Drug	187	(138–244)	219	(163–282)	400	(298–504)	709.2	(596–823)
Opioid	162	(116–216)	185	(134–243)	326	(236–418)	500.0	(416–582)
Cocaine	2	(1–4)	2	(2–3)	12	(9–16)	50.2	(38–65)
Amphetamine	5	(3–7)	8	(5–13)	20	(12–31)	30.5	(21–42)
Cannabis	5	(3–7)	5	(3–8)	6	(4–9)	13.3	(8–20)
Other drugs	14	(11–19)	18	(15–23)	37	(29–45)	115.2	(99–133)
Risk factor								
Tobacco	1198	(1065–1345)	2294	(2128–2469)	3514	(3328–3720)	3370	(3130–3622)
Alcohol	1007	(847–1195)	1259	(1111–1417)	1730	(1491–1969)	1342	(1124–1599)
Drug	267	(214–326)	381	(319–451)	640	(532–748)	921	(801–1039)

Source: Global Burden of Disease Collaborative Network [20]
CI Confidence Interval

greatest in high-income countries (709 DALYs lost per 100,000 people), followed by upper-middle-income countries (400 DALYs lost per 100,000 people), lower-middle-income countries (219 DALYs lost per 100,000 people), and low-income countries (187 DALYS lost per 100,000 people). Thus, the burdens of disease for opioid, cocaine, amphetamine, cannabis, and other drug use disorders were all highest in high-income countries and lowest in low-income countries.

Examining the burden by risk factor, the tobacco- and alcohol-attributable burdens were highest in upper-middle-income countries (3514 and 1730 DALYs lost per 100,000 people, respectively) and lowest in low-income countries (1198 and 1007 DALYs lost per 100,000 people, respectively). The drug-attributable burden was highest in high-income countries (921 DALYs lost per 100,000 people) and lowest in low-income countries (267 DALYs lost per 100,000 people).

Appendix

Table 5.4 Definitions of scientific terms

Term	Definition
2017 global burden of Disease study	The largest systematic effort to describe the global distribution and causes of a wide array of major diseases, injuries, and health risk factors, with yearly updates
Age-standardized	Rates that have been adjusted to minimize the differences in age composition of populations (used when comparing rates from different populations)
Confidence interval	A range of values where there is a given probability (in this case, 95%) that the true value (in this case, disability-adjusted life years) is contained within this range of values
Delta	The percentage change in the value of a measure between two conditions (in this case, time)
Disability-adjusted life years	A measure of population health loss or burden of disease that takes into account years of life lost due to premature mortality and years of life lost due to disability
Burden of disease	A measure of health loss from diseases, conditions, and injuries as measured by disability-adjusted life years
Incidence	The number of new cases of a disease, condition, or injury during a given period of time for a specified population
Mortality	Death
Prevalence	The number of people with a given disease, condition, or injury at any point during a given period of time (e.g., annual, lifetime, period, or point)
Systematic review	The application of search and evaluation strategies that limit bias in the assembly, critical appraisal, and synthesis of studies that are relevant to a topic
Years of life lost due to premature mortality	A measure of health loss due to premature mortality, which is calculated as an estimate of the number of years people would have lived if they had not died prematurely
Years of life lost due to disability	A measure of health loss due to disability, which was calculated in the 2010 Global Burden of Disease study as the point prevalence of a disease, condition, or injury multiplied by a corresponding disability weight (a measure of health loss caused by a disease condition compared to total health loss (i.e., death))

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Cultural Aspects and Responses to Addiction

6

Robin Room

Contents

Abstract

Use of psychoactive substances and our interpretations of the effects of the substances are affected by culture, defined broadly to include social worlds and subcultures as well as tribal, societal and linguistic groupings. Prototypical patternings of use include medicinal use, customary regular use and festival and other intermittent uses (where the psychoactivity is most attended to). A fourth pattern, addictive or dependent use, was a conceptualisation arising after the Enlightenment. Cultural norms may both encourage and discourage use and heavy use and may make the use more or less problematic. Cultural factors also shape responses to substance use, including the social handling of problematic situations and persons. Thus, there are characteristic differences between cultures in the institutional and professional location in the handling of substance use problems. In the modern world, there is substantial diffusion of practices and understandings between cultures, and in multicultural societies, drinking or drug use patterns often serve as markers of cultural distinctions. Despite all the diffusion, there are persisting cultural differences in thinking about, patterns of use of, and responses to psychoactive substance use.

R. Room (✉)
Centre for Alcohol Policy Research, La Trobe University, Bundoora, VIC, Australia

Centre for Social Research on Alcohol & Drugs, Department of Public Health Sciences, Stockholm University, Stockholm, Sweden
e-mail: r.room@latrobe.edu.au

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Norms on behaviour · Cultural practices
Social handling · Alcohol · Drugs · Concepts of behaviour

6.1 Introduction

This chapter is concerned with cultural factors in addiction. In discussing cultural aspects, we are referring to shared beliefs, norms and patterns of behaviour, both about use of psychoactive substances and about how the use should be interpreted and responded to. "Cultural" here pertains to a variety of kinds and levels of collectivity. This can range from a small tribal group, for instance, the traditional inhabitants of Easter Island in the Pacific, to a large multinational aggregation, as in a discussion of how English speakers understand addiction, in contrast, say, to French speakers.

Often in discussing cultural factors, we are dealing with multicultural situations, with a diversity of cultures or subcultures. In such situations, the particular norms and behaviours of a group may serve as markers differentiating between groups; where most people drink alcohol, for instance, abstaining from alcohol may become a mark of difference for Muslims or Mormons [33].

We also use "cultural" here to refer to "social worlds" [37, 39] within a society in which understandings, norms and behaviours are shared but in which the cultural boundaries are less marked. For instance, one can speak of a social world of heavy drinkers who know what is expected behaviour at the bar in a tavern in a particular society [10]. Are male drinkers expected to buy drinks for each other, or does each always pay just for himself? What signals are being sent between a man and a woman when he buys a drink for her and she accepts? Among young adults in Oslo, Norway, for instance, "when men buy drinks for women, this may be interpreted as a negotiation for further intimacy" [38]. Answers to such questions will be obvious to those within the social world, but may not be to outsiders.

6.2 Cultural Expectations About and Definitions of Psychoactive Substances and Their Effects

By definition, psychoactive substances change our mental state. But how we interpret that change, and how we behave under the influence, is strongly influenced by "set and setting" [43] – including our expectancies about the effects, which in turn are influenced by cultural factors as well as previous experience. Although the psychoactive effect of tobacco may not register in the consciousness of a habituated cigarette smoker, in other circumstances, the effect of tobacco use may be so strong that the user is rendered unconscious, as early Spanish observers reported in describing tobacco use among native South Americans [26]. How those under the influence of a given dose of alcohol behave differs widely between cultures, as MacAndrew and Edgerton [22] argued in their landmark work on *Drunken Comportment*. Whether or not someone taking LSD experienced a "bad trip" in the United States in the 1960s and 1970s, Bunce [9] argued, was strongly influenced not only by subcultural expectations but also by the extent of sociopolitical controversy at that particular historical moment concerning the drug.

Three social patternings of psychoactive drug use can be distinguished as prototypical: medicinal use, customary regular use and intermittent use. In many traditional societies, some drugs or formulations have been confined to medicinal use, that is, use under the supervision of a healer to alleviate mental or physical illness or distress. For several centuries after the technique for distilling alcoholic spirits had diffused from the Arab world to Europe, for instance, spirits-based drinks were regarded primarily as medicines [40]. This way of framing drug use has been routinised and made subject to official control in the modern state through a prescription system, with

physicians writing the prescriptions and pharmacists filling them. However, alongside this allopathic system in many societies, there is also legal provision for what are termed herbal, alternative or complementary medicines [12], some of which have psychoactive properties [6] – even apart from cannabis, which in the late 2010s is de facto becoming an herbal medicine in parts of North America. Drugs included in the prescription system usually are forbidden for nonmedicinal use [1], although the modern international drug control system has been fighting a losing battle to enforce this rule.

When a drug becomes a regular accompaniment of everyday life, its psychoactivity often is muted and even unnoticed, as is often the case for a habitual cigarette smoker. Similarly, in Southern European wine cultures, wine is often differentiated from intoxicating "alcohol"; wine drinkers are expected to maintain their original comportment after drinking. This may be called a pattern of *banalised use*: a potentially powerful psychoactive agent is domesticated into a mundane article of daily life that is available relatively freely in the consumer market.

Intermittent use – for instance, on sacred occasions, at festivals or only on weekends – minimises the build-up of tolerance to a drug. It is in the context of such patterns that the greatest attention is likely to be paid to a drug's psychoactive properties. The drug may be understood by both the user and others as having taken control of the user's behaviour and thus explain otherwise unexpected behaviour, whether bad or good [31]. As in Robert Louis Stevenson's fable of Jekyll and Hyde, normal self-control is expected to return when the effects of the drug wear off. In light of the power this framing attributes to the substance, access to it may be limited – in traditional societies by sumptuary rules keyed to social differentiations and in industrial societies by other forms of market restriction, including outright prohibition.

In modern societies, a fourth pattern of use is commonly recognised: addicted or dependent use that is marked by regular use, often of large doses. Where such use for the particular substance is not defined in the society as banalised, addiction tends to be defined as an individual failing rather than a social pattern. Conceptualising repeated heavy use in terms of addiction means that the categorisation becomes an explanation – an explanation of why the pattern of use continues, despite problems resulting from the use for the individual and often for others. The concept thus focuses not on the pattern of use in itself, but rather on an apparent inability to control or refrain from use despite adverse consequences.

The addiction concept became established for alcohol in general understandings of European societies in the period after the Enlightenment. Particularly as temperance movements sprang up in response to the waves of very heavy alcohol consumption that accompanied the Industrial Revolution, the addiction idea came into common use as an explanation of why backsliding was common among temperance members who had pledged to give up drinking [21, 32]. In the late nineteenth century, the concept was extended by doctors to cover other psychoactive substances, and more recently, popular and professional discourse has commonly applied it also to other behaviours such as gambling [25, 36], though not without dispute [16]. However, as terminology for psychoactive substances has shifted in the International Classification of Diseases from "alcoholism" and "addiction" to "dependence" [29], in ICD's 11th revision, ironically, a term derived from "addiction" comes up only with respect to "addictive behaviours" such as gambling, now classified alongside substance use disorders [2]. But though the addiction concept has diffused into many cultures and is applied to a range of behaviours extending beyond substance use, there are substantial differences in cultural understandings of what the concept characterises and implies [34].

6.3 Norms Concerning Use and Related Behaviour

The use of psychoactive substances in any society or cultural group is structured by norms concerning use and behaviour while and after using. Laws and regulations on these matters, such as

laws forbidding sales to or use by those under a certain age or prohibiting driving after use or regulations such as a church denomination's rubric specifying how leftover consecrated wine from a communion service is to be handled (that it is to be "reverently" consumed; [5]:198), may be described as formal norms. At least as important in structuring use are informal norms concerning use, which are often highly differentiated according to the social context [13] and to the user's demographic and social position. Bruun's division between controls at the phases of use, pattern and consequences [8] – whether use at all is disallowed or there are controls on the pattern of use or controls aiming to insulate the use from adverse consequences – describes the main strategies of both formal and informal norms in limiting the damage from substance use.

It is important to note that norms may encourage use – and indeed heavy use – as well as discourage it and may make the use riskier or more problematic. Heavy drinking or drug use is not always a matter of individual choice, but in particular social contexts may be a strong expectation. Taking alcohol as an example, in cultures where buying rounds is customary, once the round has been established, a man drinking with a group of friends will face a strong expectation to stay and drink as many drinks as there are men in the group. In a Mongolian cultural group in China, competitive drinking is a norm: "a refusal to drink signifies a refusal to engage the other on equal and respectful terms. Drinking partners take turns challenging each other to drain the cup, and the cups are inverted immediately afterward to prove the liquor is gone" [41]. Among young adult Italians, as also elsewhere in Europe, drinking games, enforced as a group ritual, serve the function of "becoming drunk quickly so as to amplify the effects of drinking: less shyness and disinhibition" [4]. Cultural expectations may thus facilitate heavy drinking and even enforce it, so that in some circumstances, addiction or dependence might better be described as located at collective levels rather than in the individual's mind or body [27]. This idea is carried by the French term *alcoolisation*, used concerning a society such as France when alcohol consumption was at its highest there in the 1950s [17].

6.4 Cultural Factors in Responses to Substance Use

Intoxication and habitual use of psychoactive substances can be problematic in many ways for those around the user, and societies and cultures respond in many ways in efforts to limit or prevent the problems. Informal responses by those around the drinker, smoker or drug user are very common (e.g. [14, 15]) – at levels ranging from a spouse's raised eyebrow to strenuous retribution.

Societies also respond to alcohol and drug problems at more formal levels. In the modern world, there is considerable uniformity across societies in the general roster of agencies and professions with responsibility for the social handling of problematic situations and persons. In most societies, there are hospitals and other health services and medical professionals, courts and police and judges, welfare institutions and social workers and churches and other faith institutions and clergy. But none of these sets of agencies and professions have clear and unchanging custody of alcohol and drug problems. Typically, all of them handle some part of drug and alcohol problems, but drug and alcohol problems are not central to the jurisdiction of any one of them [35]. The result is a diversity of competing models of how alcohol and drug problems should be handled [7]. As an eminent addiction doctor, Norman Kerr, put it already in the late nineteenth century, "in drunkenness of all degrees of every variety, the Church sees only the sin; the World the vice; the State the crime. On the other hand the medical profession uncovers a state of disease" [18].

There are characteristic cultural differences in the location of the handling of alcohol and drug problems. For alcohol problems, for instance, the welfare system has been the traditional central location in several Nordic countries; liver clinics within the medical system have played a major role in France and Italy; psychiatry has had a principal role in Switzerland and Austria [3, 19, 20]. But it is also true that, in a given society, the handling of alcohol and drug problems has often changed over time – particularly because these are "wicked problems" [42] where whatever solution is in effect will seem inadequate. As

Bruun [7] remarked about the Finnish history of the social handling of alcohol problems, "the consistent frustrations concerning the relative lack of success in fighting alcoholism made [Finland] move compulsively from one model [of response] to another."

The responses to alcohol and drug problems, both informal and formal, are thus just as subject to cultural definitions and norms as are the substance use and related behaviours. The responses are influenced both by the cultural definitions and norms concerning the substance use and by cultural beliefs and practices concerning appropriate responses. For the formal responses, general cultural and societal understandings and practices concerning the social handling of social and health problems also come into play.

6.5 Intercultural Influences and Diffusion

Almost no cultural group in the modern world is completely on its own. A particular solution to a set of problems that worked out in the cultural conditions of one society may travel far. Thus, for example, there is much about the ideas and organisation of Alcoholics Anonymous (AA) that reflects cultural understandings and practices in a particular society, the United States [24, 28]. But AA has diffused widely across the world, into cultures with considerable differences from US society. Even so, it is clear that the patterns of diffusion of AA show some regularities in terms of which societies it has flourished in, and these regularities tell us something both about core characteristics of AA and about patterns of culture [23]. And to some extent, AA practices have been adapted to the local culture [11]. Furthermore, even where AA was seen as culturally alien in some way, the news of its existence stimulated adaptations seen as more culturally congenial, and often the outcome has been AA and the adaptation coexisting side by side [30].

We have already mentioned above the tendency of cultural groups in multicultural societies to define themselves in distinction from each other, with drinking or drug use practices fairly often used as markers of the distinctions. On the other hand, it is clear that there is also some assimilation: immigrant groups take on practices from the receiving society, often forming a new cultural bricolage [33]. Influences and diffusion are also common between societies and cultures. Such influences are carried by four major forces: mass media, producers and other economic actors, intergovernmental bodies and agreements and the professions. News reports, television and film entertainment, and now also internet channels, convey information and images between cultural groups, perhaps particularly between youth cultures in different societies. In an increasingly globalised world with diminishing trade barriers, global corporations and other economic actors (and their equivalents for illicit drug markets) actively and tirelessly try out promotion methods and materials which have worked elsewhere in new cultural settings. Dissemination and influence also flow through the international drug and tobacco treaties and the agencies which implement them, as well as increasingly through other agencies such as international non-governmental organisations in a cross-national policy community. And doctors, police and other professionals, through professional societies, journals, newsletters and meetings, diffuse ideas, evidence and practices internationally.

Despite all the dissemination, cultural differences persist. In terms of cultural differentiations in psychoactive substance use and problems, and in the societal and cultural responses, it is possible to point to trends both of change and of stasis and both of convergence and of divergence, depending on where one looks. In thinking and acting across cultures concerning alcohol and other drugs, it is wise to take into account that even matters that are taken for granted in a given society or culture, or that are assumed to be universally valid in a profession's thinking, are often understood differently in different cultural traditions.

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Prevention Strategies

7

Roland Simon and Gregor Burkhart

Contents

Abstract

Prevention has the potential to positively affect problem substance use and related behaviors such as delinquency, violence, and sexual behavior. Science-based prevention interventions and strategies focus on the key determinants of successful socialization, such as nurturing and safe environments, social norms, parental skills and monitoring, executive and social skills, and impulse control. Information provision is necessary but as such contributes little to changing behavior.

Thus, universal prevention addresses the population at large and targets the development of skills and values, norm perception, and interaction with peers and social life; selective prevention addresses vulnerable

R. Simon (✉)
IFT Institute for Therapy Research,
Munich, Germany

G. Burkhart
EMCDDA, Lisbon, Portugal
e-mail: Gregor.Burkhart@emcdda.europa.eu

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groups and focuses on improving their opportunities in difficult living and social conditions; and indicated prevention addresses vulnerable individuals and helps them to deal and cope with the individual personality traits that make them more vulnerable to escalating drug use. Environmental prevention can complementarily and effectively change human behavior by modifying its regulatory, physical, and economic context. This means to subtly alter social and other environmental cues and social norms and their perception. Effective examples range from intervening at society level through market regulations of substances and changing the physical environment of nightlife and neighborhoods, to more rule-setting and monitoring within families.

The challenge for drug prevention lies therefore in helping people to adjust their behavior, capacities, and well-being in fields of multiple influences — such as behavioral opportunities and incentives, perceived norms, interaction with others, and their own personality traits — in order to reduce risk behaviors related to substances. The key challenge for this century, however, is to bridge the gap between the advances made in prevention science and the implementation of effective programs and local policies in prevention practice.

Keywords

Environmental prevention · Universal prevention · Selective prevention
Family-based prevention · Indicated prevention Norms

7.1 Introduction

Drug prevention is traditionally conceived of as interventions or policies to avoid or delay the initiation into substance use by adolescents. It is a key element of national and international drug policies. Prevention is thought to act on the demand reduction side of drug interventions, helping people to contain their use (or problem use) of psychoactive substances and their negative consequences. This understanding of prevention is complementary to treatment (which targets recovery and cure) and harm reduction (which helps people avoid the secondary negative effects of the use or problem use of addictive substances).

7.1.1 Factors for the Development of Problem Drug Use

Neuroscience has considerably contributed to prevention by providing an explanation why and how the developing brains of adolescents are particularly vulnerable to the noxious effects of alcohol, tobacco, and illicit drugs and to environmental factors. Prevention work can use findings from neuroscience to tailor interventions to the peculiarities in the functioning of adolescents.

Neuroscience has also (re)introduced concepts such as personality traits and temperament as risk factors, giving a longer-term perspective to prevention, which starts in early childhood. Many prevention professionals still focus on substance use, which should in their understanding be prevented altogether or early detected and treated. However, other variables may be of crucial importance in the transition from experimental use to substance use disorder (SUD). The same variables that predict initial acute drug effects and early use may significantly contribute to continued use, escalation, and dependence [12]. Recent research has introduced the common liability model, which suggests that early-manifesting traits such as neurobehavioral (i.e., cognitive, affective, and behavioral) disinhibition predict both early initiation of substance use and rapid escalation into problem use. Shared genetic and environmental influences and early externalizing behavior may lead to later substance use problems. Other personality traits, such as high levels of sensation seeking and low levels of shyness and avoidance, have shown to increase the risk of progressing from smoking to cannabis use. Hopelessness and sensation seeking were predictive for using alcohol, tobacco,

and marijuana. Sloboda et al. [41] provide an exhaustive revision of the risk factor models relevant for prevention, which include many developmental factors in early childhood. Instead of detecting and addressing drug users, these findings point to a need to early target individual vulnerability traits.

Findings in the field of neuropsychology have shed light on why information provision does not deter young people from drug use and other problem behaviors: at their age, behavior is determined more by social context than by individual choice, and neurobiological imbalances may result in impaired judgment of risk. More crucially, though, adolescents respond more intensely to emotional and social stimuli and have increased awareness of others' opinions. Reward seeking is increased in the presence of their peers when the brain's socio-emotional system is stimulated. The interplay of these processes explains why adolescents take risks like substance use more often in peer group environments. Therefore, it seems to be normative, biologically driven, and to a certain degree inevitable and evolutionary function that adolescents are prone to risk-taking explorations during adolescence. Mature judgment needs time to develop, and therefore, cognitive–informative strategies seem unlikely to make adolescents wiser, less impulsive, or less short-sighted.

7.1.2 An Overarching Model for Prevention

The last section has described a number of factors influencing the risk of developing problematic patterns of substance use. The following section aims to show that the challenge of prevention is more than just avoiding or delaying substance use. Instead, it should help youth to positively develop from childhood to adulthood and to adjust their behavior, capacities, and well-being to their own personality traits influenced by, among others, living conditions, social norms, interaction with peers and parents, and opportunities. Prevention could therefore be defined as evidence-based socialization where the primary focus is sustaining healthier behaviors. It includes preventing or delaying substance use initiation or related behaviors, reducing their intensification, or preventing the escalation of use into problem use.

The three classical forms of prevention defined by the Institute of Medicine [35] are based on people's vulnerability, which was found more practical for substance use prevention than the medical paradigm of primary, secondary, and tertiary prevention. While the latter works fine for the natural course of, for example, cancer and infectious diseases, it seems less adequate to describe human behavior.

The four forms of prevention described below address the most relevant spheres of behavior influence: opportunities, incentives, and behavioral norms are targeted by environmental strategies; interaction with peers and social life by universal prevention; social conditions and exclusion by selective prevention; and personality traits by indicated prevention. This simplified classification provides us with an overview of the different preventive approaches taken. Prevention can in addition be segmented according to the level of environment on which it is acting, into macro, meso, and micro level [3]. As the majority of prevention activities focus in practice on substance use and problem behavior in general, they mostly do not differentiate between alcohol, tobacco, and illicit drugs.

7.1.3 Considerations for Practice

The considerations above have manifold implications and underpin the following considerations for practice:

- Adolescent impulsivity and risk taking have an important evolutionary function. Prevention, though, can provide skills and nurturing environments in order to reduce the potential harm of these specific adolescent characteristics.

- Information provision has little impact on behavior, particularly of adolescents and in "hot" situations.
- Cultural values, descriptive norms, and the social acceptability of use influence people's initiation into substance use and problem behavior directly as well as indirectly through parenting practices.
- An increase of normative beliefs, that is, giving the implicit impression that most or many people do engage in a given problem behavior, is an important harmful effect of sub-optimal public messaging, for example, in mass media campaigns that were not perfectly pretested and evaluated.
- Publicly visible sanctions and reinforcement of social norms, for example, in schools and nightlife venues, have important potentials for changing and sustaining behavior, while legislation, which prosecutes individuals, often fails to dissuade adolescents from continuing to use substances.
- Informal social control and social sanctions (from family and peers) may have more of an impact than the certainty and severity of formal legal sanctions [37].

7.2 Prevention Strategies: Definitions and Effects

A large proportion of the general public and substantial numbers of policy makers have, for some time, seen drug prevention as purely informing or warning young people about the effects or dangers of drugs. Quite logically then, mass media campaigns (see Sect. 7.2.1) were often the first choice of prevention intervention. Environmental prevention strategies aim to alter the immediate regulatory, cultural, social, physical, and economic environments in which people make their choices about substance use (see Sect. 7.2.2).

Prevention approaches are classified according to differences in the vulnerability (and risk) of the target group. For universal prevention (see Sect. 7.2.3), all members of the population are assumed to share the same general risk for substance use problems, although the risk may vary greatly between individuals. Selective prevention (see Sect. 7.2.4) applies social and demographic indicators that roughly indicate increased levels of vulnerability among some groups. In indicated prevention (see Sect. 7.2.5), vulnerable individuals are screened and have to be defined on the basis of properly diagnosed risk conditions, such as attention deficit disorder or conduct disorders.

7.2.1 Mass Media Campaigns

Mass media campaigns can reach large and heterogeneous audiences and have shown to be beneficial in promoting health behaviors like healthier nutrition, physical activity, and participation in screening for breast and cervical cancer [50]. However, they seem to be much less successful in discouraging problem behaviors, which have a strong impulsive component. While some positive effects on tobacco smoking have been found, there is actually no evidence that simply informing adolescents about the effect of drugs has a beneficial impact on their illicit drug use, as a Cochrane Review [2] confirms. Mass media campaigns seem to be more effective in tackling adolescent use of legal drugs and when they target parents instead of young people [10]. Perceptions of normality seem to play an essential role in their success and failure, which can also lead to detrimental effects: intention to use cannabis seemed to have increased in certain subgroups with greater exposure to a US warning campaign – most likely due to misperceived high popularity and prevalence of marijuana use.

It is an important ethical concern that mass media campaigns may have iatrogenic effects by changing normative beliefs, resulting in higher intentions to use. This is even more problematic, as the target population has typically not requested this (potentially harmful) kind of social intervention.

Against this background, the lack of adequate evaluations of media campaigns is a concern. In Europe, only the Netherlands and the UK have assessed the effects of these campaigns on behavior or intentions, while the large majority of reported campaigns have not been evaluated at all or only assessed how the campaign was perceived or affected knowledge alone.

7.2.2 Environmental Prevention

This approach takes into account that potential substance users are influenced by a complex set of factors in their environment, including social norms, defining what is considered normal, expected, or accepted in their reference group; the rules, regulations, and taxes of their state; the commercial advertisements to which they are exposed; and the availability of alcohol, tobacco, and illicit drugs. Many human behaviors performed everyday are automatic and are generally reactions to common and familiar stimuli. This demonstrates the importance of environmental and social cues and automatic processes in influencing behavior. It may explain the limited success of prevention approaches that focus solely on individual responsibility for decision-making and self-control.

The purpose of environmental prevention policies and interventions is to limit the availability of opportunities for unhealthy or risky behavior and/or promote the availability of healthy ones. This approach differs from traditional behavioral prevention approaches as it targets the automatic system of behavior (one that doesn't require deliberate cognition). Thus, it requires lower individual "agency": individual personal resources such as conscious decision-making, motivation, and intent are less important in these types of intervention.

Environmental prevention strategies often entail changes at the macro level (legislation or society), such as market control using taxes and publicity bans or coercive measures including age controls and tobacco bans, which are effective but often resisted in parts of the population. Regulations and market interventions are currently considered as the only evidence-based mechanisms to prevent the harm caused by commodity industries [34]. Efforts to create protective and positive school and family climates also belong to environmental prevention.

7.2.2.1 Environmental Influences in Schools and Communities

There is evidence that the school climate and the nature of the school environment substantially influence substance use and violence in school. Students' perceptions of school safety, teacher support, and whether they are treated fairly are also related to substance use. Interventions that increase student participation, improve relationships, and promote a positive school ethos appear to reduce substance use.

Other strategies at the meso level include municipal strategies to reduce public nuisance, drug "policies" in schools, targeted policing, conditional venue and event licensing, fines and venue design guidelines, and community action strategies such as neighborhood watch schemes.

7.2.2.2 Environmental Influences in Nightlife

The known environmental determinants of alcohol abuse and violence also apply to nightlife settings: dirty conditions, poor ventilation, high levels of noise and music, low comfort, high density of patrons, predominant male patronage, high numbers of intoxicated patrons, and high boredom [33]. A European review [23] found that important environmental contributions to alcohol-related problems include a permissive environment, discounted drinks promotions, poor cleanliness, crowding, loud music, and poor staff practice. Environmental approaches addressing these factors to reduce drug use and other risky behaviors may be more profitable for a business, improve its image, reduce the risk of city and police interference, and limit problems in its neighborhood.

Reviews of prevention interventions in nightlife settings conclude that they can effectively reduce high-risk alcohol consumption, alcohol-related injury, violent crimes, access to alcohol by underage youth, and provision of alcohol to intoxicated people. Providing information and pill testing were not considered evidence based. Interventions such as "responsible beverage services" or "designated driver programs," often backed by the industry, are less effective, especially if they are not enforced. The most effective strategies were those that combined training, cooperation, and enforcement with "classical" environmental measures such as taxation, reduced blood alcohol concentration (BAC) limits for driving, and reinforced minimum legal purchasing age.

7.2.2.3 Environmental Influences within Families

The climate of norms, parental modeling and behavior, and the associated exposure to sensorial and visible cues such as substances, screens, and food are microenvironments that subtly shape adolescent behavior and attitudes. Later in this chapter, we will describe family-based programs that aim to improve the behavior of children and young people through better parenting. In this section, we address some aspects of families that are not necessarily related to direct parent–child interaction but reflect micro-level environmental influences on the socialization of youth.

One aspect is the amount of pocket money, which has been found to be associated with increased prevalence of risky alcohol use and higher odds of smoking, getting drunk, using cannabis, and using ecstasy, even after controlling for socioeconomic status and other aspects. The role of families' socioeconomic situation in this respect is still unclear. How parents tell their own substance use history may also play a role. A more recent study found an association between parents admitting their own past drug use in detail and teenagers having a more positive attitude to substances [24].

Parental ingenuousness about their offspring's substance use can have a protective function in the sense of a Pygmalion effect. In a longitudinal study [28], adolescent users whose parents indicated that their children used marijuana at baseline were more than twice as likely to continue use, compared to children of parents who assumed that their children had not initiated marijuana use, even if this assumption might have been wrong. Obviously, monitoring and family rules play major roles in creating protective environments, but since such elements imply an active role by parents, we discuss those in the section dedicated to family-based prevention.

7.2.2.4 Environment, Social Norms, and Substance Use

Even if environmental prevention targets predominantly legal drugs and antisocial behavior, its approaches are important for the whole prevention field because early, widespread, and accepted use of alcohol and tobacco is associated with illicit drug use in many countries. Alcohol has a key role in the initiation of illicit drug use, especially among adolescents. European School Survey Project on Alcohol and Other Drugs [13] data for 22 countries showed that 86% of the 15- to 16-year-old students who had used ecstasy during the last month had also consumed five or more alcoholic drinks on one occasion. Similar relationships were found for alcohol with cannabis and cocaine. In prospective longitudinal studies, tobacco smoking has been shown to mediate the initiation into cannabis and predict an earlier initiation [1]. It seems that the social and physical contexts of consumption are also influencing the level of alcohol, tobacco, and illicit drug use in the same way. Environmental prevention focuses on these contexts.

The effectiveness of environmental prevention is well established in the alcohol and tobacco fields. At the macro level, taxation and regulations have been found to be effective, reducing alcohol use and related problems [49]. At the meso level, a study showed that adolescents living in areas with lower outlet density and proximity were drinking less. In a US study [38], a legal age of below 21 years for buying alcohol was associated with an increased risk of binge drinking later in life. Additionally, drinkers who lived in states with lower minimum drinking ages were more likely to drink alcohol heavily, but not to consume more overall or to drink more frequently.

Guidelines for the creation of better environments in recreational settings, such as the "safer dancing" guidelines, were developed since the end of the 1990s. They include access to free drinking water, rules on glassware and noise, monitoring of interior space in respect of risky sexual or aggressive behavior and drugs, training staff for medical emergencies and handling drug-related problems, and excluding "problem" patrons (drug dealers, drug users, persons carrying weapons).

Besides the perceived availability of substances, environmental aspects such as cultural values, descriptive norms, and the social acceptance of use seem to influence initiation into substance use.

Close contact with substance-using peers is strongly related to individual substance use. Establishing an overarching environment of disapproval may be an effective means of preventing cannabis use by adolescents. Overall, normative beliefs are also important factors in the success or failure of interventions. While several studies confirm that behavioral change is mediated by descriptive norms, the social norms approach has to be used with caution as social groups may also develop minority norms that deliberately deviate from the healthy injunctive norm that is being promoted [9].

It is unlikely that environmental prevention will have much of an impact on the behavior of highly vulnerable individuals. However, the prevention paradox postulates that the majority of alcohol-related problems in a population are associated with low to moderate drinkers simply because they are much more numerous than heavy drinkers. A study in 23 European countries [11] confirmed this for adolescent boys' and girls' annual consumption and heavy episodic drinking; similar results were found in Brazil. Still, there are limitations to this concept. A minority of people with frequent heavy episodic drinking accounted for a large proportion of all problems in one study [11], and most illicit drug use was found in the high-risk group (15% of the sample) in a different study.

The practical consequence of the prevention paradox is that all available approaches should be used: environmental and universal prevention strategies should aim to reduce initiation and overall levels of substance use, and targeted strategies should address particularly vulnerable subgroups and individuals, addressing harm related to early-age drug use or frequent cannabis use.

7.2.3 Universal Prevention: Intervening with Populations

Universal prevention addresses the population at large, regardless of differing vulnerabilities of individuals or subgroups. It aims to reduce substance-related risk behavior by providing necessary competences to avoid or delay initiation into substance use, acting like a "behavioral vaccine." In Europe, at least, universal prevention predominantly takes place in schools, as they facilitate access to the large share of the youth populations.

The overall effectiveness of school-based universal prevention has been repeatedly questioned, but there is abundant evidence from reviews (e.g., [5, 16, 32, 43]) that programs based on the social influence approach have consistently been more effective than programs based on any other approaches. The approach consists of components such as social skills training (listening, making compliments, empathy, and communication), strengthening personal skills (goal setting, coping, identifying feelings), and correcting normative beliefs (i.e., on the level of acceptance and use of substances among peers). It has to be delivered in an interactive way that engages young people. While life skills components of such programs are well known and have been well researched, the role of social norms (see Sect. 7.2.2) has gained the attention of researchers only more recently. Evidence from trials suggests that this approach might be an additional pathway for reducing substance-use-related harm [29, 30].

Even if the effects of school-based prevention at the intervention level are often small, social influence programs can be an important mechanism for transmitting societal norms on substance use to young people. They can help them to further develop their skills to make and implement safer decisions about substance use or in situations where others are using. They also offer the potential of creating a more sympathetic environment for complementary systemic strategies, such as restrictions on advertising for legal psychotropic substances [32]. In this field, we find some "manualized" programs which provide detailed material and guidance for teachers and pupils.

"Unplugged" is the only multisite randomized controlled trial (RCT) of a school-based prevention program in Europe to date. This comprehensive social influence program consists of twelve 1-h interactive sessions delivered by class teachers. It has proven its effectiveness with respect to

drunkenness and cannabis use and problematic drug and alcohol use among boys, but not among girls [47]. Participation in the program was also associated with positive effects among adolescents from a low socioeconomic level. The program was implemented in several additional countries, in Eastern Europe, South America, and Asia, replicating in some cases the initial promising outcomes.

The "Good Behavior Game" (GBG) is a way of managing whole primary school classes during regular lessons and socializing children to be self-controlled, emphasizing the role of significant others (teachers and peers) in children's social adjustment in school. Children systematically learn over a period of one school year to respect basic class rules. RCTs reported a beneficial impact up to the middle school years and even young adulthood including reductions in alcohol and drug dependency disorders and a reduction in many other behavioral problems. Substances and substance use are not explicit themes in GBG but targeted through a focus on socialization. "Unplugged" and GBG can be accessed at the Xchange registry[1] of the EMCDDA.

7.2.4 Selective Prevention: Intervening with (Vulnerable) Groups

Selective prevention intervenes with specific groups, families, or communities that may be more likely to develop drug use or progress into dependency. Often, this higher vulnerability to problem drug use stems from social exclusion, lack of opportunities, and less nurturing family or community environments. For example, European countries most frequently report about young (drug law) offenders, youth in deprived neighborhoods, ethnic minorities and immigrant groups, school dropouts, students who are failing academically, and vulnerable families as target groups of this type of intervention. This means that – different from universal prevention – the situation and vulnerability pattern of a given target group has to be studied before starting the invention. Since this vulnerability assessment relies on the group level, individual risk cannot be assessed. Evidence for the effectiveness of selective prevention is currently limited because evaluations are difficult and scarce.

The effective components in selective prevention seem to be virtually the same as in universal prevention. Interventions that do not solely address drug use, adapt to young people's experiences, and avoid rigid abstinence-oriented messages have proven to be more effective. They address social needs connected to drug use, rather than drug use behavior as such which in these populations are considered as just one of several expressions of behavioral maladjustment.

In summary, prevention that targets vulnerable people may moderate the effect of an early developmental disadvantage, its translation into social marginalization, and progression into substance abuse. Interventions delivered during the early school years that aimed to improve educational environments and reduce social exclusion also had a moderating effect on later substance use [45], without specifically targeting youth who experiment with drugs. Such prevention programs can also be beneficial in behavioral domains beyond substance use, such as violence, delinquency, academic failure, teenage pregnancies, and unprotected sex. Smoking, drinking, safe sex, and healthy nutrition among adolescents share common factors: beliefs about immediate gratification and social advantages, peer norms, peer and parental modelling, and refusal self-efficacy.

While in Europe the concept of selective prevention has been accepted quite well, several researchers have raised concerns regarding possible iatrogenic effects when vulnerable young people are grouped together in selective interventions. Problem behavior may get worse when members of this selective group model to each other's problem behavior ("deviance modelling"), thereby corroborating their belief that their deviant behavior is "normal" while the surrounding social environment is not ("norm

[1] http://www.emcdda.europa.eu/best-practice/xchange_en

narrowing"). Such iatrogenic effects are unlikely to occur in universal prevention, where some program evaluations in school and family settings [26] found that the more vulnerable subgroups within the target population benefited more from the intervention, possibly because they adjusted their behavior to that of the "conventional" majority.

Increasingly in the EU, vulnerable groups have been primary targets for prevention interventions. In most cases, these were young offenders and pupils with academic and social problems, who share many risk factors with problem drug users. While young offenders as a group are easy to identify, interventions provided are often not appropriate for them. The manualized program for young offenders (FreD) takes a more specific approach. Developed at the national level in Germany, it has been expanded to and adapted by one-third of all EU member states. Some countries have reacted specifically to the increased vulnerability to drug use found among pupils in vocational schools, for example, with tailored programs to generally improve literacy and numeracy levels among disadvantaged students. At the community level, municipalities in Northern Europe and in Italy aim to combine drug and alcohol policies, action plans, and youth work through binding cooperation agreements between local authorities and nongovernmental organizations.

Early intervention approaches provide social, emotional, and learning support to children in the early years of life. They can delay or prevent future problems including substance misuse more effectively and economically than intervening only when problems appear. Parenting programs at a local level can be an essential part of early intervention, but proactive parental work and training is still an exception.

As the prevention of different problem behaviors belongs to segregated political portfolios in most countries, a common, cohesive, coherent, and efficient approach to adolescent vulnerability is often lacking. In those few countries where such policy responses to multiple risk behaviors have emerged, there is increasing evidence for the effectiveness of such approaches [21].

7.2.5 Family-Based Prevention: Universal and Selective

Many parents in the Western world tend to assume that a close, warm, and open relationship with their children is protective against SUD, by providing them with a space to test their own boundaries. Recent research has provided considerable support for the idea that not only parental support but also monitoring are strong determinants of lower prevalence levels of adolescent risk behavior. Research indicates that the "authoritative style" (strict and warm) is the most protective against substance use, while the "neglectful style" (lenient and distant) increases the risk of drug use. Research however is as yet inconclusive as factors beyond parenting style, such as parents' drug use, emotional support and warmth, family structure, and influence of culture have to be considered as well [7, 19].

Monitoring and warmth together appear to predict adolescents' social and interpersonal perceptions of drug use and their actual drug use. A recent study in the Netherlands suggests that clear parental rule-setting is more strongly related to lower levels of risk behaviors in adolescents than are more general parenting practices. The findings give additional etiological underpinning to an intervention study that tested the Swedish Örebro program in the Netherlands. The program combines parent and student interventions and establishes simple drinking rules, coordinated between home and school ([25]). It can be accessed at the Xchange registry[1] of the EMCDDA.

Strict family rules about drinking were also tested against a (harm minimization) model according to which alcohol use is a part of normal adolescent development while parents should supervise their children's use to encourage responsible drinking. McMorris et al. [31] compared adolescent alcohol use and related harms among adolescents in Washington State, USA, and Victoria, Australia, two states that have, respectively, adopted zero tolerance and harm minimization policies. Despite those differences, family context was related to alcohol use and harmful

use in a very similar way, but adult-supervised alcohol use resulted in higher levels of harmful alcohol consequences. Both Mediterranean drinking cultures and Danish drinking parties where parents organize and supervise alcohol consumption among their teenage offspring are based on this rationale of adult-supervised alcohol use.

The need to break intergenerational cycles of poor parenting practices was addressed by Hill et al. [22], who examined the extent to which interactions between behavioral disinhibition and family management during adolescence (from age 10) predict alcohol abuse and alcohol dependence at age 27. Young people who were high in behavioral disinhibition were at increased risk of later alcohol abuse and dependence but only in consistently poorly managed family environments, while in consistently well-managed families, high levels of behavioral disinhibition did not increase the risk of later alcohol abuse or dependence.

Most of the effective family-based programs contain elements of monitoring, rule-setting, and contingency management. A systematic review [4] of programs for substance-affected families found interventions to be effective when their duration was longer than 10 weeks and when they involved components of parenting and children and family skills training. Proximal outcomes (e.g., knowledge, coping skills, and family relations) were stronger than more distal outcomes (e.g., self-worth and substance use initiation). Apart from a few studies, the long-term effects on young people's substance use, delinquency, mental health, physical health, and school performance have rarely been assessed in the evaluations. Several of these programs can be accessed at the Xchange registry[1] of the EMCDDA.

Overall, across universal and selective interventions, Cochrane Reviews found good evidence that family-based prevention interventions are effective in reducing young people's alcohol, tobacco, and drug use [18].

7.2.6 Indicated Prevention: Intervening with (Vulnerable) Individuals

Indicated prevention aims to identify individuals with behavioral or psychological problems that may be predictive of developing problem substance use later in life and to target them individually with special interventions. Indicators of increased risk can be dissocial behavior and early aggression as well as alienation from parents, school, and peer groups. The aim of indicated prevention is not necessarily to prevent substance use but to prevent or at least delay development of a dependence or to prevent more risky patterns of use. Problematic substance use is seen as just one among the behavioral or mental health problems that lead to SUD, which can be diagnosed at the individual level. This is highly relevant for practice and policy because vulnerabilities at the social (demographic) level, those at the individual (mental health) level, and those at the environmental level affect the pathways to substance use disorder in quite distinct ways and phases of life [41]. The focus of the respective prevention strategies should match the kind of vulnerability found at the target populations.

There are no systematic reviews or meta-analyses assessing the effectiveness of interventions that target individuals with behavioral or psychological problems independent of substance use. Nevertheless, the few available single intervention studies in Europe tend to be better designed and to provide stronger outcomes than those in selective prevention.

For example, the school-based program "Preventure" targets adolescents (aged 13–14 years) with specific personality risk factors for early-onset substance use disorder and other risky behaviors in only two sessions. Even when implemented by nonspecialists, participants showed a lower likelihood of later onset of drinking or a less steep increase in consumption and binge drinking. Effects beyond substance use included reduced scores in depression, panic attacks, truancy, and shoplifting [36]. SKOLL

(www.skoll.de), a 10-week program of training in self-control for young people with risky substance use, was implemented nationwide in Germany at schools and in other settings. Results showed reductions in drug use and risky behaviors over the course of several months, more self-confidence, alternatives to risky behavior, and social contacts. Those young people who were more vulnerable benefited the most.

Brief interventions (BI) consist of one-to-one counselling sessions, sometimes including follow-up sessions, which are delivered by trained health and social workers to people at risk. BI were found to be effective for alcohol-related problems when delivered in the primary healthcare system and colleges. This approach is increasingly used also to target young people and their cannabis use. Putting these one-to-one personal interventions to scale continues to be a challenge, and their overall effectiveness is under debate [8, 17, 20, 44]. They are increasingly delivered via interactive counselling websites or m-health technologies [15], which might attract substance users who would not approach any regular assessment or counselling service. BI often makes use of the technique of motivational interviewing (MI), which in a Cochrane Review [42] showed significant effects in short- to mid-term follow-ups in comparison to nonintervention. For club-goers, Kurtz et al. [27] suggest that even simple assessment and feedback interviews can reduce substance use.

As young alcohol or drug users mostly have no self-perception of problems, screening and assessing them for possible problems is a particular challenge. In Europe, drug tests are very rarely used for assessing drug-related problems in pupils (under suspicion), and in most countries, testing is not allowed since they are judged as ethically questionable and ineffective [14], In the USA, by contrast, even random drug tests seem to be common.

Overall, indicated prevention could reduce the negative impact of neurobehavioral problems, such as early aggression on later substance use, and other problem behavior from childhood on.

7.2.7 Considerations for Practice

The considerations above underpin a number of considerations for practice:

- The use of mass media campaigns should be considered with highest caution, since warning campaigns can backfire. They are useful if targeted at parents, if they correct erroneous normative beliefs, or if they support environmental strategies by explaining their rationales (e.g., "protect our youth from industry influences").
- The underused potentials of environmental prevention are gaining more attention. Public (often local) policies modifying the regulatory, economic, and physical environments, which inconspicuously shape human behavior, can achieve positive changes in substance use behaviors and sustain them. An intrinsic dilemma for policy makers might be that such strategies are either invisible or unpopular: contrary to mass media campaigns, they don't deliver political capital.
- Universal prevention in schools should focus both on conveying social and personal behavioral skills by means of evidence-based programs and on guaranteeing safe and positive school climate.
- Selective prevention is in Europe often delivered through prevention services rather than by programs. There is much potential for improvement of intervention content (skills and competence training instead of information and counseling). Concerns exist about their safety because of the small number of evaluations and the particular risk of grouping young people with problem behaviors together.
- Indicated prevention offers an important potential of targeting early temperamental and behavioral issues, which might increase the propensity for SUD later in life. Few promising programs are available, but coverage is very low, and the most frequently found intervention type targets regular substance users

with brief interventions. New e-health methods might reduce the obstacles in scaling up their delivery.
- Families are an important but underused resource in helping adolescents in adjusting their behavior to environmental and social influences. Evidence-based approaches range from environmental (rules and monitoring) to universal and selective (parenting techniques). However, reaching and engaging parents and promoting parental monitoring is a major challenge for implementation. For this purpose, mass media campaigns can be helpful.

After careful development and evaluation of effects, prevention strategies and programs need proper implementation to affect a relevant part of the population.

- Despite the limited evidence, it is possible that mass media campaigns still have a wider role to play in comprehensive social marketing strategies, such as those trying to support environmental strategies.
- A practical problem for different strategies is that many parents cannot be reached using the classic instruments such as parents' evenings or invitations for a talk during office hours.
- Some universal programs might predominantly attract the well-off, low-risk families; however, effective (often selective) programs tackle this imbalance by offering transportation, childcare, and food at the venues – elements that might be essential for families in need.
- Addressing all families using a universal prevention approach might allow more vulnerable families to adopt educational, normative, and behavior models from the more conventional families in the same group, and more vulnerable families may profit the most.
- As developing prevention programs is expensive, transfer of well-established programs should be a very interesting approach. Despite some difficulties and hesitations [40], a number of manualized prevention programs from North America have been successfully transferred to European environments.

More details on these programs, results of their effectiveness in European evaluation studies, and the experiences of practitioners in implementing them can be found at the EMCDDA Xchange registry[1].

7.2.8 Transfer of Prevention Technologies

Prevention research in North America is generally more developed than in Europe. This is related to structural differences in social policies and prevention practice as well as to research funding. In the European Union, however, services such as health and social care and education are generally of higher quality and are widely available, which is not the case in most other regions of the world. As a consequence, in these regions outside of Europe, prevention programs are developed or used to promptly address a range of emerging social problems; this approach might hence be a consequence of a lower availability of universal social, youth, and health services.

The evidence for the effectiveness of substance use disorder prevention comes almost exclusively from evaluations of sophisticated manualized programs (e.g., [18, 46]). Their implementation is more likely to be manualized to assure accuracy and reach of implementation. Such programs are also more likely to have been pretested, to have been checked for unintentional (iatrogenic) effects, and to prove positive behavioral outcomes. Overall, such interventions could be considered "high-tech prevention." In medicine, most people would naturally expect such a level of "technology assessment", especially of medications, before they can be distributed to the population. In Europe, such high-tech programs are rare, especially outside classrooms. Prevention strategies consist in most cases of varying combinations of policies for vulnerable populations; activities for school-aged youth to raise their awareness, self-competence, social skills, and/or autonomy; and events and advice for parents and in some countries in local environmental prevention policies. Such approaches make use of the existing infrastruc-

ture, and they allow for innovation and adaption to local needs and perceptions. However, they are sometimes based on little more than common sense and, except for the environmental approaches, often lack evidence of effectiveness and have possible iatrogenic effects. In broad terms, it seems that the relative lack of prevention infrastructure in the USA has led to more prevention research and program development. Europe, on the other hand, relies on a more elaborate infrastructure but spends much less energy on ensuring the quality, effectiveness, and safety of interventions.

Well-developed programs from North America have been culturally adapted to suit other parts of the world. Using an existing program means that the resources, manuals, and methodologies are ready for immediate use, facilitating implementation. However, in Europe, there has been an aversion to the standardization inherent in manualized interventions and a belief that cultural and organizational differences between North America and Europe would make the adaptation problematic. Countries in Latin America and in Asia do not appear to have such problems in adopting and adapting evidence-based programs from other parts of the world.

Despite the difficulties and hesitations described above, in the past decade, a number of manualized substance use prevention programs from North America have been successfully transferred and adapted to European environments. They and their effectiveness ratings can be accessed at http://www.emcdda.europa.eu/best-practice/xchange_en alongside the experiences of the implementers in Europe that adaptation and implementation are both feasible and effective (where outcomes are available). While a considerable amount of time and effort was necessary to adjust the programs to culture and context, in most cases, it was preferable to adapt an available effective program than to develop a new one from scratch. Yet, several American flagship programs appear to yield less convincing results when implemented in Europe, either due to better services provided to the control conditions, questions of fidelity, or the noninvolvement of the developers in the evaluations.

7.3 Conclusion

7.3.1 Prevention, Treatment, and Harm Reduction

Prevention has made considerable progress in recent years, but there is still much room for improvement. Despite considerable support also through findings from neurosciences, evidence is still limited, which might hinder a broader use of prevention. However, the number of options available to tackle substance-related problems is limited. Harm reduction interventions are important but limited in scope, and treatment often comes late after problem substance use has started and reaches only a part of people in need. So we have to use all tools at hand to work on the drug problem, and prevention is absolutely core in this respect despite its limitations and shortcomings.

Reflecting on the criticism that prevention is only abstinence oriented, the term "risk reduction" has been coined as a viable alternative for vulnerable or drug-using youth. In fact, the evidence, intervention examples, and theoretical frameworks discussed here show that "risk reduction" is intrinsically included in all prevention measures, and most prevention interventions in fact try to achieve generally better behavioral control and adequate socialization or to avoid rapid escalation from experimental use to SUD or even addiction, hence reducing risk and harms.

Especially for selective and indicated prevention, we do see a considerable overlap with treatment where low treatment rates and considerable delays before treatment initiation have led to a more generic debate on the role of treatment itself. Putting more emphasis on outcomes targeting "healthy lifestyle" instead of "avoidance of addiction" and "low-risk use" instead of "abstinence," the conceptual gap between treatment and prevention is shrinking [6]. The vicinity between these concepts becomes obvious when we look at websites for cannabis users, which offer information and self-tests on one side and access to treatment in case of need on the other side.

7.3.2 Conceptual Developments

Findings from country-level ecological analyses on the health of young people [48] show that the strongest determinants of adolescent health worldwide are structural factors such as national wealth, income inequality, and access to education. As a consequence, nurturing environments, with safe and supportive families and schools, together with positive and supportive peers, are crucial in addressing risk and building protective factors in the course of child and adolescent development.

Social norms and other environmental cues have a strong influence on behavior, suggesting that the effect of informal social control and social sanctions (from family and peers) may be more important than the certainty and severity of formal sanctions. This illustrates that comprehensive prevention policies ought not only to address individual vulnerabilities and illicit drug use. Informal social norms have a major but largely underestimated influence on initiation and level of substance use and related behaviors.

Also based on neuropsychological findings, prevention has become more unified at conceptual level, and a number of problematic behaviors, including antisocial and violent behavior, substance use, and pathological use of computer and the Internet, today are targeted often with the same interventions. The need for a strong evidence base, critical reflection of practice, and adequate training of the staff involved remains central to all these approaches.

In terms of gender differences, a number of program evaluations found, overall, less or no effects for girls. One possible explanation might be a lower vulnerability at baseline, which could also reflect the fact that neurobehavioral disinhibition is found more frequently in boys. Alternative hypotheses are that these interventions are less appealing to girls or that the timing of delivery with regard to their cognitive, social, and emotional development is less appropriate, since girls mature earlier. So girls who, overall, use psychoactive substances less and have fewer problems might also gain less from existing prevention programs.

7.3.3 Implementation

Overall, the field still seems to be dominated by interventions that might attract more public attention than be effective in changing and sustaining consumption behavior. Policy interest in selective prevention has increased, but this has not translated into better interventions for vulnerable youth or more evaluation research. There has been some recent interest in indicated prevention in Europe, and well-designed evaluation studies have taken place, but the intervention coverage as such is still limited to a few countries. Too many prevention interventions continue to appeal to cognitive processes only, namely, information provision, regardless of the lacking evidence. Policy makers and professionals have only reluctantly begun to acknowledge that social norms and their perception (environmental prevention) as well as impulse control (indicated prevention) are powerful determinants of adolescent behavior. The potential for addressing emotional and unconscious processes in prevention is virtually unacknowledged.

But on the implementation side also, promising developments can be found:

- There is a (limited) number of prevention programs with well-proven evidence of effectiveness that are relatively easy to implement through manuals and other supporting materials. Better use could be made of these interventions.
- A further potential lies in the complementary approach of developing environmental prevention strategies at local level, which provide safe and nurturing environments within and around schools (no outlets nearby), at nightlife venues, and during leisure time. These are, for example, the key component of the so-called Icelandic approach [39].
- Web-based offers are already widespread and should be developed further. BI and MI can serve as tools. While prevention has been traditionally linked to school curricula, and TV, today, Internet and social media approaches play an important role which should be further developed.

- Standards can help to better implement new programs and interventions. Since the publication of the international standards for prevention by UNODC and the European drug prevention quality standards (EDPQS), a steadily increasing number of countries are introducing such quality standards in their own strategies.
- A unified prevention training syllabus for relevant professionals has the potential to improve prevention systems by developing skills and competences in evidence-based prevention. The Universal Prevention Curriculum (UPC)[2] is a first step into this direction. Based on the UNODC standards of evidence and the EDPQS it transmits key competences such as needs and resource assessment, selection and implementation of interventions and/or policies, and monitoring and evaluation. A much shortened European version is now available the EUPC https://www.emcdda.europa.eu/best-practice/european-prevention-curriculum.
- Very heterogeneous professional cultures, beliefs, and assumptions are a challenge for transferring the progress made in prevention science into routine practice. In order to achieve this, further training and development of the prevention workforce is crucial.
- A focus on informational and educational approaches is still common in many countries despite the known limited evidence to their effectiveness.
- Despite often necessary adjustments to national culture and conditions, the transfer of well-developed prevention programs mainly from Northern America has shown to provide a considerable chance to improve the quality of services also in other parts of the world.

Taking all these elements together, we do see prevention as highly promising tools to work on substance-related behaviors and problems. There has been a considerable number of developments in recent years, and more investment in research, training of professionals, and especially implementation of findings from preventions science would seem a good investment.

[2] https://www.issup.net/training/universal-prevention-curriculum

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8 Diagnostic Definitions and Classification of Substance Use Disorders

John B. Saunders and Noeline C. Latt

Contents

Abstract

Diagnostic terms exist to identify forms of substance use which are causing clinical impairment or risk and to distinguish them from normality. Both repetitive substance use and single-occasion use exist along a gradation of severity. Repetitive substance use which confers the risk of harmful consequences is termed Hazardous Substance Use,

J. B. Saunders (✉)
Centre for Youth Substance Abuse Research, University of Queensland, St Lucia, QLD, Australia

Disciplines of Psychiatry and Addiction Medicine, Faculty of Medicine, University of Sydney, Camperdown, NSW, Australia
e-mail: mail@jbsaunders.net

N. C. Latt
Disciplines of Psychiatry and Addiction Medicine, Faculty of Medicine, University of Sydney, Camperdown, NSW, Australia

Formerly Northern Area Drug and Alcohol Service, Royal North Shore Hospital, St Leonards, NSW, Australia
e-mail: Unknown_6574809@Meteor.com

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which is a new diagnostic term in the latest (eleventh) revision of the International Classification of Diseases (ICD-11). Harmful Substance Use in ICD-10 and ICD-11 denotes repetitive substance use which has caused physical or mental harm but where the guidelines for the diagnosis of Substance Dependence have not been met. At the top of this hierarchy in ICD-10 and ICD-11 is Substance Dependence. This is defined as a psychobiological syndrome that is a disorder of regulation of substance use. It comprises impaired control over substance use, continued use of the substance despite harmful consequences and often increased tolerance and withdrawal symptoms. It is underpinned by enduring neurobiological changes in brain reward, stress, salience and control systems, which result in an "internal driving force" to use and continue to use a substance (or group of substances) in a self-perpetuating way. The most recent (fifth) edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) changed the diagnostic landscape with its deletion of its forerunner, DSM-IV's diagnoses of Substance Dependence and Substance Abuse (which denoted a maladaptive and repetitive pattern of substance use causing social problems), and replacing them with a broader condition of "substance use disorder" that can exist in varying degrees of severity (mild, moderate or severe) depending on the number of criteria fulfilled. In addition to these forms of repetitive substance use, single-occasion use may lead to substance intoxication (in both ICD and DSM), and episode of Harmful Substance Use (ICD-11). Where substance use is curtailed in substance-dependent individuals, substance withdrawal can occur, this being a cluster of symptoms and features specific to the substance taken. In general, the features of substance withdrawal are opposite to those of the pharmacological effects of the substance concerned. There are also numerous mental and neurocognitive sequelae which occur in both the ICD and DSM systems, some with rather different diagnostic names and definitions. They include substance-induced mental disorders, such as substance-induced mood disorder, and similarly termed anxiety disorder, psychotic disorder, sleep-wake disorder, sexual dysfunction, obsessive-compulsive disorders, and substance-induced delirium. Neurocognitive disorders include substance-induced amnestic syndrome and substance-induced dementia. The ICD system also has comprehensive coverage of all physical disorders induced by psychoactive substance use. DSM-5 does not include the medical/physical complications of substance use and has abandoned the multiaxial system, which included (as Axis III) associated physical conditions. For all these disorders, diagnosis is based on a set of specific diagnostic guidelines (ICD) or criteria (DSM), which reflect the substance used, the pattern of use and the specific features of the disorder.

8.1 Introduction and Background

8.1.1 Introduction

Psychoactive substance use exists as a continuum and substance use disorders as a hierarchy. Some forms of substance use in small amounts, for example, alcohol, are not harmful, or at least low risk. Other psychoactive substances such as prescribed opioids or benzodiazepines are medically necessary and appropriate in many situations. Illicit drugs, such as cannabis (marijuana), may have functional value to some people, and there may be a threshold of use for some beneath which little harm occurs. The line between substances which are medically prescribed and those which are medically inappropriate (and typically illegal) is becoming increasingly blurred, with the more widespread use of psychostimulants for various disorders and the availability of medicinal cannabinoids (and in some countries legally available cannabis (marijuana) and the prescribing, albeit uncommonly, of oxybate (gamma-hydroxybutyric acid) as a treatment for alcohol

dependence. A fundamental property of all the substances covered by this chapter is their inherent capacity to cause intoxicating effects and reinforcement of use and to induce neurobiological processes that lead to Substance Dependence/Addiction, withdrawal syndromes (in most cases) and a range of physical, neurocognitive, psychological and social harms.

Diagnoses are made to facilitate communication between different healthcare providers and to provide a basis for an intervention. Diagnosis is an intellectual discipline characteristic of medicine that seeks to define the patient's symptoms, behaviours and clinical features and match them against an array of human disorders such that the disorder that most satisfactorily covers what the patient experiences is selected. The intellectual process underlying diagnosis also serves to distinguish the patient's condition from normality. Some diagnoses indicate forms of substance use that confer the risk of harmful consequences in the future, others a syndromal disorder and others a complicating disorder or impairment. A coherent system of diagnosis and classification provides a vital structure for the practice of addiction medicine.

The present time is a period of considerable change in diagnostic concepts and terms. The latest edition (the fifth) of one of the principal diagnostic systems, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), was published by the American Psychiatric Association (APA) in 2013 [4]. In mid-2019, the latest revision (the eleventh) of the International Classification of Diseases, which is the international basis for disease, morbidity and mortality diagnosis and coding, was approved by the World Health Organization (WHO) [72]. Whereas there was considerable similarity between the major substance use diagnoses in their forerunners DSM-IV and ICD-10, there is a divergence in the central disorders of repetitive substance use in DSM-5 and ICD-11. Specifically, ICD-11 has retained the central ICD-10 [70] diagnoses of Substance Dependence and Harmful Substance Use, with some modifications, whereas DSM-5 has combined the DSM-IV diagnoses of Substance Dependence and Substance Abuse [3] into an umbrella diagnosis of substance use disorder [4]. Many addiction medicine specialists in North America and elsewhere adopt the diagnostic concepts and criteria developed by the American Society of Addiction Medicine (ASAM) and the International Society of Addiction Medicine (ISAM) [5, 25]. The conceptual understanding of substance disorders is rather different in these formulations, and the diagnostic criteria have only passing resemblance to those employed in the DSM and ICD systems. A further contrast is provided by the emphasis in the fields of epidemiology and public health on quantification of substance use and not to define specific behavioural or psychophysiological disorders.

It will be apparent from the foregoing comments that a synthesis of diagnostic concepts in the current classification systems is not possible. In this chapter, we shall present a history of common concepts of substance use disorders and then review the key diagnoses in the current international diagnostic systems. Before this, we shall briefly review the range of addictive (dependence-inducing) and potentially harmful psychoactive substances and also the patterns of substance use that need to be captured by a diagnostic classification system.

8.1.2 The Range of Addictive Substances

There are many thousands of naturally occurring and synthetic substances that have the capacity to induce addiction, and new ones are continually being synthesised. Substances with addictive potential tend to have acute psychological effects which consumers find pleasant, at least initially and in the majority of cases. They tend to cause euphoria and, in many cases, a sense of relaxation. Certain substances are valued because they relieve pain or sickness and therefore are described as having a medicinal effect as opposed to a primary hedonic one. The pharmacokinetic properties of the substance influence its addictive potential, with the rapidity of absorption (and therefore action), ease of penetrating the blood/

brain barrier and duration of action influencing the likelihood of recurrent self-administration and therefore addiction. Addictive potential is also influenced by the mode of administration, with the smoking and intravenous injecting routes inducing more rapid addiction than oral ingestion. Addictive substances tend to have a biphasic action, whereby the hedonic effect is typically followed by negative symptoms consequent on declining blood and tissue levels of the substance. The neurobiological changes which occur in this phase could be regarded as "restorative", with the aim of returning neuronal systems to their normal functioning state.

The propensity of psychoactive substances to induce addiction therefore ranges considerably depending on the mode of administration, the substance's pharmacodynamic and pharmacokinetic properties, individual vulnerability and also the social setting in which the substance is taken. Caffeine as occurs in coffee, tea and certain soft drinks and once considered a minor stimulant at the lowest end of the addiction spectrum is listed in DSM-5, ICD-10 and ICD-11. Certain other substances have psychoactive properties and are harmful but are not or only rarely addictive. These include most of the hallucinogens, where the acute psychoactive effects (often of a psychedelic or psychotomimetic nature) commonly result in clinical presentations but where addiction/dependence is uncommon. Other substances such as sugar and certain commercial soft drinks exist in a borderline area where addiction is described but is not typical and is often rare. Substances in this last domain will not be further considered in the present chapter.

Many prescribed and proprietary ("over the counter") medications have addictive potential. Because of the therapeutic benefits (and commercial value) of these medications, there has been controversy as to whether they should be termed addictive substances as opposed to their inducing physiological dependence. The DSM system has an exclusion for tolerance and withdrawal as diagnostic criteria where the drug has been prescribed medically. There is a divergence of opinion between those who would exclude medication use when it is being prescribed by a medical practitioner and those authorities who regard the occurrence of a desire for repeated administration of such medications and the occurrence of withdrawal symptoms to indicate that addictive processes are present in the individual. This debate has entered the public domain with the huge and increasing number of deaths in the USA and many other countries from prescribed opioids, the risks of overdose and clear evidence of their addictive capacity.

Both the ICD and DSM systems aim to encompass the range of psychoactive substances used recreationally and medically. Substances may be used individually, but increasingly, they are used in combinations, each of which has its own psychiatric and physical morbidities [15]. ICD-11 has an expanded listing of psychoactive substance groups in its primary structure. This reflects the emergence in many parts of the world of new psychoactive substances such as synthetic cannabinoids, synthetic psychostimulants and hallucinogens [40]. Table 8.1 compares and contrasts those substances covered in DSM-IV, DSM-5, ICD-10 and ICD-11.

8.1.3 Mechanisms Underlying Repetitive Substance Use

There are numerous psychological and social influences which determine whether a substance with psychoactive properties is actually used, periodically or repeatedly, and may potentially lead to harmful consequences and addiction. An important determinant is the availability of a particular substance in a society, and this in turn may be determined by whether it is of plant origin and requires particular climatic conditions or level of rainfall to grow. Other substances are chemically synthesised and require a corresponding level of knowledge and technical equipment to produce.

Psychological mechanisms are involved in substance use becoming repetitive use, and classical conditioning theory, operant conditioning theory and social learning theory [8] all contribute to our understanding of how this eventuates.

Table 8.1 Coverage of psychoactive substance groups in DSM-IV and DSM-5 and ICD-10 and ICD-11

Class	DSM-IV	DSM-5	ICD-10	ICD-11	Comments
CNS depressants	Alcohol	Alcohol	Alcohol	Alcohol	
	Cannabis	Cannabis	Cannabinoids	Cannabis	
				Synthetic cannabinoids	
	Inhalants	Inhalants	Volatile solvents	Volatile inhalants	
	Opioids[a]	Opioids[a]	Opioids[a]	Opioids[a]	
	Sedatives, hypnotics or anxiolytics	Sedatives, hypnotics or anxiolytics	Sedative-hypnotics	Sedatives, hypnotics or anxiolytics	
	Nicotine	Tobacco	Tobacco	Nicotine	
CNS stimulants	Caffeine	Caffeine	Other stimulants including caffeine	Caffeine	
	Amphetamines	Stimulants		Stimulants including amphetamines, methamphetamine or methcathinone	The stimulants category in DSM-5 includes amphetamine-type substances, cocaine and other or unspecified stimulants. For some diagnoses, the type of substance can be specified
				Synthetic cathinones	
	Cocaine		Cocaine	Cocaine	
Hallucinogens, Empathogens and dissociative drugs	Hallucinogens	Hallucinogens	Hallucinogens	Dissociative drugs including ketamine and phencyclidine	In DSM-5, there are separate descriptions for phencyclidine and for other hallucinogens. MDMA is classified under other hallucinogens
	Phencyclidine			Hallucinogens	
				MDMA and related drugs including MDA	
Polysubstance use	Polysubstance		Multiple drug use and use of other psychoactive substances		The category polysubstance use does not appear in DSM-5 or ICD 11
Other and unknown substances	Other substances	Other or unknown substances		Other specified psychoactive substances	There is no category for unknown or unspecified substances in DSM-IV
				Unknown or unspecified psychoactive substances	

[a]Includes prescription opioids

The reader is referred to suitable reviews for further reference.

Neurobiological mechanisms come into play in particular when a pattern of repetitive substance use has developed and result in that repetitive use tending to become more stereotyped and self-perpetuating, being driven by internal cues rather than external circumstances. The essential result of the neurobiological mechanisms of addiction is the generation of an internal driving force, which is enduring and which promotes further substance use even in the absence of external

cues and continues to do so even when circumstances are inappropriate for substance use and the person may actually be experiencing harm as a result of that use. The driving force of what is termed Substance Dependence or Addiction results in substance use occupying a more and more central role in the person's life, with other interests, enjoyments, activities and responsibilities being relegated to the periphery. Much has been learnt about the neurobiological processes, and it appears there are interlinked neurocircuits which are "reset" in a person with addiction. These subserve reward, alertness (excitation) and salience on behavioural control.

In summary, in the early period of psychoactive substance use, that use is influenced strongly by external circumstances and also by the person's mood state. As repeated use continues and dependence develops, the repetitive use reflects more the internal neurobiological mechanisms that have developed. It is these mechanisms that result in repetitive substance use becoming more and more syndromal and to produce the clinical disorders we recognise as addiction.

8.2 Concepts of Substance Use Disorders

8.2.1 Personality Disorder

In the first edition of DSM, published in 1952, substance misuse was included in the personality disorders [1]. Drug addiction was not specifically defined, but there was a statement that it was usually symptomatic of a personality disorder. The second edition, published in 1968 [2], had substance use disorders classified within the personality disorders. There were no specific definitions or criteria and little description of the conditions. The diagnosis of drug dependence required "evidence of habitual use or a clear sense of a need for the drug" [2].

8.2.2 The Disease Concept

Many groups view substance use disorders as reflecting a disease process, which is biologically determined and results in the individual having an individualistic reaction to a psychoactive substance and a relatively predictable natural history. This conceptualisation influenced and was subsequently embraced by the self-help movements, such as Alcoholic Anonymous. Jellinek developed the concept of the disease of alcoholism in the 1940s and 1950s [26], although in his later work he increasingly recognised the role of environmental influences. During the 1960s and 1970s, the concept that substance misuse might represent a disease process was dismissed by most scientists and professionals. Likewise, the role of genetic predisposition was thought to be inconsequential, with the familial aggregation of substance misuse explained by cultural influences, role modelling or malfunction within families. With the increasing understanding of neurobiological changes underpinning Substance Dependence/Addiction, the concept of their being a primary disease entity has become more popular with statements such as "addiction is a brain disease" [35]. The question is more whether addiction is a primary disease or an acquired one, with most recent neurobiological data indicating the latter. This is discussed further below.

8.2.3 Epidemiological and Sociological Formulations

A third tradition may be described as the epidemiological and sociological one. Put simply, substance misuse and problems arise fundamentally because of the overall level of use of that particular substance in society. In the 1950s, Ledermann [32] proposed a relationship between the level of alcohol consumption in a community and the prevalence of alcoholism. The level of use is, in turn, influenced by the availability of alcohol, its manufacture and distribution, its price (importantly) and cultural traditions and sanctions. Inherent in these conceptualisations is that individual pathology is considered of secondary importance. The social constructionist school views substance use problems as disaggregated, with no special

relationship among them. This school of thought was concerned about the stigma attributable to diagnostic labels and the potential of treatment as a form of social control [48].

8.2.4 Learnt Behaviour

The 1970s saw the rise of social cognitive theory [8] as an influential paradigm to explain the development and resolution of alcohol and drug problems. This school of thought teaches that the (many) influences that determined behaviour in general apply to the uptake of substance use and the development of disordered use. Positive consequences encourage repeated use, negative ones the opposite. Patterns of substance use behaviour could become established in this way, but equally, repetitive substance use could be "unlearnt". This led to the development of a range of cognitive behavioural therapies, some of which aimed at moderated or "controlled" substance use.

8.2.5 Clinical Syndrome

The need for an understanding of substance misuse which spanned these various discipline-bound conceptualisations and terms was largely met by the formulation of the concept of a "substance dependence syndrome" originally proposed with regard to alcohol dependence by Edwards and Gross in 1976 [19]. The basis of the dependence syndrome was a clinical description of key clinical features in a way that was essentially theoretical and was not based on any aetiological understanding of the disorder, be it biological, behavioural or sociological. Rather, certain experiences, behaviours and symptoms related to repetitive alcohol use were identified as tending to cluster in time and to occur repeatedly. The advantage of a descriptive account of dependence is that it can accommodate aetiological models but not be beholden to them.

The concept of the dependence syndrome applies to many other psychoactive substances that have the potential for reinforcement of use, including benzodiazepines, illicit and prescribed opioids, cannabis, inhalants, psychostimulants such as cocaine and the amphetamines, nicotine, caffeine and anabolic steroids [21, 39, 51, 65]. It may also apply to repetitive behaviours that do not involve self-administration of a psychoactive substance. These include pathological gambling and compulsive shopping and exercise [34, 42]. "Disordered gambling" has now been added to DSM-5 [4].

The dependence syndrome has been at the heart of the classification systems of psychoactive substance use disorders since the 1980s [57]. It is the principal substance use disorder in DSM-IV [3], ICD-10 [70] and ICD-11 [72]. However, in DSM-5, the dependence syndrome is subsumed under substance use disorder [4].

8.2.6 Neurobiological Disorder

Neurobiological mechanisms come into play particularly when a pattern of repeated use has become established. They induce a driving force to use the substance in preference to other human activities or interests and do so in a continuing and seemingly compulsive way. They cause reinforcement and indeed self-perpetuation of psychoactive substance use. Increases in tolerance favour consumption of larger and larger doses of the substance. The three key neurobiological changes in dependence are as follows:

(i) Activation and then inhibition of brain reward systems, particularly involving dopaminergic transmission and opioidergic transmission. These have the effect of resetting the reward systems such that larger amounts of the substance are needed to produce the desired effect and natural rewards are not as reinforcing [67, 68].
(ii) Recruitment of brain stress systems, including those subserved by glutamate neurotransmission and corticotrophin-releasing factor (CRF) [29] and suppression or uncoupling of antistress systems [49].
(iii) Impairment of inhibitory control pathways from the prefrontal cortex to the mesolimbic systems, resulting in impaired decision-making capacity [73].

(iv) Resetting of the salience circuitry arising from the cingulate gyrus of the frontal lobe and changing the importance of substance use relative to other interest, activities and responsibilities [28].

A publication on the neuroscience of addiction by the World Health Organization summarises the key developments in biomedical research over this period [71].

8.2.7 Genetic Influences

Investigations into possible genetic influences have accompanied this research on neural circuitry. Biometric genetic studies have shown that children born of parents with Substance Dependence are more likely to have Substance Dependence themselves [56] and that this is largely explained by genetic transmission rather than environmental factors [16, 17, 33, 56]. Genomic analysis in human and laboratory animals has identified several areas of the genome where mutations are associated with increased risk of substance use disorders [16, 17, 20].

8.3 Diagnoses Applied to Use of Psychoactive Substances in DSM-IV, DSM-5, ICD-10 and ICD-11

8.3.1 Overview

The current versions of the DSM and ICD systems are DSM-5 [4] and ICD-10 [70], respectively. In May 2019, ICD-11 was formally published by the World Health Organization (WHO). Accordingly, the diagnoses listed and discussed in this section will include those in DSM-5, ICD-10 and ICD-11. In addition, certain DSM-IV diagnoses [3] will be described as they are well known and much of the empirical basis for modern treatment draws upon them as the basis for recruitment into both pharmacological and psychological therapies. DSM-IV and ICD-10 diagnoses were developed almost simultaneously and were underpinned by the US National Institute of Health Joint Project on Diagnosis and Classification [55].

The DSM and ICD systems differ in their emphasis. The DSM system focuses on the needs of clinicians and researchers and encompasses the range of mental, behavioural and addictive diagnoses. Diagnostic criteria are provided for each diagnosis and these are quite specific.

The ICD system, which is overseen by the WHO, is a compendium of all human disorders including physical and psychiatric disorders, external causes such as trauma and also health risk factors. In addition to being a resource for clinicians and researchers, it is also the basis for the systematic recording, compilation and analysis of morbidity and mortality statistics worldwide. The ICD listing includes definitions of all the disorders. For mental, behavioural and addictive disorders, there is a more detailed version also containing diagnostic guidelines and explanatory material which is termed the ICD Clinical Descriptions and Diagnostic Guidelines (CDDG). The term "diagnostic guidelines" is employed in the ICD in preference to the term diagnostic criteria to emphasise the more flexible nature of the guidance provided, which is intended to allow scope for clinical judgement and cultural variations. It attempts to avoid strict cut-offs in duration or symptom count, unless these have been widely accepted and specifically validated [22]. The ICD-11 has also been developed with an explicit public health framework [45], and this is evident from the spectrum of repetitive substance use ranging from hazardous use, harmful use and Substance Dependence that it incorporates (Fig. 8.1). It comprises diagnoses which reflect a single occasion of use (substance intoxication and episode of Harmful Substance Use) and those which reflect a pattern of repeated use.

8.3.1.1 Substance Intoxication (ICD-10, ICD-11, DSM-IV, DSM-5) (See Table 8.2)

Substance intoxication is an episode of excessive use, producing clinically significant pharmaco-

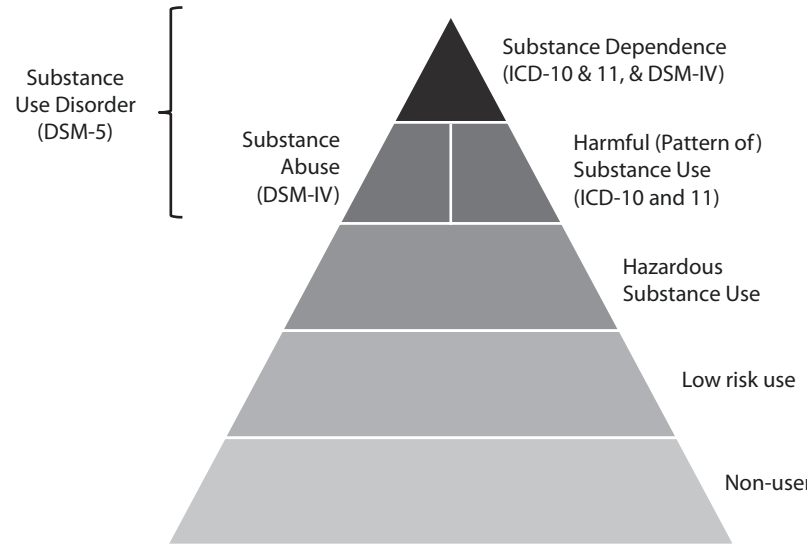

Fig. 8.1 Pyramid ICD-10, ICD-11, DSM-IV, DSM-5

Table 8.2 Diagnostic guidelines for substance intoxication (DSM-5, ICD-10, ICD-11)

	DSM-5	ICD-10	ICD-11
Primary definition	Acute intoxication is a transient condition following administration of a psychoactive substance resulting in disturbance of level of consciousness, cognition, perception, affect or behaviour or other psycho-physiological functions and responses. Symptoms of intoxication are substance specific and may produce different types of effect at different levels	A transient condition following the administration of alcohol or other psychoactive substances, resulting in disturbances in level of consciousness, cognition, perception, affect or behaviour, or other psycho-physiological functions and responses	Substance intoxication is a clinically significant transient condition that develops during or shortly after the consumption of a substance that is characterized by disturbances in consciousness, cognition, perception, affect, behaviour or coordination. These disturbances are caused by the known pharmacological effects of the substance, and their intensity is closely related to the amount of substance consumed. They are time limited and abate as the substance is cleared from the body
Additional guidelines and text	Acute intoxication is closely related to dose levels. Exceptions occur with certain underlying organic conditions such as renal or hepatic insufficiency where smaller doses may produce an intoxicating effect	Acute intoxication is a transient condition. Intensity of intoxication lessens with time and effects eventually disappear in the absence of further use of the substance. Recovery is therefore complete except where tissue damage or another complication has arisen Acute intoxication is usually closely related to dose levels. Exceptions may occur in individuals with certain underlying organic conditions. Disinhibition due to social context should also be taken into account	Further guidelines describe it as a reversible substance-specific syndrome with requirements of: A. Recent ingestion of a substance B. Clinically significant problematic behavioural or psychological changes that develop during or shortly after use C. The signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance. Substance intoxication is common in those with a substance use disorder but may occur in individuals without a substance use disorder
Explanatory notes	*Note that substance-specific features of intoxication are listed under the primary criteria*		*Note that substance-specific features of intoxication are listed under the primary definitions*

logical effects but which may in severe cases be termed poisoning or overdose. Substance intoxication is defined in DSM-5 as a reversible substance-specific syndrome due to recent ingestion of a substance, together with clinically significant problematic behavioural or psychological changes that develop during, or shortly after, use of the substance, and the signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance [4]. ICD-10 and ICD-11 define substance intoxication quite similarly, namely, a clinically significant transient condition that develops during or shortly after the consumption of a substance that is characterised by disturbances in consciousness, cognition, perception, affect, behaviour and coordination. There is a further statement that these disturbances are caused by the known pharmacological effects of the substance, their intensity is closely related to the amount of substance consumed and the disturbances are time-limited and abate as the substance is cleared from the body [70, 72].

Substance intoxication can be life threatening particularly in non-tolerant individuals. Patients may present with coma following intoxication with CNS depressants like alcohol, benzodiazepines or opiates; the risk is compounded when a mixture of these drugs is taken, as is often the case. In addition to neuropsychiatric complications such as paranoia and psychosis, intoxication with psychostimulants (MDMA, amphetamines, cocaine) may lead to a variety of cardiovascular, central nervous system, musculoskeletal, electrolyte and renal complications [61].

8.3.1.2 Episode of Harmful Use of a Substance

This is a new diagnosis in ICD-11 [72] and is designed to capture harm which is considered to be due to substance use but where there is no or insufficient evidence that the person either had an episode of substance intoxication or had a repetitive pattern of substance use where Harmful Substance Use or Substance Dependence could be diagnosed. This diagnosis has proven useful in early studies of the ICD-11 system in capturing persons attending emergency departments who had an alcohol-related injury but no available information about a prior pattern of alcohol consumption [9].

8.3.1.3 Repetitive Substance Use which Does Not Fulfil Dependence Criteria

Repetitive substance use which does not fulfil the criteria for the dependence syndrome is still of clinical significance. It is handled differently in the two systems. In ICD-10 and ICD-11, the term Harmful Substance Use applies to repetitive use of a psychoactive substance which has caused physical or mental harm to that person [70, 72]. In DSM-IV, the term Substance Abuse refers to repetitive use of a psychoactive substance which essentially is causing social harm or problems [3]. There is no equivalent term in the ICD system; indeed, the ICD eschews the notion of a disorder that is defined by social criteria. In addition, ICD-11 has defined an entity of Hazardous Substance Use which is a health risk factor and is at the mid-range of the hierarchy of substance use and misuse (Fig. 8.1).

Hazardous Substance Use (ICD-11)

Hazardous Substance Use (Fig. 8.1) is listed in a separate chapter "Factors Influencing Health Status" and not included with substance use disorders [72]. Hazardous Substance Use is defined as a pattern of psychoactive substance use that appreciably increases the risk of harmful physical or mental health consequences to the user or to others to an extent that warrants attention and advice from health professionals. The risk may be related to the short-term effects of the substance or to longer-term cumulative effects on physical or mental health or functioning. Hazardous Substance Use has not yet reached the level of having caused harm to the physical or mental health of the user or others around the user.

In support of including hazardous use in a diagnostic system is the evidence that it can be defined and it responds to therapy, the evidence base for the effectiveness of interventions for hazardous alcohol consumption being particularly strong [27].

Hazardous alcohol use is also termed "risky", "high-risk" use, or "unhealthy" use [10, 36, 37]. Hazardous use defines men and women drinking in excess of national low-risk guidelines.

In the USA, the National Institute on Alcohol Abuse and Alcoholism defines risky drinking as men under 65 years drinking more than 14 standard drinks per week on average or more than four standard drinks on any day and women and adults 65 years and older consuming more than seven standard drinks per week on average or more than three standard drinks on any day where one standard drink is defined as 12 grams of ethanol, 5 ounces of wine, 12 ounces of beer or 1.5 ounces of 80 proof spirits [53, 54]. Heavy episodic drinking, defined as repeated heavy drinking episodes of more than five standard drinks (65 g alcohol) by men and more than four US standard drinks (50 g alcohol) by women, confers a risk of alcohol use disorders, acute and chronic illnesses and injuries [37, 52].

In Australia, hazardous or risky consumption is now defined as daily consumption by men and women of more than two standard drinks (20 g alcohol) for some years [36]. In the UK, drinking in excess of 14 units of alcohol per week on a regular basis is considered risky drinking. For people regularly drinking more than 14 units per week, it is recommended to spread drinking evenly over three or more days [66, 69].

Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicate that hazardous alcohol consumption (defined as the US 5+/4+ standard drink criterion) exists within the continuum of abuse and dependence criteria. As the frequency of this level of consumption increases, this experience moves along the severity continuum to overlap with abuse and dependence criteria [52].

Unhealthy alcohol use is an umbrella term encompassing a whole range of alcohol use disorders and a practical means of grouping all the diagnoses [53].

Harmful Substance Use (ICD-10) or Harmful Pattern of Substance Use (ICD-11)

Harmful Substance Use (Fig. 8.1) is an ICD term which denotes a repetitive pattern of substance use, which does not fulfil the criteria for Substance Dependence but has caused damage to a person's physical or mental health or (in ICD-11) has resulted in behaviour leading to harm to the health of others [72]. The pattern of substance use is evident over a period of at least 12 months if substance use is episodic or at least one-month use is continuous, i.e. daily or almost daily [70, 72]. The harmful effects may be acute or chronic. Examples of acute complications include fractures and other forms of trauma, acute gastritis and acute psychotic symptoms following substance use. Chronic medical complications encompass liver disease, (e.g. alcoholic liver disease or hepatitis C-induced liver disease following injecting drug use), cardiovascular diseases, respiratory diseases, various neurological sequelae and many others. Examples of mental complications are depressive episodes secondary to heavy alcohol intake and substance-induced psychosis. In clear distinction to DSM-IV, social complications per se are insufficient to justify a diagnosis of Harmful Substance Use in the ICD [70, 72].

Substance Abuse (DSM-IV)

Substance Abuse in DSM-IV was defined as repetitive substance use which has resulted in one or more social or occupational problems. Substance Abuse was envisaged as one axis of a biaxial conceptualisation of substance use disorders, which separates the core syndrome of dependence from the consequences. However, there is blurring of this conceptualisation because of its hierarchical relationship with dependence, i.e. as a less severe disorder. DSM-5 does not have a separate diagnosis of Substance Abuse, as this has been subsumed within DSM-5 substance use disorder.

8.3.1.4 Substance Dependence (DSM-IV and ICD-10; ICD-11)

Substance Dependence was the central substance use diagnosis in DSM-IV and ICD-10 and remains so in ICD-11 [3, 70, 72]. Essentially, it is a syndrome where there is an "internal drive" to continued and self-perpetuating use [57, 59, 61, 63].

Substance Dependence is defined similarly in DSM-IV, ICD-10 and ICD-11 (Table 8.3). Essentially, Substance Dependence is a syndromal cluster of behavioural, cognitive and physiological phenomena that develop after repeated substance use. In ICD-11, two or more of the three diagnostic guidelines set out below need to be present within a 12-month period or continuous for at least 1 month [43, 44, 58, 63, 72]. The diagnostic guidelines are the following:

1. *Impaired control* over substance use – in terms of the onset, level, circumstances or termination of use, often but not necessarily accompanied by a subjective sensation of urge or craving to use the substance.
2. Substance use becomes an increasing *priority in life* in such that it takes precedence over other interests or enjoyments, daily activities, responsibilities or health or personal care. Substance use takes an increasingly central role in the parson's life and relegates other areas of life to the periphery. Substance use often continues despite the occurrence of problems.
3. *Physiological features* (indicative of neuroadaptation to the substance) as manifested by i) tolerance, ii) withdrawal symptoms following

Table 8.3 Diagnostic criteria for substance dependence and substance use disorder in DSM-IV and DSM-5 and ICD-10 and ICD-11

	DSM-IV dependence	DSM-5 substance use disorder	ICD-10 substance dependence	ICD-11 substance dependence
Stem	A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three or more of the following occurring at any time in the same 12-month period	A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following occurring within a 12-month period	A cluster of physiological, behavioural and cognitive phenomena in which the use of alcohol takes on a much higher priority for a given individual than other behaviours that once had greater value. Three or more of the following (six) manifestations should have occurred together for at least 1 month or occurred together repeatedly within a 12-month period	A disorder of regulation of alcohol use arising from repeated or continuous use of alcohol. The characteristic feature is a strong internal drive to use alcohol. The diagnosis requires two or more of the three central features to be present in the individual at the same time and to occur repeatedly over a period of at least 12 months or continuously over a period of at least 1 month
1	No equivalent criterion – Mentioned in text	Craving or a strong desire or urge to use the substance	A strong desire or sense of compulsion to take the psychoactive substance (craving or compulsion)	1. Impaired control over substance use – In terms of the onset, level, circumstances or termination of use and often, but not necessarily, accompanied by a subjective sensation of urge or craving to use the substance
2	There is persistent desire or unsuccessful attempts to cut down or control substance use	There is persistent desire or unsuccessful efforts to cut down or control substance use	No equivalent criterion but text states that the subjective awareness of compulsion is most commonly seen during attempts to stop or control substance use	
3	The substance is often taken in larger amounts or over a longer period of time than was intended	The substance is often taken in larger amounts or over a longer period than was intended	Difficulties in controlling substance-taking behaviour in terms of its onset, termination or levels of use *(loss of control)*	

Table 8.3 (continued)

	DSM-IV dependence	DSM-5 substance use disorder	ICD-10 substance dependence	ICD-11 substance dependence
4	Important social, occupational or recreational activities are given up or reduced because of drinking or psychoactive substance use	Recurrent substance use resulting in a failure to fulfil major role obligations at work, school or home	Progressive neglect of alternative pleasures and responsibilities because of psychoactive substance use or increased amount of time necessary to obtain or take the substance or to recover from its effects	2. Substance use becomes an increasing priority in life such that its use takes precedence over other interests or enjoyments, daily activities, responsibilities or health or personal care. It takes an increasingly central role in the person's life and relegates other areas of life to the periphery. Substance use often continues despite the occurrence of problems
5	A great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects	A great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects	Subsumed in the above criterion	
6.	The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance	Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by that substance	Persisting with substance use despite clear evidence of overtly harmful consequences	
7.	Tolerance: As defined by either (a) a need for markedly increased amounts of the substance to achieve the desired effects or (b) markedly diminished effect with continued use of the same amount of the substance	Tolerance is defined by either of the following: a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect or b) a markedly diminished effect with continued use of the same amount of the substance	Tolerance: Such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses	3. Physiological features (indicative of neuroadaptation to the substance) as manifested by (i) tolerance, (ii) withdrawal symptoms following cessation or reduction in use of that substance or (iii) repeated use of the substance (or pharmacologically similar substance) to prevent or alleviate withdrawal symptoms. Withdrawal symptoms must be characteristic for the withdrawal syndrome for that substance and must not simply reflect a hangover effect
8.	Withdrawal as manifested by either (a) the characteristic withdrawal syndrome for the substance or (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms	Withdrawal is manifested by either of the following: a) the characteristic withdrawal syndrome for the substance or b) the substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms	A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance, or use of the same (or a closely related substance) with the intention of relieving or avoiding withdrawal symptoms	

(continued)

Table 8.3 (continued)

	DSM-IV dependence	DSM-5 substance use disorder	ICD-10 substance dependence	ICD-11 substance dependence
9.Former DSM-IV abuse	Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g. arguments with spouse about consequences of intoxication, physical fights)	Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance	To some extent subsumed in criterion no. 4	To some extent subsumed in criterion no. 2
10. Former DSM-IV abuse	Recurrent substance use in situations in which it is typically hazardous (drink driving)	Recurrent use in situations in which it is physically hazardous	No equivalent criterion	No equivalent criterion
11. Former DSM-IV abuse	Recurrent substance use which results in failure to fulfil major obligations at work, school or home	Important social, occupational or recreational activities are given up or reduced because of substance use	To some extent subsumed in criterion no. 4	To some extent subsumed in criterion no. 2
Former DSM-IV abuse, now omitted	Recurrent substance-related legal problems (e.g. driving an automobile or operating a machine when impaired by substance use)			

In DSM-5, the diagnosis of substance use disorder is further classified according to severity: presence of 2–3 symptoms, mild; presence of 4–5 symptoms, moderate; and presence of 6 or more symptoms, severe

cessation or reduction in use of that substance and iii) repeated use of the substance (or pharmacologically similar substance) to prevent or alleviate withdrawal symptoms. Withdrawal symptoms must be characteristic for the withdrawal syndrome for that substance and must not simply reflect a hangover effect.

The concordance of the ICD-11 Substance Dependence diagnostic guidelines with their counterparts in ICD-10 and the criteria in DSM-IV have been found to be in almost perfect agreement for alcohol dependence, cannabis dependence and prescribed opioid dependence with the ICD-10 and DSM-IV classifications of dependence [12, 13, 30]. However, there is much less agreement with DSM-5 substance use disorder for alcohol or cannabis [12, 30].

Substance Dependence typically occurs in people who use large amounts of psychoactive substances, for example, people consuming alcohol in excess of 120 g/day (men) or 80 g/day (women). The diagnosis of Substance Dependence is not, however, made primarily on the level of consumption.

8.3.1.5 Substance Use Disorder (DSM-5)

DSM-5 has radically restructured the conceptualisation and classification of substance-related disorders [4]. Substance Dependence and Abuse have been replaced by the broader concept of sub-

stance use disorder. Substance use disorder is now the central diagnosis and represents essentially a combination of the diagnostic features of DSM-IV Substance Dependence and Substance Abuse (Table 8.3), with one Substance Abuse criterion omitted and the ICD-10 criterion of craving added. This offers a simplified diagnostic system.

In DSM-5, substance use disorder is defined as a problematic pattern of substance use leading to clinically significant impairment or distress, manifested by at least two of the following 11 criteria occurring within a 12-month period:

1. The substance is often taken in larger amounts over a longer period than was intended.
2. There is persistent desire or unsuccessful efforts to cut down or control substance use.
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects.
4. Craving or a strong desire or urge to use the substance.
5. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school or home.
6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
7. Important social, occupational or recreational activities are given up or reduced because of substance use.
8. Recurrent substance use in situations in which it is physically hazardous.
9. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by that substance.
10. Tolerance as defined by either of the following: (a) a need to markedly increase amounts of substance to achieve intoxication or desired effect or (b) a markedly diminished effect with continued use of the same amount of substance.
11. Withdrawal as manifested by either of the following: (a) the characteristic withdrawal syndrome for the substance or (b) the substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

The severity is graded on the number of criteria met, namely, mild, 2–3; moderate, 4–5; and severe, 6 or more (Table 8.3). Moderate to severe substance use disorder in DSM-5 is roughly equivalent to Substance Dependence in ICD-10 and ICD-11 [24, 72].

DSM-5 substance use disorder is a very broad and heterogeneous condition, and there is a risk that its extended scope means that it is less useful for determining treatment than the concept of Substance Dependence. The change occurred despite Substance Dependence being a psychometrically robust syndrome [11, 23, 38, 57, 64]. An example of this is the requirement for dependence on heroin or other opioids for there to be justification in prescribing opioid agonist maintenance therapy with methadone or buprenorphine.

8.3.1.6 Other Definitions of Dependence or Addiction

The two systems that have most impact internationally are the ICD and the DSM, under the auspices of the World Health Organization and the American Psychiatric Association (APA), respectively. Several professional organisations have developed definitions for use by their own members/fellows (the APA is a national professional organisation. But the DSM has such international reach that it is more appropriately classified as an international system). Foremost of these other organisations is the American Society of Addiction Medicine (ASAM). It employs the term "addiction" rather dependence or "use disorders". The ASAM definition of "addiction" [5] is as follows:

> Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviours.

> Addiction is characterized by inability to consistently abstain, impairment in behavioural control, craving, diminished recognition of significant problems with one's behaviours and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

This is a fundamentally different concept to those of dependence in the ICD and DSM systems and even more distant to the DSM-5 understanding of substance use disorders. The main points of distinction are as follows:

1. The disorder is described as "primary" and suggests a fundamental (presumably) biological difference between those who are addicted and those who are not, rather than the notion of an acquired syndrome which is the nature of the dependence syndrome.
2. The disorder is described as "progressive" in an unqualified way, which is different to the concept that dependence can undergo "natural" remission (i.e. without treatment).
3. There is no sense of a spectrum of disorder.

There are five central features of addiction in this conceptualisation, which are the following:

(a) Inability to consistently abstain
(b) Impairment in behavioural control
(c) Craving or increased "hunger" for drugs or rewarding experiences
(d) Diminished recognition of significant problems with one's behaviours and interpersonal relationships
(e) A dysfunctional emotional response

These features might be considered diagnostic criteria for addiction, although it is not clear how many are required for the diagnosis and in what combination. The psychometric performance of the criteria is unknown. Despite these shortcomings, the ASAM definition well summarises the experience of patients at the severe end of the spectrum of substance use disorders. It has an intuitive appeal to many clinicians, particularly those working in in-patient treatment programmes and residential recovery programmes. The definition has been adopted, on a temporary basis, by the International Society of Addiction Medicine and the Canadian Society of Addiction Medicine.

8.3.1.7 Substance Withdrawal (DSM-IV, DSM-5, ICD-10 and ICD-11)

Substance withdrawal refers to a state which may occur when substance use is curtailed in persons with Substance Dependence or a physiological dependence on a psychoactive substance even though the diagnosis of Substance Dependence may not apply. Substance withdrawal is also likely to occur in DSM-5 substance use disorder of the moderate or severe subtypes. It is an important manifestation of the neurobiological changes that underpin dependence. In general, the features of the withdrawal syndrome are opposite to those of the acute pharmacological effects of the substance. In contrast to dependence, the withdrawal syndrome varies appreciably according to the substance. Psychostimulant withdrawal is very different to withdrawal from sedative-hypnotics. Substance withdrawal is often listed as a "substance-induced disorder"; however, given its intimate relationship with dependence, it is discussed at this point.

Substance withdrawal is generally stated to be a clinically significant cluster of symptoms specific to the known withdrawal state of that substance. The ICD system specifies that there has been repeated and usually prolonged and/or high-dose use of that substance. The withdrawal syndrome develops in a period from hours to a few days (or more rarely longer) after cessation or reduction in use. There is variable severity and duration of symptoms. The DSM system requires that the signs or symptoms cause clinically significant distress or impairment in social, occupational or other areas of functioning. The specific criteria in DSM-5, ICD-10 and ICD-11 are listed in Table 8.4. The onset and course of the withdrawal state are time-limited and are related to the type of substance and the dose being used immediately before abstinence. Three types of

Table 8.4 Diagnostic guidelines for substance withdrawal (DSM-5, ICD-10, ICD-11)

	DSM-5	ICD-10	ICD-11
Primary definitions and criteria	A. Characteristic withdrawal syndrome that develops within hours or a few days after the cessation of (or reduction in) heavy and prolonged substance use B. The development of two or more signs/symptoms specific to the substance, developing within hours to a few days after cessation or reduction in use C. The signs or symptoms cause clinically significant distress or impairment in social, occupational or other areas of functioning	A group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a substance For diagnosis of withdrawal syndrome, there should be clear evidence of recent cessation or reduction of substance use after repeated and usually prolonged and/or high dose use of that substance. A withdrawal state is one of the main indicators of the dependence syndrome	A clinically significant cluster of symptoms, behaviours and/or physiological features, varying in degree of severity and duration that occurs upon cessation or reduction of use of a substance in individuals who have developed substance dependence or have used the substance for a prolonged period or in large amounts
Additional guidelines		Symptoms and signs compatible with the known features of a withdrawal state from the particular substance or substances. Physical symptoms vary according to the substance being used. Psychological disturbances (e.g. anxiety, depression, sleep disorders) are also common features of withdrawal. Typically, the patient reports that withdrawal symptoms are relieved by further substance use. The features are not accounted for by a medical disorder unrelated to the substance use, and not better accounted for by another mental or behavioural disorder	Physical symptoms vary according to the substance being used. Psychological disturbances (e.g. anxiety, depression, sleep disorders) also are common features of withdrawal. Typically, the patient reports that withdrawal symptoms are relieved by further substance use Onset and course of the withdrawal state are time limited and are related to the type of substance and the dose being used immediately before abstinence. Less commonly, the withdrawal state is complicated by seizures. Substance-induced delirium includes withdrawal states which are complicated by delirium
Explanatory notes	*Note that substance-specific features of withdrawal are listed under the primary criteria*		*Note that substance-specific features of withdrawal are listed under the primary definitions*

withdrawal are recognised in DSM-5 and ICD-10, but in ICD-11, withdrawal with delirium is subsumed in the diagnosis of substance-induced delirium [72]. More broadly, substance withdrawal may vary from mild to very severe. For example, alcohol withdrawal may vary from mild features of autonomic hyperactivity to delirium tremens (DTs) [62]. Convulsions generally herald the onset of delirium tremens which has a mortality rate of about 15%. The acute alcohol withdrawal syndrome needs to be differentiated from Wernicke's encephalopathy [31]. Benzodiazepine withdrawal has a similar picture but may persist for weeks or months [41]. Opioid withdrawal resembles a flulike illness [61] with aches, pains, rhinorrhoea, nausea, vomiting, sweating, features of autonomic hyperactivity, irritability, agitation, insomnia and strong cravings for opioids. Dilatation of the pupils is a characteristic physical sign. Cannabis withdrawal

[61] includes irritability, restlessness, anxiety, insomnia and mood changes. Cannabis withdrawal was not recognised in DSM-IV, although it is now included in DSM-5 [4]. Withdrawal from psychostimulants [61] is an exaggeration of the "crash" and is characterised by craving, low mood, irritability, sleep disturbance, anxiety, dysphoria, depression and increased risk of suicide.

8.3.1.8 Substance-Induced Disorders

Substance-induced or substance-related problems or disabilities encompass the multiple physical disorders, mental health disorders, neurocognitive impairments and social, personal, occupational and legal problems. The World Health Organization Committee conceptualised substance-related problems or disabilities as the *consequences* of repetitive substance use [18, 19, 57, 59].

Substance-Induced Mental and Neurocognitive Disorders (DSM-IV, DSM-5, ICD-10 and ICD-11)

In DSM-IV and ICD-10, there are several substance-related mental disorders. These include substance-induced depression, substance-induced anxiety disorder, substance-induced bipolar disorder and substance-induced psychotic disorder. In DSM-5, the same disorders are present, but they are located in the chapters describing the respective generic mental disorder. For example, substance-induced anxiety disorder is grouped within the anxiety disorders section.

In addition, there are neurocognitive consequences of substance use disorders. Here, we shall briefly describe one of the former – psychotic disorder – and two of the latter, delirium and amnesic syndrome. In DSM-IV, DSM-5, ICD-10 and ICD-11, there are several substance-related mental disorders of variable in severity and duration. They are usually temporary but may persist over weeks or more rarely months [61, 72]. They include substance-induced mood disorders, anxiety disorder, sleep-wake disorder, sexual dysfunction and for psychostimulants substance-induced obsessive-compulsive disorder. Different syndromes are caused by different substances. Here, we shall discuss just three of them: delirium, psychotic disorder and amnesic syndrome.

(i) *Substance-Induced Delirium (DSM-IV, DSM-5 and ICD-11)*

Delirium is an uncommon feature of substance misuse, although sometimes the diagnosis is made in persons with acute intoxication. Substance intoxication with delirium is an accepted diagnosis in DSM-IV and DSM-5 [3, 4] but not in ICD-10 [70], but it is included in ICD-11 [72]. Most commonly, it is seen in those with a severe withdrawal syndrome from alcohol or sedative drugs [62].

The classical disorder is delirium tremens (DTs) [62], which is a short-lived but occasionally life-threatening toxic confusional state with accompanying somatic disturbances. It is usually a consequence of absolute or relative cessation of alcohol in severely dependent drinkers with a long history of use. Its onset may be preceded by features of simple withdrawal and/or by withdrawal convulsions. A similar withdrawal delirium is seen after cessation of benzodiazepines and other sedative hypnotics although with less tremor. In DSM-5, substance intoxication delirium is differentiated from substance withdrawal delirium in the chapter on neurocognitive disorders [4].

(ii) *Substance-Induced Psychotic Disorder (DSM-IV, DSM-5, ICD-10 and ICD-11)*

Psychosis or psychotic symptoms occur in many people with substance use disorders. In some, the psychosis is a consequence of drug use. In others, it reflects an underlying independent disorder such as schizophrenia. Sometimes the aetiology and mechanisms are unclear.

Substance-induced psychotic disorder is presented as an example of a mental disorder induced by substance use. It features in both the DSM and ICD systems. Substance-induced psychotic disorder is a phenomenon that occurs during or soon after (usually within 48 hours) intoxication with, or withdrawal from, a psychoactive substance. It is characterised by psychotic symptoms, e.g.

delusions, vivid hallucinations (typically auditory but often in more than one sensory modality), disorganised thinking, grossly disorganised behaviour, misidentifications, psychomotor disturbances (excitement or stupor), and an abnormal affect, which may range from intense fear to ecstasy. The disorder typically resolves within 1 month and fully within 6 months. The sensorium is usually clear, but some degree of clouding of consciousness, though not severe confusion, may be present. The disorder typically resolves at least partially within 1 month and fully within 6 months. The diagnosis is excluded if the psychotic state is a manifestation of substance withdrawal syndrome. The ICD-11 definition emphasises that the amount and duration of substance use must be capable of producing psychotic symptoms and that the symptoms are not better explained by a primary mental disorder, for example, if they preceded the onset of substance use or persisted for a substantial period of time after cessation of substance use or if there is a pre-existing primary mental disorder with psychotic symptoms.

In DSM-5, substance/medication-induced psychotic disorders are mentioned in the chapter on schizophrenia spectrum and other psychotic disorders with the psychotic disorder associated with alcohol, cannabis, phencyclidine, other hallucinogens, inhalants, sedative/hypnotic/anxiolytic, amphetamine (or other stimulant), cocaine and other unknown substance. The psychotic symptoms are thought to be a physiological consequence of a drug of abuse (medication or toxin) and cease after removal of the agent. The diagnostic criteria in DSM-5 are the following:

A. The presence of one or both of the following symptoms: (a) delusions and (b) hallucinations.
B. Evidence that the symptoms developed during or soon after substance intoxication or withdrawal and the substance is capable of producing the symptoms.
C. The disturbance is not better explained by an independent psychotic disorder (not substance-induced), as evidenced by the following: (a) the symptoms preceded the onset of substance use, (b) the symptoms persist for a substantial period of time (e.g. about 1 month) after cessation of acute withdrawal or intoxication, and (c) there is no evidence of non-substance-induced disorder (e.g. history of recurrent non-substance-related episodes).
D. The disturbance does not occur exclusively during the course of a delirium.
E. The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning [4].

For psychostimulants such as amphetamines and cocaine, there is a dose-response relationship, with psychosis occurring especially in those who have been using high doses and/or using the drug over a lengthy period. According to ICD-10, a diagnosis of psychotic disorder should not be made merely on the basis of perceptual distortions or hallucinatory experiences when substances having primary hallucinogenic effects (e.g. lysergic acid, mescaline and cannabis in high doses) have been taken. In such cases, and also for confusional states, a possible diagnosis of substance intoxication should be considered.

(iii) *Substance-Induced Amnesic Syndrome (DSM-IV, DSM-5, ICD-10 and ICD-11)*

Amnesic (amnestic) syndrome is an example of a substance-related disorder where there is anatomical brain damage, caused in this case by the combined effects of thiamine deficiency and toxicity of the substance, typically alcohol [7, 61]. The most common chronic form is characterised by impairment of recent memory, with relative preservation of remote memory and with normal immediate recall. Disturbances of time sense and ordering of events are usually evident, as are difficulties in learning new material. Confabulation may be marked but is not invariably present and should not be regarded as a prerequisite for diagnosis. Importantly, other cognitive functions are usually relatively well preserved; the amnesic defects are, therefore, out

of proportion to other disturbances. Personality changes, often with apparent apathy and loss of initiative, and tendency towards self-neglect may be present but are not necessary for the diagnosis.

Substance-induced amnesic syndrome is classified in DSM-5 within the neurocognitive disorders and not as a substance-induced mental disorder. The diagnostic criteria are those of substance/medication-induced neurocognitive disorder, and although an amnesic-type disorder seen with alcohol is noted, no specific criteria are included. In ICD-10, substance-induced amnesic syndrome is included in the substance disorders chapter, with a specific definition and diagnostic guidelines. However, in ICD-11, it is included in the neurocognitive disorders chapter within the section of amnestic disorders (and therefore distinct from the dementias) and under the heading of "Amnestic Disorder Due to Psychoactive Substances Including Medications".

Substance-Induced or Substance-Related Physical Disorders

Complications arising from repetitive substance use stem not only from the pharmacological properties of a particular substance but also from unknown potency and purity and sterility from contaminants and adulterants with which the substance is prepared, unsafe injecting practices and the associated lifestyle of the user. The spread of bacterial infections and viral infections, such as hepatitis C and HIV and to a lesser extent hepatitis B, is important in this regard [61]. The disinhibiting effect of alcohol and substance use also places users at risk of sexually transmitted diseases.

In DSM-III, DSM-IIIR and DSM-IV, relevant physical disorders were noted in Axis III of the multiaxial system. DSM-5 has abandoned this multiaxial system, and comorbid physical disorders receive little attention. ICD-10 by contrast lists an array of these disorders, in keeping with its objective of encompassing all human disorders irrespective of aetiology.

Alcohol consumption can cause disease in virtually every organ system in the body and is also associated with a range of malignancies. Cannabis and tobacco use commonly induce respiratory disorders with the latter being a major cause of bronchial cancer [46, 47, 50, 61].

In the ICD system, substance-induced physical disorders are not included with the main grouping of disorders due to substance use but are classified in the respective organ and body systems sections. For example, alcoholic cirrhosis of the liver is included as one of several forms of alcoholic liver disease in the section on diseases of the liver within the chapter "Diseases of the Digestive System". It should be noted that alcohol and certain other substances are risk factors for many physical disorders in addition to those for which they are a principal causal agent. At the same time, to examine relationships between use patterns and consequences without considering whether a diagnosable substance use disorder is present, as is usual in epidemiological studies, is limiting. In support of including hazardous use in a diagnostic system is the evidence that it can be defined and it responds to therapy, the evidence base for the effectiveness of interventions for hazardous alcohol consumption being particularly strong [6, 14, 60, 61, 69]. Thus, in a comprehensive diagnostic system, there are grounds for having a dependence category, a non-dependence disorder that is of clinical consequence and a "subthreshold" disorder that indicates risk to individuals and populations.

Substance-Related Social Problems

The adverse consequences of a substance use disorder are legion. Some will be the presenting problem(s) and will be uppermost in the patient's (or relative's) mind. Examples of social problems are the following:

- Relationship problems
- Interpersonal difficulties
- Financial problems
- Work-related problems/unemployment/prostitution
- Legal/forensic problems such as drunk driving

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Part II

Drugs of Abuse and Pharmacotherapies for Substance Disorders

Jag Khalsa and Kristopher Bough

9 Drugs of Abuse and Pharmacotherapies for Substance Use Disorders: Introduction

Jag H. Khalsa

Contents

Abstract

Substance use/abuse remains a major problem in the world. The use of both *legal* (alcohol, tobacco, caffeine) and *illegal* drugs (androgenic anabolic steroids, amphetamines, benzodiazepines, cannabis, cocaine, heroin/opiates, hallucinogens, inhalants, khat, and prescribed/misused drugs) is associated with serious morbidity (health consequences) and mortality. Several chapters in this section discuss epidemiology, pharmacology, and various therapeutic interventions available for clinical management of health consequences of various substance use disorders. It should be noted that even though the treatment of substance use disorders with a wide range of clinical symptoms is complex, effective clinical management is achievable with integrated programs of health care. It is anticipated that the reader at the global level will benefit from the current knowledge on clinical management of health effects of drugs of abuse presented in this section.

Keywords

Drug abuse · Pharmacotherapies · SUDS

9.1 Introduction

Substance abuse and associated addiction/dependence continue to remain some of the major problems in the world. According to the 2018 WHO Drug Report [1], an estimated 275 million people worldwide, which is roughly *5.6 percent of the global population* aged 15–64 years, used drugs at least once during 2016. Some 31 million people who use drugs

J. H. Khalsa (✉)
Division of Therapeutics and Medical Consequences, National Institute on Drug Abuse, National Institutes of Health, Aldie, VA, USA
e-mail: jag.khalsa@nih.gov

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suffer from drug use disorders, meaning that their drug use is harmful to the point where they may need treatment. Roughly 450,000 people died as a result of drug use in 2015. Of those deaths, 167,750 were directly associated with drug use disorders (mainly overdoses). Opioids continued to cause the most harm, accounting for 76 percent of deaths where drug use disorders were implicated. In the USA, an estimated 19.7 million American adults (aged 12 and older) battled a substance use disorder in 2017 [2]. Almost 74% of adults suffering from a substance use disorder in 2017 struggled with an alcohol use disorder. There were 70,000 deaths from opiate overdoses. In addition, the total economic cost to the USA alone was $740 billion (tobacco, $300B; alcohol, $249B; illicit drugs, $193B; prescription drugs, $78.5B); the health-related costs were estimated to be $168B, $27B, $11B, and $26B for tobacco, alcohol, illicit drugs, and prescription drugs, respectively.

Regardless of the incidence and prevalence of legal and illegal drug use/abuse, we must recognize that we will never be able to completely eradicate drug abuse. But we *must* be able to recognize and characterize the wide range of serious health and medical consequences of both legal and illegal drugs and reduce their impact on society by using the best and effective intervention (prevention and treatment) strategies. The health consequences of legal substances (e.g., caffeine, tobacco, and alcohol), prescription drugs (e.g., benzodiazepines, opioid pain medications, and androgenic anabolic steroids), and illegal substances (e.g., amphetamines, cocaine, opiates, hallucinogens, and marijuana) involve almost every biochemical and physiological system, and these may include psychiatric, cardiovascular, metabolic, and hepatic complications and infectious diseases.

In the first edition of the textbook on drug treatment, all the important aspects of medical consequences of substance abuse were discussed. This section of the second edition of the text book will have updated chapters discussing the currently available interventions (prevention and treatment) for reducing the impact of health consequences of substance abuse.

A typical patient with a substance use disorder (SUD) has multiple problems rather than single pathology, yet it is not generally feasible for multiple specialists to become involved. In addition, it is also not adequately covered in medical school training. Consequently, the addiction medicine specialist needs a broad range of clinical skills to adequately manage patients with complex health problems including pain. Alcohol and other drugs particularly affect the neurological systems but may also involve other physiological and biochemical systems including gastrointestinal, cardiovascular, hepatic, and metabolic systems as well. The medical comorbidities may include psychiatric, cardiovascular, co-occurring infections, or other physiological system involvement; this section will briefly address specific non-infectious drug-related consequences and their clinical management.

9.2 Use/Abuse of Legal Substances

The two most toxic substances of use, alcohol and tobacco, are legal and are associated with significant morbidity and mortality. In Chap. 10 on *alcohol* use disorder (*AUD*), Trick and LeFoll discuss several pharmacological combined with behavioral and psychosocial interventions that are effective for treating AUD. In addition to the already approved medications such as disulfiram, naltrexone, acamprosate, and nalmefene, some "off-label" medications are also under investigation for treating AUD. Research is underway to better understand predictors of treatment response which may ultimately lead to improved treatment outcomes in the future.

In Chap. 15 on *tobacco* use and its treatment, Sasiadek, Durham, and George point out that even though the rates of tobacco use and tobacco use disorder have reduced substantially over the past 40 years, an estimated 1.1 billion people worldwide and 34 million people in the USA still smoke tobacco. A substantial number of these people develop tobacco use disorder (*TUD*) with significant morbidity and commonly, cancer-related mortality. An estimated 10% are successful in

quitting smoking (CDC [3]). The chapter presents the available research on clinical assessment; various psychosocial and pharmacological treatments, including the FDA-approved pharmacotherapies: nicotine replacement therapies (NRTs), sustained-release bupropion, and varenicline; and finally the integration of tobacco use disorder treatment into mental health settings. There are future challenges such as developing safer and more effective therapies for smoking cessation and making these therapies available to all smokers who want to quit.

Finally, in the chapter on *caffeine* (Chap. 16), Favrod-Coune and Broers report on a substance that is used by >90% of the world's population. They provide insight into health consequences of caffeine and other xanthines, especially focusing on coffee, tea, or energy drinks. They recommend the distribution of more and better information to the population about the risk of acute intoxication of caffeine, the nutritional and metabolic risks of energy drinks, and the problems of mixing these with alcohol. They recommend placing warning messages on caffeine-containing food or drinks as well as a legal limitation of the content of caffeine. In addition, they discuss possible treatment modalities for their excessive use and abuse.

9.3 Illegal or Medically Prescribed but Misused Drugs

With regard to addiction to *amphetamine*-type stimulants (*ATS*, Chap. 14), Elkashef and Khalsa discuss the consequences of and pharmacotherapies for treating addiction to amphetamine-type stimulants. They suggest that treatment to ATS addiction should begin early, be comprehensive and integrated, and should be long term and that treatment modalities such as psychotherapeutic interventions, medications including agonists like d-amphetamine and methylphenidate and other medications like bupropion, modafinil, naltrexone, and topiramate have been found to be promising for treating addiction to ATS.

In the chapter on *anabolic androgenic steroids* (Chap. 21), Kanayama and Pope report that AAS use was common among athletes in the past, but now their use has spread widely in the general population with an estimated 2.9 to 4.0 million users in the USA. The AAS use is associated with significant morbidity resulting in cardiovascular, psychiatric, endocrine, and musculoskeletal complications and dependence in AAS users. Though there are no known specific anti-AAS medications available to treat AAS consequences, medications have been used to treat specific consequences of AAS such as endocrine effects and muscle dysmorphic syndrome.

The use of *benzodiazepine and benzodiazepine-like drugs (z-type)* such as sedatives, hypnotics, antiepileptics, and muscle relaxants continues to be a major problem in the world. Umbricht and Valez (Chap. 11) report that the use of these drugs, particularly among adolescents, women, elderly, and polydrug abusers, is associated with significant morbidity and mortality. In the USA alone, 12.5% of adults aged 65 years old are prescribed BZDs or Z-drugs in spite of a clear increase in mortality in this age group. An estimated 3–41% of patients with alcohol use disorder also misuse BZDs. Opioids are also involved in about 75–86% of benzodiazepine deaths. Nearly 30% of fatal opioid overdoses in the USA also involve benzodiazepines. The authors present an excellent discussion on adverse consequences of BZD in various populations and currently available prevention and non-pharmacologic interventions for benzodiazepine users.

As mentioned above, *cannabis* remains the most illicit drug used in the world, and its associated cannabis use disorder (*CUD*) poses a major public health problem. In a chapter on CUD (Chap. 12), Budney, Sofis, and Borodovsky discuss cannabis use, the associated social and health problems, and intervention therapeutic (tested and novel), pharmacologic, and behavioral (MET/CBT/CM) modalities for treating CUD and relapse. They also discuss novel approaches of modulating the endocannabinoid system; alternative dosing with CB1 agonists, and combinations of medications targeting withdrawal and co-occurring symptoms and disorders that may interfere with cannabis reduction or prompt relapse.

Cocaine use is also associated with significant morbidity and mortality. Currently, there are no specific FDA-approved medications for treating cocaine use disorder (*CUD*). However, in a chapter on cocaine (Chap. 13), Gorelick reports that treatment strategies such as "off-label" medications including disulfiram, tricyclic antidepressants such as desipramine and imipramine, the anticonvulsant topiramate, and behavioral modalities are being used for treating CUD. He suggests that by understanding neurobiology of cocaine addiction, one could develop innovative treatment modalities for treating CUD. Importantly, clinicians should keep in mind the distinctions between efficacy and effectiveness and between a statistically significant and clinically meaningful treatment effect.

According to Odenwald, Kline, and Warfa (Chap. 17), although the epidemiology of *khat* use is not very clear, its use is associated with neurocognitive deficit and other health problems similar to those produced by other CNS stimulants. The authors highlight that not much is known about any effective treatments for khat addiction. Thus, Odenwald suggests the following measures: there is a strong need to (a) develop reliable and cross-culturally valid diagnostic instruments, (b) develop effective and adequate treatment strategies applicable in traditional khat use countries and among immigrant communities elsewhere in the world, (c) support strong empirical research designs to guide national and international politics, and (d) support the development of law and public health strategies, both in the "khat belt" and among the diaspora.

In the chapter on *hallucinogens* (Chap. 19), Farre and her colleagues describe a heterogeneous group of substances that act via 5-HT2A, NMDA, and opioid-kappa receptors, producing primarily perception but also substance use disorder with acute tolerance but without withdrawal syndrome. For treating hallucinogen use disorder, there are no specific therapeutic modalities available, but the aim would be to reduce consumption and achieve abstinence. According to the authors, hallucinogens like LSD, psilocybin, ayahuasca, and the designer drug MDMA are being evaluated for the treatment of different mental disorders. With regard to *inhalant* use, Real and her colleagues discuss (Chap. 20) the epidemiology, policy issues, pharmacology, short- and long-term health effects, and prevention and treatment interventions, with particular attention to special and vulnerable populations including children, adolescents, students, indigenous groups like workers exposed to solvents, and anesthesiologists, affected by inhalant use.

Opiate abuse and resulting epidemic have become a major problem in the world. In Chap. 18 on opioid use disorder (*OUD*) and its treatment, Torrens and colleagues have discussed pharmacology of different opioid drugs and currently available pharmacotherapies including methadone and buprenorphine, combined with psychosocial interventions to treat opioid use disorder and associated complications including overdose or naltrexone depot formulations for preventing relapse. They also discuss the possibility of using alternative pharmacotherapeutics such as slow-release morphine and diacetylmorphine for treating opiate use disorder.

Finally, the use of *prescription* drugs including sedatives, stimulants, hypnotics, and analgesics has recently caused havoc in the USA and elsewhere. The use of these drugs is associated with serious morbidity (adverse health consequences) and mortality as discussed by Bramness. Chapter 22 discusses a number of important aspects of prescription drugs, differences between various class of prescription drugs, their pharmacokinetics, assessment of adverse effects, and various prevention and treatment strategies available to the treating clinician.

In summary, this section describes the morbidity and mortality that can result from substance use/abuse. Although treatment of drug addiction and associated medical and health consequences is complex, effective clinical management is achievable with integrated programs of health care. Societally, it will begin with providing the population with an accurate description of consequences of substance use/abuse and highlighting options for treatment. And, medically, the information contained herein will also provide care providers a better understanding of the disorders and outline possible options for treatment and future research. It is anticipated that the reader at the global level

will benefit from the current knowledge on clinical management of health effects of drugs of abuse presented in this section.

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Pharmacological Treatment of Alcohol Use Disorder

10

Leanne Trick and Bernard Le Foll

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L. Trick
Translational Addiction Research Laboratory, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada
e-mail: Leanne.Trick@camh.ca

B. Le Foll (✉)
Translational Addiction Research Laboratory, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

Alcohol Research and Treatment Clinic, Acute Care Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada

Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada

Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada

Division of Brain and Therapeutics, Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada
e-mail: Bernard.LeFoll@camh.ca

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Abstract

Alcohol use disorder (AUD) is a severe condition associated with negative health, social and economic consequences, yet it often remains untreated. Pharmacological treatments for AUD are effective, especially in combination with other behavioural or psychosocial interventions. Disulfiram, naltrexone, acamprosate and nalmefene are approved pharmacological treatments for AUD. In addition, medications for other health conditions can be prescribed 'off-label', and further potentially useful drugs are under investigation. Current research is seeking to better understand predictors of treatment response which may ultimately lead to improved treatment outcomes in the future. This chapter provides a summary of approved pharmacological treatments and other medications that may prove useful in the treatment of AUD.

Keywords

Alcohol use disorder · Pharmacological treatment · Pharmacotherapy · Medication Abstinence · Relapse

10.1 Introduction

Alcohol use disorder (AUD) is a chronic relapsing condition characterized by compulsive alcohol use and loss of control over drinking, accompanied by clinically important impairment or distress. Current diagnostic criteria (DSM-5; *American Psychiatric Association*) require the presence of at least 2 out of 11 symptoms, with severity intensifying as the number of symptoms increase. In the USA estimates of 12-month and lifetime prevalence of AUD in adults are 13.9% and 29.1%, respectively [1]. According to a 2018 report by the *World Health Organization* [2], the harmful use of alcohol results in three million deaths each year, and 5.1% of all disease burden worldwide is related to alcohol use. AUD is associated with a variety of other physical and mental health conditions including neurological impairments, cardiovascular disease, liver disease, cancer, mood and anxiety disorders and foetal alcohol syndrome, along with other adverse outcomes such as risk of injury [3]. Furthermore AUD imposes a huge economic burden, for example, in the USA alone AUD has been estimated to cost $223.5 billion annually [4].

Despite the prevalence of AUD and increased morbidity, mortality and economic costs associated with it, many people with AUD remain untreated. A large US survey suggests that only 14.6% of those with a diagnosis of AUD receive treatment [5]. Thus, a large proportion of people with AUD do not receive treatment despite the availability of effective interventions (e.g. studies show that treatments for AUD are associated with reductions in risk for relapse and AUD-associated mortality [6, 7]).

Available treatments for AUD include pharmacotherapy, behavioural or psychosocial therapies involving professional counselling and mutual support groups such as *Alcoholics Anonymous*. These treatments are complementary; each addresses a different aspect of alcohol dependence, while they share the common goal of maintaining abstinence. Pharmacological treatments for AUD are recommended in conjunction with other behavioural or psychosocial approaches, and such combinations have proven to be successful [8, 9]. The US *National Institute on Alcohol Abuse and Alcoholism* recommends pharmacological treatment particularly where patients who have recently stopped drinking are experiencing problems with craving or 'slips', or in cases where behavioural or psychosocial treatments alone have previously failed.

Existing pharmacological treatments work to eliminate or reduce drinking and prevent relapse by causing unpleasant side effects if alcohol is consumed, by blocking the rewarding effects of alcohol or by suppressing craving for alcohol. Several of these medicines have been approved for the treatment of AUD by regulatory agencies (e.g. the US *Food and Drug Administration*; FDA), although approval status varies by country. Additionally, medications developed and

licensed for the treatment of other health conditions, but which have shown utility in the management of AUD, can be used 'off-label', and other new medications are under investigation which may provide treatment alternatives in the near future.

This chapter provides an overview of approved pharmacological treatments for AUD, along with other medications that appear to be useful in the treatment of AUD. Factors influencing the choice of pharmacotherapy and predictors of treatment response are briefly discussed. Other medicines used in the early stages of treatment to assist with safely managing symptoms of withdrawal from alcohol (e.g. benzodiazepines) will not be considered since this chapter focuses on pharmacological treatments intended to reduce alcohol consumption and prevent relapse. The information presented here is based on a synthesis of evidence from any country where relevant research has been conducted. In general, where reviews or meta-analyses exist (especially systematic or Cochrane reviews), these are presented in favour of the results of individual studies.

10.2 Approved Pharmacological Treatments

Four pharmacological treatments are widely approved for the treatment of AUD: disulfiram, naltrexone, acamprosate and nalmefene. This section summarizes available information about the mechanism of action, efficacy and administration of each medication in turn, followed by a head-to-head comparison of the four drugs.

10.2.1 Disulfiram

Disulfiram (marketed under the trade name Antabuse®) is licensed in many countries for the treatment of AUD including the USA, Canada and in Europe and has been in use since the 1940s.

The potential of disulfiram as a treatment for AUD was discovered by chance in the 1930s after factory workers in the rubber industry reported feeling sick when they drank alcohol, following exposure to a by-product of rubber manufacturing – disulfiram. It was later learned that disulfiram interferes with the metabolism of alcohol and discourages alcohol consumption by causing unpleasant effects such as nausea, vomiting, flushing and palpitations if alcohol is consumed. Early attempts to utilize disulfiram as a treatment for alcoholism were based on a paradigm of aversion conditioning using high doses, although this led to a number of serious adverse side effects and even deaths. Subsequently the dose was lowered, and the focus of treatment shifted to supporting abstinence by strengthening the patient's motivation to avoid alcohol.

The use of disulfiram is indicated, following initial withdrawal, for complete cessation of alcohol consumption in highly motivated patients.

10.2.1.1 Mechanism of Action

The effect of disulfiram is thought to be mainly due to its interference with the metabolism of alcohol. The majority of alcohol taken into the body is metabolized by the liver. First, the enzyme alcohol dehydrogenase (ADH) converts alcohol molecules into acetaldehyde, a toxic chemical compound. Then acetaldehyde is converted by another enzyme, aldehyde dehydrogenase (ALDH), into acetic acid. Finally, acetic acid can be broken down into water and carbon dioxide and eliminated from the body. Disulfiram blocks the natural degradation of alcohol by inhibiting the liver enzyme ALDH, which results in an accumulation of acetaldehyde. This accumulation of toxic acetaldehyde causes symptoms such as nausea, vomiting, headache, flushing, diarrhoea and hypotension. Given a sufficiently high dose of alcohol, the interaction with disulfiram can cause serious adverse events and even death. Several genetic polymorphisms exist in the genes that encode the liver enzymes ADH and ALDH, and these can have implications for drinking behaviour, responses to alcohol, risk for dependence and potentially also the treatment of AUD. For example, ALDH2 is one of two main genes responsible for encoding ALDH, and variants of this gene have been identified that are either 'active' or 'inactive' in the elimination of acetaldehyde. The

inactive form of ALDH2 (the ALDH2*2 allele) is found among approximately 50% of the Asian population and is responsible for the 'flushing' response seen after alcohol consumption, thought to be due to the accumulation of acetaldehyde (since the inactive variant of the gene inhibits breakdown of acetaldehyde). This allele is also associated with lower risk for alcohol dependence and slower development of symptoms of alcohol dependence. Polymorphisms of both ALDH2 and other genes that encode ADH (e.g. ADH1A) have also been associated with increased risk of cancer and other physical illnesses such as liver disease and diabetes in heavy drinkers, and it is proposed that this is due not only to differences in levels of alcohol consumption but also to the way alcohol is metabolized.

Disulfiram also acts as a dopamine beta-hydroxylase inhibitor [10, 11]. This inhibition creates a decrease of norepinephrine and an increase of dopamine levels in the brain. Such an imbalance may have therapeutic properties for the treatment of substance use disorders and could explain why disulfiram can affect behavioural responses related to addiction (even in animals never exposed to alcohol).

Finally, some consider disulfiram a form of psychological treatment, since the anticipation of adverse effects (if alcohol is consumed) is a key element of successful treatment. For example, randomized controlled studies have shown that disulfiram is only effective at reducing alcohol consumption when it is administered in open-label (i.e. unblinded) conditions and where patients receive clear and repeated information about the adverse effects produced by the disulfiram-alcohol interaction [12].

10.2.1.2 Efficacy

Evidence of the effectiveness of disulfiram for the treatment of AUD is limited. Several reviews report mixed findings, with a reduction in the amount of alcohol consumed and/or a reduction in the number of drinking days in disulfiram-treated patients compared to placebo in some studies but no improvements in relapse rates. Concerns have also been raised about heterogeneity among existing trials and weak study quality [13–16].

A recent meta-analysis of 22 randomized controlled trials (cumulative total $N = 2414$) highlighted several methodological inconsistencies among existing studies [12]. Importantly, this review also demonstrated the impact of study design on appraisals of effectiveness. Two-thirds of the studies included in the meta-analysis used an open-label design, and the remainder used a blinded design. Results showed that disulfiram was effective only in open-label trials. While the 'gold standard' for trials of this type would usually dictate blinded treatment administration, the findings here are in fact consistent with disulfiram's mechanism of action; since the expectation of unpleasant effects due to the disulfiram-alcohol interaction is thought to motivate abstinence, it follows that the certain knowledge of having received active treatment is a necessary condition for its success.

Treatment supervision has been identified as another important variable that appears to impact on efficacy. For example, in one small review, the only study that showed a positive effect of disulfiram compared to placebo was also the only study to use supervised administration. The authors reported a further comparison of five studies using supervised versus unsupervised treatment and concluded that best outcomes were achieved where disulfiram administration was supervised by a healthcare provider [17]. Some existing studies have been criticized because of poor treatment compliance and low retention rates (e.g. 46% of patients dropped out before the end of one study), and this has been particularly problematic in studies where treatment was unsupervised [15]. This suggests that enhanced compliance may be one mechanism by which treatment supervision might improve outcomes.

The optimal duration of disulfiram treatment is currently unclear. A review comparing short- and long-term treatments found improvements in days until relapse and number of drinking days with short-term disulfiram treatment compared to placebo, but only limited positive effects of disulfiram with longer-term (12 months) treatment [18]. On the other hand, in a single study of patients with severe AUD in long-term treatment, an abstinence rate of more than 50% was observed

using guided administration of disulfiram over 9 years follow-up. This suggests that extended treatment with disulfiram might be useful but only in the context of comprehensive outpatient treatment with adequate supervision [19].

Studies showing reduced craving and increased consecutive days of abstinence in alcoholics with co-morbid psychiatric diagnoses [20] and reductions in alcohol consumption in poly-substance users [21] following disulfiram treatment suggest that disulfiram may have value in patients with other psychiatric and substance use co-morbidities.

10.2.1.3 Administration

Dose and Regimen

An oral dose of disulfiram should be taken once daily, tapered up over 1–2 weeks to an average maintenance dose of 250 mg daily (maximum dose 500 mg). Patients should receive a thorough explanation of the rationale and effects of disulfiram treatment, including information about the disulfiram-alcohol interaction, strong cautions about drinking while taking disulfiram and warnings about ingestion of products that may not obviously contain alcohol (e.g. sauces, cough mixtures, liniments, sanitizing gels, etc.). It is not necessary to 'test' the disulfiram-alcohol interaction (i.e. to induce an aversive reaction by administering alcohol under supervision) since this does not improve efficacy as long as adequate education is provided [19].

Non-compliance is one of the biggest problems with disulfiram use. It is therefore important that patients are committed to treatment and it is administered under supervision. Ideally, the clinician should arrange for the pill to be taken under supervision by a family member to ensure better adherence to treatment. Treatment may last for months or years, and after initial treatment has been discontinued patients may choose to restart disulfiram in anticipation of exposure to high-risk situations or during periods of acute stress that may challenge their resolve to remain abstinent.

Contraindications

Patients must be detoxified (ideally for a few days), free of alcohol for at least the past 12 hours and free of withdrawal symptoms before treatment with disulfiram can commence. It should be noted that a disulfiram-alcohol reaction can occur for up to 2 weeks after disulfiram has been discontinued.

Disulfiram is contraindicated in patients with psychosis, severe myocardial disease and coronary occlusion and in pregnant or nursing mothers. Caution is recommended in patients with cardiac disease, diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, kidney disease, cirrhosis of the liver, liver failure and hepatitis C. Caution is also recommended in children, adolescents and older adults (dose reductions should be considered in adults aged over 60 years). Prescribers should be aware of interactions with other drugs including benzodiazepines, isoniazid, monoamine oxidase inhibitors, tricyclic antidepressants, warfarin, metronidazole, theophylline, phenytoin and lithium. Dose adjustments and careful monitoring may be necessary to ensure patient safety.

Side Effects

If alcohol is not consumed, side effects associated with disulfiram are generally mild and appear within the first 1–2 weeks of treatment. Tiredness is the main side effect. Other common side effects include headache, metallic taste in the mouth, skin rash, impotence in men and a swollen or sore tongue. Less common but serious side effects include optic neuritis, peripheral neuropathy, hepatitis, liver failure and psychosis.

A meta-analysis of randomized controlled trials investigating the efficacy of disulfiram also collated information relating to adverse effects. While more adverse events were reported in disulfiram-treated groups overall compared to controls, there was no difference in the number of deaths or serious adverse events requiring hospitalization suggesting that disulfiram is safe in carefully screened groups, such as those included in clinical trials [12].

10.2.2 Naltrexone

Naltrexone is approved for use in the treatment of AUD in over 30 countries worldwide [22]. The FDA approved an oral formulation in 1994, followed in 2006 by an extended-release injectable formulation that was developed to improve treatment retention and adherence. Oral naltrexone is marketed under trade names including ReVia®, Natrel® and Depade® and extended-release as Vivitrol®.

In the treatment of AUD, naltrexone may be useful in preventing relapse by blocking the pleasurable rewarding effects of alcohol. It is indicated in detoxified patients who are not currently using, or who have not recently used, opioids.

10.2.2.1 Mechanism of Action

Naltrexone is an opioid receptor antagonist with high affinity for the μ-receptor and weaker affinity at δ- and κ-receptors. The mechanism by which naltrexone reduces alcohol consumption is not fully understood, although it is thought to be mediated by the endogenous opioid and dopamine systems. In the brain, acute alcohol consumption triggers the release of the endogenous opioid β-endorphin, which in turn stimulates dopamine release in the nucleus accumbens and other areas of the mesolimbic-dopamine pathway involved in the processing of reward and thought to be responsible for the positive reinforcing effects of alcohol. Due to its antagonist properties at the μ-opioid receptor, naltrexone may suppress alcohol consumption by blockade of the receptor (therefore also blocking dopamine release), thus disrupting the pleasurable positive reinforcing effects of alcohol and reducing alcohol craving. This hypothesis is supported by animal studies showing that mice without the μ-opioid receptor do not self-administer alcohol, presumably due to lack of positive reinforcement [23].

10.2.2.2 Efficacy

Interest in naltrexone for the treatment of AUD was stimulated by two early clinical trials which showed that among alcohol-dependent patients 12 weeks of treatment with naltrexone as an adjunct to psychosocial interventions improved drinking outcomes including abstinence, relapse rates, number of drinking days, severity of alcohol-related problems and craving. Both studies suggested that naltrexone was particularly effective in preventing relapse to dependence following alcohol exposure [24, 25]. Approval of naltrexone by the FDA soon followed, along with a raft of controlled and randomized controlled trials.

Several meta-analyses have supported the early positive findings, with modest improvements in a variety of drinking outcomes, most commonly relapse to heavy drinking [16, 26–31]. The most recent Cochrane review of opioid antagonists for the treatment of alcohol dependence identified 47 randomized controlled trials involving naltrexone as an adjunct to psychosocial interventions [32]. Oral naltrexone significantly reduced two of three primary outcomes, return to heavy drinking (number needed to treat (NNT) = 10, i.e., ten patients require treatment to prevent one patient returning to heavy drinking) and the number of drinking days (NNT = 25), but had no effect on return to any drinking. All secondary outcomes were improved by naltrexone including a 3% reduction in number of heavy-drinking days and an almost 11 g reduction in alcohol consumption on drinking days. In the majority of studies, a standard 50 mg daily dose was used, and treatment typically lasted for 3 months. A small subset of studies that included post-treatment follow-ups indicated that the benefits of treatment fade after discontinuation, although naltrexone-treated patients had a 14% lower risk of return to heavy drinking compared to placebo at up to 12 months follow-up. Extended-release naltrexone was not associated with significant improvements, although few studies were available for review.

A small number of studies have not shown any positive effects of oral naltrexone, although these studies have tended to be limited by small sample sizes or poor treatment compliance or have used samples with other psychiatric or substance use co-morbidities (e.g. severe depression, eating disorders).

Of all the approved treatments for AUD, naltrexone has the largest evidence base regarding efficacy. However, previous reviews have highlighted several issues with the existing evidence, including the following:

(a) Heterogeneity in study design which has limited the generalizability of findings of individual studies.
(b) A large number of outcome measures have been used, and there is inconsistency among studies in the measure for which largest or most consistent effects have been observed.
(c) In many studies treatment duration was short, and so it is still unclear how long treatment effects will last and what the appropriate length of treatment may be.
(d) Currently there is limited evidence of the efficacy of injectable naltrexone, although existing studies suggest specific subgroups may see benefit with this formulation, e.g. males and individuals with lead-in abstinence [33, 34].

On the other hand, consistent positive observations are that (a) many individual studies are of moderate to high quality; (b) time to relapse is the most consistently improved outcome variable, suggesting that naltrexone is particularly effective for relapse prevention; and (c) naltrexone should be given in combination with psychosocial therapy.

Research is increasingly turning its attention to predictors of treatment response. This may help to explain inconsistencies in treatment effects but also suggests the possibility of optimizing efficacy in the future by tailoring treatments. Pharmacogenetic studies, for example, have initially suggested that variants of the OPRM1 gene that encodes the μ-opioid receptor may affect naltrexone treatment response in AUD patients [35, 36]. However, this result was not replicated in a prospective cohort study [37], and so at this point pharmacogenetic tailoring is not yet ready to be implemented in routine clinical care until more robust findings emerge from further studies.

10.2.2.3 Administration

Dose and Regimen

The standard dose of oral naltrexone is 50 mg once daily, taken for 3–6 months (although it can be continued for up to 24 months if required). The optimal duration of treatment is unclear, although some studies suggest that after initial treatment has been discontinued a regimen of targeted use at 'high-risk' times may maintain treatment effects [38, 39].

Extended-release naltrexone is available as a 380 mg dose, given by intramuscular injection approximately every 4 weeks.

Contraindications

Patients should not be drinking at treatment initiation, and naltrexone should not be used in patients with current, recent (past 7 days) or anticipated use of opioid medication since naltrexone can precipitate severe opioid withdrawal.

Naltrexone is contraindicated in patients with acute hepatitis or liver failure. Caution is advised in patients with active liver disease, kidney disease and pregnant or nursing mothers.

Side Effects

Naltrexone is generally well tolerated, with mainly mild side effects. The most common side effects include nausea, vomiting, headache, tiredness, anxiety and insomnia. Less common side effects include gastrointestinal complaints (e.g. diarrhoea, abdominal pain, constipation), joint/muscle aches, rash, dizziness, increased or decreased energy, ringing in the ears, sweating, mild depression and delayed ejaculation. Uncommon but serious side effects include liver toxicity and failure (usually at higher than standard doses, so naltrexone can typically be initiated even in patients with mild liver problems, i.e. AST or ALT levels below 3 times normal), suicidal thoughts, hallucinations, blurred vision, swelling of the face, feet or legs and shortness of breath.

A meta-analysis of efficacy studies found no significant difference between naltrexone versus placebo in the number of patients who

experienced at least one adverse event or in the number of patients who discontinued due to an adverse event, suggesting that side effects do not impact upon naltrexone compliance or discontinuation [30].

10.2.3 Acamprosate

Acamprosate (also known by the trade name Campral®) was first approved for the treatment of AUD in Europe in 1989. It is currently approved worldwide including in the USA, Canada, South America, Australia and parts of Asia and Africa.

It is indicated for the prevention of relapse in patients with established abstinence. Unlike naltrexone, acamprosate can be used in patients receiving opioid treatment, e.g. for chronic pain conditions.

10.2.3.1 Mechanism of Action

While its exact mechanism of action is unknown, it is believed that acamprosate may work by modulating activity of the glutamatergic neurotransmitter system. Chronic excessive alcohol use is thought to cause neuroadaptive changes that result in an imbalance between the excitatory glutamatergic and inhibitory GABAergic neurotransmitter systems. In turn this is thought to be involved in the development of tolerance to alcohol and symptoms of alcohol withdrawal (such as craving). It has been proposed that acamprosate may normalize pathological glutamatergic hyperactivity by modulating activity at NMDA and mGLu5 glutamate receptors, thereby restoring the balance between glutamatergic and GABAergic systems and blunting the negative effects of alcohol withdrawal thought to trigger relapse [40, 41].

10.2.3.2 Efficacy

Many randomized controlled trials have been conducted to compare the efficacy of acamprosate with placebo for the treatment of AUD. The majority of these trials have shown moderate improvements with acamprosate treatment on outcomes including continuous abstinence rates, cumulative number of abstinent days, return to any drinking and percentage of patients remaining in treatment [16, 27, 31, 42]. One review reported a 7–13% improvement in outcomes with acamprosate compared to placebo [31]. Beneficial effects of treatment may persist after treatment is discontinued, with improvements in abstinence rates (but not number of drinking days) having been reported at 6–12 months post-treatment [43].

A Cochrane review identified 24 randomized controlled trials investigating the effectiveness of acamprosate (cumulative total $N = 6915$). Treatment typically commenced after patients had achieved 3–7 days of abstinence and was administered for 6 months as an adjunct to psychosocial interventions. The most commonly used outcome measure was return to any drinking (or the opposite; continuous abstinence). Analysis of pooled data showed that acamprosate reduced the risk of return to drinking to 86% of that in the placebo group (NNT = 9) and increased cumulative abstinence duration by 11%. However, there was no significant positive effect of acamprosate treatment on the secondary outcomes return to heavy drinking or gamma-glutamyl transferase (a biochemical marker of heavy alcohol use) [44].

A small number of studies have shown no improvement in drinking outcomes following acamprosate treatment. Aspects of study design such as small sample sizes, short treatment duration and a long lead-in abstinence period may have contributed to the failure to find treatment benefit in these studies. However, two large well-designed trials (the US COMBINE study [45] and the PREDICT study conducted in Germany [46]) have also reported no improvement in drinking outcomes following 3 months (PREDICT) or 4 months (COMBINE) of treatment. It is not immediately clear why these trials should have found no positive effect of acamprosate. The authors suggest that differences in patient characteristics and treatment settings may explain the contrary findings. The details of psychosocial interventions are not well described in many reports, but it is also possible that more comprehensive psychosocial interventions employed in COMBINE and PREDICT may have masked any beneficial effects of acamprosate.

A strength of the existing evidence base is that individual studies have generally been of adequate quality and are reasonably comparable. These studies demonstrate that as an adjunct to psychosocial interventions acamprosate appears to be helpful in maintaining abstinence in AUD patients who have recently stopped drinking. On the other hand, acamprosate does not seem to be as effective in preventing return to heavy drinking [16], and it is unclear whether the type of psychosocial intervention impacts on efficacy.

Several potential predictors of treatment response have been identified. For example, sex, psychiatric and substance use co-morbidities (including anxiety), family history of alcoholism or late age of AUD onset may be factors that modify treatment response [47]. In the COMBINE study, where no overall positive treatment effects were found, a subgroup analysis showed that acamprosate improved abstinence from heavy drinking in patients with shorter duration of abstinence at treatment initiation, those who had received prior treatment or those with a goal of total abstinence. This may suggest that individuals with more severe AUD respond better to acamprosate (e.g. since they have greater upregulation of the glutamatergic system, the supposed target of acamprosate treatment [48]) and that motivation to abstain is an important factor in the success of acamprosate treatment. Finally, pharmacogenetic studies have identified potential genetic markers of treatment response including variants of the GATA binding protein 4 [49], GABARA6 and GABARA2 [40] genes.

10.2.3.3 Administration

Dose and Regimen

Treatment with acamprosate is generally initiated after 5 days of alcohol abstinence, although it is safe to begin treatment prior to cessation of drinking or during alcohol withdrawal. Acamprosate is available in 333 mg tablets, and an oral dose of 666 mg should be taken three times per day. A lower dose (333 mg three times per day) may be used for some patients including those with impaired kidney function. Treatment should be administered as an adjunct to behavioural or psychosocial interventions and should persist even if the patient relapses.

Contraindications

Since acamprosate is excreted primarily by the kidneys, it is contraindicated in patients with severe renal impairment. Caution is advised in patients with moderate renal impairment, children, adolescents, older adults (65 years and older) and pregnant or nursing mothers.

Side Effects

Side effects of acamprosate are generally mild and transient. The most common side effect is diarrhoea. Other less common side effects include gastrointestinal complaints (cramps, flatulence), headache, change in libido, insomnia, anxiety, muscle weakness, nausea, itchiness and dizziness. Suicidal ideation is a rare but serious side effect.

10.2.4 Nalmefene

Nalmefene is the most recently approved pharmacological treatment for AUD and is currently available within Europe and a small number of other countries (including Australia and Hong Kong). It was approved by the *European Medicines Agency* in 2012 and has been marketed since April 2013 under the brand name Selincro®.

The use of nalmefene is indicated for reducing the number of heavy-drinking days as part of a harm reduction strategy. In the UK the *National Institute for Health and Care Excellence* (NICE) recommends the use of nalmefene for patients with high drinking levels (greater than 60 g alcohol daily for men and greater than 40 g alcohol daily for women) who do not have physical withdrawal symptoms and who do not require immediate detoxification.

10.2.4.1 Mechanism of Action

Nalmefene is a selective opioid antagonist, structurally similar to naltrexone, with high affinity to μ-receptors and medium affinity to δ-receptors, although unlike naltrexone it is also a partial ago-

nist at κ-receptors. The therapeutic action of nalmefene in the treatment of AUD is thought to be due mainly to its antagonist effect at μ-receptors, which blocks the positive reinforcing effects of acute alcohol consumption. However animal studies suggest that in addition to μ-receptor-mediated blockade of positive reinforcing effects of alcohol, the activity of nalmefene at κ-receptors may also play an important role in its mechanism of action by blocking negative reinforcing effects of alcohol.

10.2.4.2 Efficacy

Few trials of nalmefene efficacy have been conducted to date, although the majority of existing studies have shown small positive effects, with fewer heavy-drinking days and a reduction in total alcohol consumption among AUD patients and heavy drinkers [50]. Improvements in drinking outcomes have been found following daily dosing as well as targeted (i.e. 'as needed') administration of nalmefene [51, 52]. Studies indicate that nalmefene is effective in reducing heavy drinking even among AUD patients who are unable to abstain from drinking [53]; indeed it may be most effective in subgroups of AUD patients who do not abstain from drinking prior to treatment initiation [52]. To date the best effects of nalmefene have been found in the first 4 weeks of treatment although evidence supports treatment durations of 6–12 months.

One relatively small multisite study found that 12 weeks of nalmefene treatment combined with motivational enhancement therapy had no effect on heavy drinking, craving, time to first heavy-drinking day or biochemical markers of alcohol use compared with placebo [54]. Variation between study sites and the relatively small sample size may explain the failure to find a positive effect in this study however.

Moving forward, more careful specification of the populations included in studies of nalmefene treatment is required. There is currently little or no evidence of safety or efficacy in adolescents, older adults and patients with other medical or psychiatric co-morbidities. It is also unclear whether the type or intensity of psychosocial intervention that patients engage with may impact on the efficacy of nalmefene, since in the majority of existing studies these were either unstandardized or poorly described.

Little work has investigated potential predictors of nalmefene treatment response. Preclinical research suggests the possibility that nalmefene may be more effective in severe alcohol dependence, although this remains to be confirmed in humans [55]. In addition, while pharmacogenetic studies suggest a role for the OPRM1 gene in predicting naltrexone treatment response, no moderating effects of OPRM1 genotypes on drinking outcomes following nalmefene treatment were found [56].

10.2.4.3 Administration

Dose and Regimen

An oral dose of 20 mg nalmefene can be taken daily, or 'as needed', 1–2 hours before drinking alcohol. It is recommended that nalmefene is used in conjunction with psychosocial support.

Contraindications

Since nalmefene can cause severe opioid withdrawal, it should not be used in patients with recent, current or anticipated opioid use. It is also contraindicated in patients with severe liver or renal impairment or recent acute alcohol withdrawal syndrome.

Although there are no dose-dependent effects of nalmefene on liver toxicity, caution is advised in patients with mild or moderate liver dysfunction. Caution is also advised in patients with mild or moderate renal dysfunction, a history of seizures (including alcohol withdrawal seizures), conditions that interfere with the absorption of lactose and concurrent use of potent UGT2B7 inhibitors, older adults (aged over 65 years) and pregnant or nursing mothers.

Side Effects

Nalmefene is reasonably well tolerated at daily doses of 20–40 mg [50]. The most common side effects are mild to moderate nausea, dizziness, insomnia and headache. Other side effects that have been reported include loss of appetite, confusion, restlessness, reduced libido, drowsiness,

tachycardia, dry mouth, diarrhoea, excessive sweating, muscle spasms, weakness, hallucinations, dissociation, itching, rash and swelling in the face, lips or tongue.

10.2.5 Comparison of Approved Treatments

Few head-to-head comparisons of disulfiram with other approved medications exist. However, studies suggest that disulfiram is superior to acamprosate in patients with a long duration of alcohol dependence [57], that disulfiram is more effective than naltrexone at reducing alcohol consumption but not craving in alcohol-dependent men [58] and that disulfiram in combination with a brief cognitive behavioural intervention is more effective than both naltrexone and acamprosate at reducing alcohol consumption and number of heavy-drinking days, extending time to first drink and increasing total number of abstinent days [59].

Of the four approved medications, acamprosate and naltrexone have the best evidence to support their use, showing they are both effective adjuvant treatments. However, trials directly comparing acamprosate with naltrexone have not established significant differences between them in treatment outcomes. The most recent Cochrane review reported that the evidence base comparing them was too small to draw conclusions [33] and another that drug choice may be more usefully guided by other factors such as ease of administration, adverse effects and availability [16]. On the other hand, it has been suggested that acamprosate and naltrexone may impact on different facets of alcohol dependence, with studies showing that acamprosate may be more useful for eliminating drinking while naltrexone is better for achieving controlled consumption [60]. Limitations in the design of some of these studies make it unclear whether this observation is reliable.

Nalmefene is structurally similar to naltrexone but with potential pharmacological and clinical advantages including more effective binding at opioid receptors, higher bioavailability and lack of dose-dependent liver toxicity [61]. However, there is limited evidence directly comparing these drugs. A laboratory study in non-treatment seeking alcohol-dependent patients showed that both nalmefene and naltrexone reduced alcohol consumption, although more side effects were noted in the nalmefene condition [62].

10.3 'Off-Label' Pharmacological Treatments

A number of medications approved for treating other health conditions, but not currently AUD, have been suggested for 'off-label' use. This includes drugs from a variety of classes including anticonvulsants, serotonergic agents and GABAergic agents. This section briefly summarizes the most promising 'off-label' treatments for AUD.

10.3.1 Topiramate

Topiramate is approved for the treatment of epilepsy and migraine. It is thought that it may reduce the positive reinforcing effects of alcohol and alcohol craving due to suppression of dopamine release via a dual process of glutamatergic blockade and GABAergic facilitation. Through this mechanism it is also likely to be able to prevent/attenuate withdrawal symptoms, which are an important contributor of drinking, notably at the beginning of treatment. It should be noted that in the seminal trials performed by Johnson et al. [63, 64], topiramate is typically started when the patient is still drinking and the dose is gradually titrated up over 2 months. Usually patients will gradually decrease their alcohol intake and ultimately abstain from alcohol during the same period, an effect likely produced through the direct impact of topiramate on withdrawal symptoms and possibly also on the reinforcing effects of alcohol.

Few studies evaluating the efficacy of topiramate in AUD have been conducted to date. The first randomized controlled trials showed that, compared to placebo, a daily oral dose of up to

300 mg topiramate combined with a brief psychosocial intervention improved drinking outcomes including percentage of heavy-drinking days, percentage of days abstinent, drinks per day, craving for alcohol and biochemical markers of heavy alcohol use [63, 64]. Other studies have showed improvements in outcomes related to relapse. For example lower relapse rates in topiramate treated patients compared to placebo (67% vs. 86% [65]), although in one study relapse rate was superior after 4 weeks of treatment but not at 8 or 12 weeks so it is unclear how long treatment benefits are maintained [66]. A minority of studies have found no effect of topiramate although these have tended to be limited by weak study design (e.g. unblinded design or lack of placebo control), and one was unusual in using a sample of inpatients and an intense psychosocial intervention which may have masked topiramate effects [67, 68]. Interestingly, preliminary evidence suggests that a gene involved in encoding a subunit of the glutamate receptor (GRIK1) may moderate topiramate treatment effects [69].

Several side effects of topiramate have been reported including headache, numbness, taste abnormalities, cognitive impairments, anorexia and, more rarely, serious visual problems including glaucoma. There is a teratogenic risk, so pregnancy testing should be conducted in women of child-bearing age, and women should be informed of this risk and ideally use contraceptive measures. Gradual dose titration is important due to the adverse side effect profile, although the optimal dose and duration of treatment for AUD is still unclear. The fact that topiramate is started while patients are still drinking makes it quite useful for situations in which individuals are not ready to detoxify or in which there is no medical infrastructure to oversee detoxification (in which case topiramate treatment can be initiated on an ambulatory basis with close monitoring).

10.3.2 Gabapentin

Gabapentin is another anticonvulsant medication, also used for the treatment of neuropathic pain. Animal models suggest its mechanism in the treatment of AUD may be due to indirect modulation of GABAergic neurotransmission. Laboratory and clinical studies support the safety and efficacy of gabapentin for the treatment of AUD, although the evidence base is currently small. A recent review identified six small randomized controlled trials that reported drinking outcomes among alcohol dependent patients. Five of the studies demonstrated positive effects of 4–12 weeks of treatment with gabapentin (daily doses 600–1800 mg), combined with behavioural support. Several outcomes related to drinking quantity and frequency were improved. Gabapentin also delayed onset of relapse to heavy drinking, reduced craving and improved sleep quality [70]. Positive effects were particularly evident at higher doses and where patients were already abstinent at commencement of treatment. Side effects are generally mild but can include headache, insomnia, fatigue, muscle aches and gastrointestinal complaints. Abrupt withdrawal has precipitated seizures and so dose titration is necessary. Reports of abuse have been documented in high-risk populations, and so these patients should be monitored for potential gabapentin misuse.

10.3.3 Baclofen

Baclofen is a $GABA_b$ receptor agonist, approved for the treatment of muscle spasticity. $GABA_b$ receptors are thought to be involved in emotion regulation, and a role for baclofen in treating AUD in patients with co-morbid mood and anxiety disorders has been proposed [71]. A recent narrative review found beneficial effects of baclofen on a number of drinking-related outcomes in some studies (e.g. case studies, open-label studies), although in studies with more rigorous design (i.e. randomized controlled trials) findings have been mixed despite the fact it is widely used as an off-label treatment for AUD [72]. Randomized controlled trials have used baclofen doses of 30–180 mg per day, given over 3–26 weeks, and have demonstrated that it is well tolerated with few side effects in AUD patients, even among patients with cirrhosis. However,

these studies have typically excluded patients with psychiatric co-morbidities, and inconsistent effects of baseline anxiety or depression levels on treatment response have been found. At this point in time, the use of baclofen seems appropriate for patients that have AUD associated with liver cirrhosis. It should still be considered experimental otherwise.

10.4 Other Pharmacological Agents Under Investigation

While research has shown that existing pharmacological treatments can be efficacious, effect sizes are typically only small to moderate, and relapse rates are often high [73]. Thus, there is a need to develop more effective treatments. As our understanding of the neurobiology of alcohol addiction grows, new treatment targets are emerging (for a review see [74]). Covering the different drug targets is beyond the scope of the present chapter. Instead, this section describes only varenicline, a partial agonist at α4β2* acetylcholine nicotinic receptors, that is approved for smoking cessation.

In animal models varenicline has been shown to reduce alcohol self-administration and cue-induced relapse. In humans, it attenuates alcohol intake and craving for alcohol among non-dependent heavy drinkers [75], and neuroimaging studies show that in heavy-drinking smokers it decreases cue-elicited activation in areas related to reward (e.g. anterior cingulate cortex, nucleus accumbens and orbitofrontal cortex).

A recent review identified four randomized controlled trials of the safety and efficacy of varenicline in alcohol dependent patients [76]. One of these was a large multisite trial that found moderate positive effects of varenicline: after 13 weeks varenicline-treated patients had fewer heavy-drinking days per week (38% vs. 48%) and fewer drinks per day (4.4 vs. 5.3) compared to a placebo group. The varenicline group also reported less craving than the placebo group, although drinking outcomes related to abstinence were not different [77]. Two smaller trials also showed beneficial effects of varenicline treatment, with decreased craving being the most consistent finding. The evidence for outcomes related to alcohol consumption and abstinence was more mixed. Subgroup analyses suggest that varenicline may be most effective at reducing heavy drinking among alcohol-dependent patients who are also smokers, smokers who also reduce their tobacco consumption and individuals with less severe alcohol dependence [77, 78]. Varenicline may therefore be especially effective in reducing alcohol craving and consumption among AUD patients who are highly motivated to decrease both alcohol use and smoking. The subgroups for whom varenicline is most effective, and for which outcomes, remain to be confirmed. Existing studies have all used relatively short treatment durations, and so it is also unclear what the optimal length of varenicline treatment should be.

Regarding safety, the majority of studies have found that varenicline is generally well tolerated, with mild nausea being the most frequently reported adverse effect. Therefore, varenicline represents a good option for individuals with AUD who are smokers. It could also be tested for patients that are non-smokers; however it is still experimental for this group.

10.5 Choice of Pharmacotherapy

The choice of pharmacological treatment for any given AUD patient is likely to depend on multiple factors, e.g. other medical, psychiatric or substance use co-morbidities, concurrent medication, patient preference and motivation, the goal of treatment (complete abstinence vs. reduction of alcohol consumption) and specific challenges the patient may face, whether the patient is already abstinent, ease of administration, side effects and adherence. Sequential use is common and may be necessary where the treatment initially selected is not successful, although there is no evidence to suggest a ‘best order’.

It is unclear if combinations are more effective than single drug therapy. Alcohol dependence is a complex disorder involving multiple neurotransmitter and other systems, suggesting that a combination of drugs acting at different sites may

provide the most comprehensive treatment strategy. However, studies comparing combination treatments with monotherapy have provided no or mixed evidence of enhanced treatment effects [45, 79, 80]. Combination therapy may be warranted if initial monotherapy is not successful.

10.6 Predictors of Treatment Response

Inconsistent treatment effects have been observed for some pharmacotherapies. Research is increasingly investigating predictors of treatment response to make sense of these mixed findings. Better understanding the characteristics of populations for whom treatments are most effective could also provide a strategy for maximizing treatment benefits by facilitating the development of personalized treatments.

One such avenue is pharmacogenetics. Research is currently investigating genetic heterogeneity in multiple systems in the body involved in both the positive and negative reinforcing effects of alcohol including the opioid system (the OPRM1 gene that encodes the μ-opioid receptor), GABAergic system (the GABRA2 and GABRG3 genes that encode the $GABA_A$ receptor), serotonergic system (the short versus long allele of the serotonin transporter gene) and corticotrophin-releasing factor system (the CRFR1 gene).

10.7 Conclusion

This chapter reviewed available information about approved and other pharmacological treatments for AUD. Key points are summarized below:

- Few treatments with clear evidence of safety and efficacy are available, and effect sizes tend to be modest.
- Disulfiram, naltrexone, acamprosate and nalmefene are the only currently approved medications for AUD.
- Disulfiram may be appropriate under certain conditions (especially with open-label, supervised administration where treatment compliance is good) but the existing evidence base is limited.
- There is reasonable evidence to support the use of acamprosate and naltrexone as adjunct treatments, although it is unclear which produces best effects.
- Nalmefene is approved for the reduction of alcohol consumption, but its use is relatively recent, and it is not available yet in North America.
- Topiramate, gabapentin and varenicline appear to be promising agents, although further research is required.
- Baclofen may also be worth considering, particularly in patients with liver disease, although evidence of efficacy is mixed and more research is required.
- Pharmacological treatments are recommended as an adjunct to psychosocial interventions, although the impact of the type of psychosocial intervention is unclear.
- There is currently limited evidence of efficacy in special populations, such as those with other medical, psychiatric or substance use co-morbidities, adolescents, older adults and minority groups.
- Optimal duration of treatment with pharmacological agents is unclear. Guidelines recommend continuing treatment for at least 3 months, although acamprosate is the only agent for which long-term efficacy and safety have been established.
- Better understanding predictors of treatment response may lead to improvements in treatment, including use of personalized treatment approaches.

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11 Benzodiazepine and Nonbenzodiazepine Hypnotics (Z-Drugs): The Other Epidemic

Annie Umbricht and Martha L. Velez

Contents

A. Umbricht · M. L. Velez (✉)
The Johns Hopkins University School of Medicine,
Baltimore, MD, USA
e-mail: mvelez@jhmi.edu

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Abstract

Benzodiazepines (BZDs) are CNS depressant drugs with sedative, hypnotic, anticonvulsant, and muscle relaxant properties. BZDs replaced barbiturates and other hypnotics in the late 1950s and became the most prescribed medications in 1977. Generally considered effective and safe for short-term use, long-term BZD use beyond 6 weeks is controversial due to loss of efficacy and cognitive adverse outcomes. Side effects include alteration of sleep architecture, nightmares, agitation, amnesia, cognitive impairment, confusion, depression, and dementia. BZD-induced psychomotor impairments lead to increased risks of falls and motor vehicle accidents. Abrupt BZD discontinuation may lead to rebound of the symptoms for which they were prescribed and withdrawal symptoms. The mortality risk of BZD use disorder is of special concern in vulnerable populations given the current opioid overdose epidemic, as BZDs use by patients with opioid use disorders (OUD) contributes significantly to an increase in opioid-related death. In the early 1990s, nonbenzodiazepine $GABA_A$ receptor agonists at the BZD receptor site, the Z-drugs (zaleplon, zolpidem, zopiclone, and eszopiclone), were introduced for treatment of insomnia. Z-drugs have been promoted as safer than traditional BZDs and rapidly gained wide acceptance with the public and practitioners. However, given their similar mechanism of action, their risks and side effects are similar. Given the risks, prescription of sedatives should be avoided or, if necessary, should be limited to short-term use for acute issues. Studies demonstrate that BZD discontinuation after long-term use is associated with improved quality of life once the withdrawal syndrome has been overcome.

Keywords

Benzodiazepines · Sedative use disorder
Nonbenzodiazepine hypnotics
Benzodiazepine withdrawal · Z-drugs

11.1 Scope of the Problem

From 1996 to 2013, the proportion of the population prescribed benzodiazepines (BZDs) doubled from 3% to 6.2% and the quantity prescribed tripled from 1.1 to 3.6 kg of lorazepam equivalent per 100,000 population [27]. Chlordiazepoxide sedative activity was serendipitously discovered by Sternbach in 1955, and it was approved in 1960 for the treatment of anxiety and insomnia, followed by diazepam in 1963. Given a lower toxicity, BZDs soon replaced barbiturates and other hypnotic drugs and became the most prescribed medications in 1977. Generally considered effective and safe for short-term use, the long-term use of BZDs is much more controversial due to a loss of efficacy (tolerance) and their association with adverse outcomes. Nevertheless, BZDs are frequently prescribed for long time despite recommendations to use evidence-based behavioral therapies first, such as relaxation techniques, sleep hygiene, or psychotherapy, or prescribe antidepressants [36]. In the USA, 12.5% of adults aged 65 and older are prescribed BZD or Z-drugs in spite of a clear increase in mortality in this age group [5, 29, 36].

Although the abuse liability of BZDs has been disputed in the general population, the risk of BZD use disorder including physical dependence is undisputed in vulnerable populations, contributing to the lethality of the current opioid overdose epidemic of the twenty-first century. Public health problems associated with BZDs are due to chronic prescriptions for legitimate symptoms, diversion to other persons than the patients for whom the prescription was initially ordered, and broader illegal trade for recreational use. Diversion of prescription drugs has soared in the last decades, and, after marijuana, prescription drug misuse is the most common type of nonmedical drug use. Data from the 2015–2016 National Surveys on Drug Use and Health estimate that in the past year 12.5% adults used BZDS, 2.1% misused BZDs at least once, and 0.2% had BZD use disorder. Among BZD users, 17.1% misused them, and 1.5% had BZD use disorder [7].

The illegal trade on the dark web of counterfeited tranquilizer, mostly alprazolam, is increasing, targeting teens and young adults. These pills may be adulterated with fentanyl or fentanyl analogues, making them deadly [3]. BZD use is associated with emergency room visits, suicidal ideation, use of other substances, and psychiatric disorders [7]. Treatment programs for substance use disorders (SUDs) and emergency departments' data indicate that 95% of patients with BZD use disorders are polysubstance users, with 82% reporting primary abuse of another substance and 12.9% reporting primary abuse of BZD [40]. An estimated 3–41% of patients with alcohol use disorders also misuse BZDs.

Between 1998 and 2008, the proportion of admissions to addiction treatment for BZD use disorder tripled in the USA compared to an 11% overall increase in substance abuse admissions. The number of annual admissions for combined abuse of benzodiazepine and narcotic pain reliever increased 570% from 2000 to 2010. After opioids, BZDs are the second most common medication class linked with overdose deaths, the rate of which grew more than fourfold from 1996 to 2013 [5]. Despite the increased risk of overdose in patients taking BZDs with other substances such as alcohol or opioids, rates of co-prescription of benzodiazepines and opioids nearly doubled between 2001 and 2013, including among patients receiving medication for opioid use disorder. Emergency department (ED) visits involving combined use of opioids and BZDs (19.1%) were higher than that for ED visits involving opioids without benzodiazepines (12.6%) and for ED visits involving benzodiazepines without opioids (11.4%). Opioids are involved in between 75 and 86% of benzodiazepine deaths. Nearly 30% of fatal "opioid" overdoses in the USA also involve benzodiazepines, suggesting that some of the increase in opioid-related deaths might be caused by increases in cocurrent benzodiazepine/opioid use over time [41].

In the early 1990s, a new group of nonbenzodiazepine $GABA_A$ receptor ($GABA_AR$) agonists at the benzodiazepine receptor site, the Z-drugs (zaleplon, zolpidem, zopiclone, and eszopiclone), was introduced for the treatment of insomnia. Chemically distinct from the BZDs, Z-drugs have been promoted as safer than traditional BZDs and rapidly gained wide acceptance with the public and practitioners. However, given their similar mechanism of action at the benzodiazepine site of the $GABA_AR$, their side effects are similar. The FDA, on May 14, 2013, released a safety announcement recommending a dose reduction for zolpidem extended release as well as a warning not to operate a vehicle or machinery requiring mental alertness on the day following the use of zolpidem due to residual psychomotor impairment. Next day sedation, cognitive and psychomotor impairment, and physical dependence and withdrawal are observed in patients receiving Z-drugs. Abuse of Z-drugs is on the increase, and studies suggest that Z-drugs may also increase the risk of depression. The extent of their participation to untoward effects of public health importance is minimized due to the fact that common toxicology screens do not include detection of these Z-drugs. The use of Z-drugs such as zolpidem and eszopiclone alone or in combination with opioids is also associated with increased mortality although the documentation is lacking as toxicology screen may fail to detect Z-drugs. For simplification, in this chapter, the use of the word benzodiazepine also covers Z-drugs.

BZD misuse disproportionately impacts vulnerable populations, including the elderly, adolescents, young adults, pregnant women, victims of sexual assaults, and those with a history of SUD or other psychiatric disorders. BZD misuse is among the most widespread forms of adolescent prescription drug misuse. The 2017 Monitoring the Future reported annual prevalence rates of prescription BZD use of 2.0%, 4.1%, and 4.7% in grades 8, 10, and 12, respectively. A longitudinal study showed that by age 18, the lifetime medical or nonmedical use of BZD was 20.1% and was a predictor of SUD at age 35. Given their risks, prescription of sedatives especially in pediatric populations is best avoided and, if necessary, should be limited to short-term use for acute issues.

Although difficult, studies demonstrate that BZD discontinuation after long-term use is associated with improved quality of life once the withdrawal syndrome has been overcome. This chapter will describe specific patient populations at risk for BZD use disorders, how to identify them, as well as best management practices, including interventions for BZD taper.

11.2 Pharmacology of Benzodiazepines and Other BZD-Site Agonists

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter, and its actions are mediated by receptors that are widely distributed throughout the CNS. BZD, Z-drugs, barbiturates, and ethanol are positive modulators of the gamma-aminobutyric A receptor ($GABA_AR$) functions (i.e., their binding induces a neuronal response only in the presence of the actual agonist GABA). The $GABA_ARs$ are ligand-gated ion channels allowing influx of chloride (Cl-), causing hyperpolarization of the neuronal membrane, thus inhibiting the firing of new action potentials. The $GABA_AR$ is a transmembrane receptor made of five subunits (2 a, 2 b, and 1 g) binding GABA on the extracellular side of the receptor. Two GABA molecules are needed to open the chloride channel. BZDs and Z-drugs act as GABA potentiators by increasing the frequency with which the chlorine channel opens when two GABA molecules bind to $GABA_AR$. The increase in intracellular chloride concentration hyperpolarizes the neuron, reducing its excitability [20, 43].

It is through their ability to increase the $GABA_AR$'s affinity for GABA that BZDs and Z-drugs produce a transient subjective relaxation effect for patients with anxiety or insomnia disorders. In addition to symptom relief, data from animal models indicate that BZDs, by modulating $GABA_ARs$, increase firing of dopaminergic neurons in the ventral tegmental area, in effect stimulating the mesolimbic reward system and setting the stage for further drug seeking and explaining further the addictive properties of BZDs [44]. The shorter the onset of action after drug taking, the more efficient is the learning of the rewarding effect associated to the drug. When using BZDs with short onset of action (30 minutes), the individual learns that relaxation, stress relief, or sleep is obtained by taking a pill rather than by learning effective practices of stress reduction and healthy sleep habits (or sleep hygiene). Repeated use induces alterations of the $GABA_ARs$ with the development of tolerance, requiring increases in doses and frequency of dosing to maintain the effects. Attempts to discontinue medications after several ($\geq$4) weeks of regular intake lead to resurgence or rebound of the primary symptom of anxiety or insomnia, triggering further drug seeking and leading to automatic and compulsive drug-taking behaviors or initiating the cycle of addiction [17]. Like with ethanol, abrupt benzodiazepine discontinuation unmasks the "downregulated" state of inhibitory transmission leading to the characteristic hyperexcitable state or withdrawal symptoms of anxiety, panic, insomnia, irritability, autonomic hyperactivity, sweats, increased sensorium, and possibly seizures.

Given their specific binding and allosteric modulation of $GABA_AR$, Z-drugs have similar long-term negative effects to BZDs including adverse cognitive (amnesia) and psychomotor effects, compromise in balance, unsteadiness, night falls, and driving impairments. Due to their heterogeneous chemical classes, routine toxicology screens for drugs of abuse do not include the Z-drug hypnotics, so the extent of their impact on emergency room visits and other societal costs remains underreported. In clinical trials, these sedative hypnotics were found to more than double the risk of depression compared to the groups taking placebo. Consequently, the long-term use of sedative hypnotic drugs increases the suicide risk as well as overall mortality risk. The Z-drugs have similar risks of rebound and withdrawal as BZDs.

11.3 Pharmacokinetic

Pharmacokinetic differences between BZDs relate to their respective time to peak effect (onset of action) and duration of action, as well as

whether metabolites are psychoactive. BZDs are rapidly absorbed by the gastrointestinal tract after oral administration with onset of action within 30 minutes (diazepam) to 2 hours (chlordiazepoxide). A shorter onset of action leads to higher abuse liability. BZDs are metabolized by the liver via two pathways: glucuronide conjugation by the cytochrome P450 system and/or microsomal oxidation (demethylation and hydroxylation). Some metabolites are psychoactive and undergo further metabolism, thus prolonging the drug duration of action. Intravenous administration of BZDs has quasi immediate onset of action due to fast delivery to the CNS and is reserved for use in emergency (grand mal seizures) or hospital setting (pre-anesthesia). Most BZDs cannot be administered intramuscularly due to erratic absorption, except for midazolam.

Upon discontinuation, BZD pharmacokinetic characteristics predict the time of onset, duration, and severity of the BZD withdrawal syndrome: BZD with shorter half-life and no active metabolites, like alprazolam, is more likely to cause withdrawal symptoms even between scheduled doses. This tends to increase its abuse liability. Long-acting BZDs or those with long-acting metabolites (diazepam, chlordiazepoxide, and active metabolite desmethyldiazepam among others) tend to have an insidious onset of withdrawal starting about 24 hours, with peak intensity 7–14 days after the last dose. Other drugs inhibiting or activating the cytochrome P450 system may change BZD duration of action, causing increase in impairment or withdrawal. The long half-life of some BZDs and metabolites mean that the terminal elimination time can last for up to 4 weeks, even after one dose, longer after chronic dosing since BZD accumulates in fat.

11.4 Clinical Indications for BZDs and Z-Drugs

In this section, we are first reviewing accepted indications for BZDs, reminding the reader that BZDs and other BZD-site agonists are only indicated for incidental or short-term use (less than 4–6 weeks) and at the lowest effective dose, as physical dependence can develop after just 1 month of continuous BZD use. Indications for this type of use include phobias preventing specific functions or procedures (e.g., flying in an airplane, undergoing an MRI for patients with claustrophobia). They are also indicated for short-term management (7–10 days) of reactive anxiety (e.g., sudden stressor such as grief); short-term management of insomnia, including insomnia associated with alcohol withdrawal; and management of withdrawal from alcohol or sedatives with short half-lives. Another indication is the intravenous emergency intervention for grand mal seizures. BZDs have been shown to reduce mortality in acute cocaine toxicity, or in the treatment of acute delirium tremens, a severe complication of alcohol withdrawal. BZD can be used in short-term intervention of psychiatric emergencies accompanied by psychosis or mania, before the onset of action of lithium or other antipsychotic medications (neuroleptics). BZDs are indicated for premedication in anesthesia and for sedation in intensive care (to facilitate mechanical ventilation and/or sedate patients in distress). Note that this indication is coming into question as the use of BZD in this setting has been associated with intensive care delirium and longer ICU length of stay.

11.5 Problems Related to the Long-Term Use of BZDs

The long-term clinical use of BZDs is controversial given the increased morbidity and mortality associated with sedatives. Advocates of long-term management with BZDs claim the patients' acceptability and widespread belief of safety and efficacy. However, several academic and public health policies strongly advise against long-term use of BZDs for PTSD, generalized anxiety disorder (GAD), insomnia, depression, and panic attacks due to the lack of evidence of demonstrated long-term efficacy and their problematic side effects (Table 11.1). Sedatives adversely affect cognitive (memory, attention) and psycho-

Table 11.1 Potential problems related to the use of BZDs

Side effects of BZDs
Sedation, psychomotor impairment impacting driving and operating machinery
Cerebellar dysfunction: unsteadiness (falls), nystagmus, poor coordination, slurred speech, disorientation (space)
Cognitive impairment of memory, attention, disorientation (time), amnesia, decreased learning efficiency, and consolidation
Decreased self-awareness (metacognition) and self-regulation
Increased impulsivity associated with disinhibition and poor working memory
Potentiation of respiratory depression in combination with other substances (alcohol and opioids, including buprenorphine) or in chronic lung disease and obstructive sleep apnea
Reinforcement of avoidance, inflexibility prevents coping/learning of adaptive response
In elderly, TBI and other CNS disorders: acceleration of cognitive decline or dementia
Behavioral problems with forensic implications: increase in motor vehicle accidents (60–80% more accidents in drivers on BZDs or Z-drugs)
Problems of disinhibition in persons with borderline personality disorders or impulse disorders, with paradoxical increase in anxiety and agitation, with consequent aggressive or even violent actions; due to anterograde amnesia (black-out), the person may not have any recollection of the incident (fugue states)

motor functions impacting daily activities and performance. BZD-associated impairments in reaction time, attention, and visuospatial skills increase vulnerability for motor vehicle accidents. Emerging research indicates that BZD use in older adults may increase the risk of developing dementia [19], risk of falls, fractures, and traffic accidents [18]. Similarly, psychomotor impairment, falls, and hip fractures are more likely to occur with Z-drugs that have longer half-lives.

Among war veterans with PTSD, BZD prescriptions are not effective and may increase the risk of misuse and worsening outcome in the setting of SUD. BZD-induced disinhibition has been described in patients with traumatic brain injury (TBI), an important issue, given the frequent comorbid (often underdiagnosed) conditions of TBI and PTSD among veterans returning from war zones. The use of BZDs in this population is also increasing their risk of suicide.

Given the fact that physical dependence may develop after just 30 days of daily BZD use, prescriptions should be for 14 days, with warning about the risk of developing physical dependence and strong resistance for renewing the prescription. If a patient is already under psychiatric care, a general or emergency room practitioner should not prescribe BZD as it will undermine the therapeutic alliance and encourage doctor shopping.

11.6 BZD Use Disorders

Most people prescribed with sedatives take them responsibly and may benefit from their use, if they are taken for short term (less than 4–6 weeks). Longer duration or high doses of benzodiazepine, however, increase the odds of developing BZD use disorders including dependence [23]. BZD should be avoided in those who have preexisting cognitive impairment (elderly, TBI) and patients with panic disorders, suicidal ideations, and underlying SUD due to their elevated odds of developing dependence on benzodiazepines [46].

Overuse of psychoactive medications may also stem from an erosion of quality health-care service. Health-care providers may inadvertently play a role in misuse behaviors by failing to recognize a patient's vulnerability for developing a SUD, missing depression diagnoses when evaluating insomnia or anxiety complaints, overprescribing medications, or just due to time pressure: it takes more time to refuse a patient's request and teach alternative behavioral strategies for anxiety or insomnia than to agree and write the requested prescription. Of patients started on BZD, 36% will still be taking them at 3 months and 15% at 1 year. Very worrisome is the fact that 46–71% of OUD patients on medication-assisted treatment (methadone, buprenorphine) are also prescribed BZDs in spite the overwhelming risk of overdose and untoward treatment outcome. Similarly worrisome is the concurrent chronic prescription of opiates and sedatives for chronic pain, given the increased potential for respiratory depression and cardiac arrest especially with

comorbid diagnoses of chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea (OSA). The fact that these drugs are considered "medication" and are endorsed by physicians may give a false sense of safety. Some people intentionally seek to use sedatives for their direct rewarding psychoactive properties (e.g., to get euphoric feelings similar to those induced by alcohol or other illegal drugs; [48]) but also to alleviate negative emotions, such as to lessen anxiety and decrease inhibitions, thus facilitating social encounters or other situations. Recreational BZD users purchase them from legal or illegal sources, from acquaintances, or from family members who have prescriptions. Other sources include illicit sales of diverted supplies and/or the Internet where counterfeited drugs are sold without any quality assurance or regulations [15].

While "doctor shoppers," nonethical physician behaviors, and the Internet receive much media attention regarding diversion, data suggest that numerous active street markets involving patients, pharmacies, distributors, and pharmaceutical corporations are involved in fraudulent practices as well [21].

11.7 BZD Withdrawal Syndrome

Onset of BZD physical dependence can occur after as little as 4 weeks of daily BZD use and occurs in about half of the patients after 4 months or more of daily use [13]. Withdrawal symptoms as well as the resurgence, or even rebound (increase in intensity), of the initial symptoms for which the drug was prescribed are to be expected when BZDs are voluntarily or involuntarily reduced or stopped after more than a month of regular use.

Onset and duration of BZD withdrawal symptoms are function of their pharmacokinetics, duration of use, underlying diagnoses, and individual personality. Onset of BZD withdrawal may start within hours of the last dose for short-acting BZD or within 1–10 days after long-acting BZD. Withdrawal symptoms may linger for 6–8 weeks or even months after discontinuation. However, many patients report more restorative sleep and improved quality of life due to improved cognitive and psychomotor functioning after resolution of withdrawal symptoms. Therefore, it is worth encouraging and supporting patients during these efforts.

The onset of withdrawal symptoms can be insidious, producing a subjective "need" or craving for BZDs in spite the realization that they are no longer effective and are causing adverse effects [4]. BZD withdrawal corresponds to CNS hyperexcitability and autonomic hyperarousal. Symptoms can be divided into physical, autonomic, sensory, and psychological clusters [39].

Physical and neurological symptoms include muscle tension, weakness, twitching or spasms, tremor, unsteadiness, and grand mal seizures.

Autonomic symptoms include flu-like illness, sweats, shivering, decreased appetite, nausea, tachycardia (palpitations), increased blood pressure, and dry mouth.

Sensory symptoms include pain, myalgia, paresthesia, blurred vision, hyperacusis, tinnitus, headaches, photophobia, dysesthesia, allodynia, hypersensitivity to touch, hyperosmia, altered taste, and eye soreness.

Psychological symptoms include anxiety, panic attack, restlessness, agitation, depression, mood swings, decreased concentration, fatigue made worse due to inability to fall asleep, lethargy, light-headedness, faintness, depersonalization, derealization, hallucination, and delirium.

Kindling, a neurologic sensitization phenomenon, leads to increased withdrawal intensity upon repeat and successive withdrawal episodes, including increased propensity to seizures.

11.8 BZD Use in Specific Populations

The growing problems related to prescription drug affect individuals of both genders and of all ages, starting in middle school-aged children (ages 12–16) worldwide. The high prevalence of BZD use and BZD use disorder among specific populations reflects the presence of underlying conditions that explain in part the known rela-

tionship between sedatives and morbidity/mortality. For example, the presence of underlying psychiatric conditions, such as anxiety, ADHD, and bipolar disorders, explains partially the prevalence of use among these at-risk populations. In addition, other preexisting conditions such as obesity or respiratory insufficiency mediate the known relationship between sedative use and increased morbidity/mortality. For example, sedatives increase the risk of sudden death in obesity-related OSA or in COPD. This creates a vicious cycle since respiratory insufficiency and chronic sleep disruption are both anxiogenic.

11.8.1 Adolescents and Young Adults

The lifetime prevalence of anxiety ranges between 15% and 20%, and the median age of onset is 11 years of age, constituting one of the most common and earliest type of psychopathology among children and adolescents [32]. Anxiety disorders are found in 5–19% of all children and adolescents. Sleep disorders are also very common in pediatric populations, with as many as 17% of adolescents having unrestorative sleep. Sleep problems among children often go unrecognized, in part because of parents underreporting them. Awareness of the importance and potential consequences of sleep problems on academic performance, neurocognitive function, and daytime behavioral problems must be emphasized. Children and adolescents are frequently sleeping less than 9 hours at night, the required minimum amount of sleep for this age group. Intrinsic contributors to inadequate sleep patterns in children and adolescents include developmental changes causing a shift in circadian rhythm during puberty, delayed sleep-phase syndrome (7% of adolescents), sleep-disordered breathing, and insomnia-type symptoms found in up to 34% of adolescents. Extrinsic factors include early school start time and poor sleep habits such as use of electronic devices near or during bedtime and caffeine consumption, especially problematic when undisclosed in soda or other foods [42].

Anxiety, poor academic performance, behavioral problems, and sleep problems have been recognized as risk factors for later SUDs, and the nonprescribed use of sedatives among adolescents and young adults is a cause of concern in many countries. Fast brain development during this life stage, especially the development of executive function and learning acquisition, implies that exposure to amnesia-inducing drugs may stunt development and result in neurobiological changes and behavioral consequences such as academic problems, increased impulsivity (inversely correlated with short-term memory), and school dropouts. Young people report using sedatives to relieve anxiety symptoms and insomnia, and a high percentage of teenagers and some parents believe that prescription drugs, even taken nonmedically, are safer than illegal drugs. Due to dramatic societal changes, children and adolescents are increasingly exposed to direct-to-consumer advertisement of medications, rushed medical visits promoting fixing of problems via prescription while decreasing patient-clinician interaction, increased media distractions, and increased time competition for numerous activities all potentially resulting in increased anxiety. Parents must closely monitor the children who have been prescribed these drugs, making sure they are safely stored and not diverted.

11.8.2 Elderly

Published guidelines advise against the prescribing of benzodiazepines or Z-hypnotics (BZD-Z) to patients over 65 years old [2]. However, inappropriate use of BZDs and Z-drugs among this age group is widespread despite a risk-benefit ratio that is clearly greater than 1, as BZDs are proven to increase mortality. As sleep disruption and insomnia increase with age affecting more than 30% of older people, studies report that a third to half of seniors in North America and the UK are prescribed either a Z-drug or BZD for sleep disturbance [16, 35]. Given the high illness burden and accompanying polypharmacy in older adults and their decreased drug metabolism, their susceptibility to toxic effects due to drug interac-

tions and cumulation is increased. BZDs may also interact with over-the-counter medications and dietary supplements, which are consumed in significant quantities by seniors. Cognitive adverse events (memory loss, confusion, disorientation, dementia), psychomotor-type adverse events (dizziness, loss of balance, falls), and morning impairment (residual morning sedation) can lead to accidents, including when operating vehicles. In addition, patients over 65, being less flexible, are significantly less likely to stop BZDs than younger patients, and drug dependence is often unrecognized among older adults. Nevertheless, when successful, BZD taper and change to more appropriate medications such as antidepressants result in improved quality of life for both patients and their caregivers.

11.8.3 Women

Women are more likely than men to suffer from depression, anxiety, and victimization, all of which are associated with SUD. Frequently women report starting drug use in an attempt to cope with stressful situations or traumatic memories. Women are significantly more likely than men to engage in "doctor shopping" and to be prescribed medications with high abuse liability for long periods of time or in combination.

It is estimated that between 1% and 4% of pregnant women use benzodiazepines and/or Z-hypnotics [28]. BZDs cross the placenta and have the potential to accumulate in the embryo/fetus. Although the general consensus is that BZDs have low teratogenic potential, studies of their safety in pregnancy have been neglected, compared to other psychotropic substances. There has been inconsistent reporting on the relative risk of orofacial clefts among infants exposed to benzodiazepines during the first trimester. Risks of congenital malformations may increase with exposure to more than one psychotropic: higher risks of congenital heart defects were found in children born to pregnant women taking SSRIs and BZDs. Studies evaluating the neurodevelopmental effects on children prenatally exposed to BZD or Z-drugs have yielded mixed results, with some reporting gross motor and communication impairments in toddlers [28]. During pregnancy, it is best to taper BZDs, or if absolutely indicated, BZDs should be prescribed at the lowest effective dose and for the shortest possible duration, avoiding use in the first trimester and avoiding polypharmacy [12].

It is known that BZD use in poly-SUD is a poor prognostic indicator of recovery, and the same holds true during pregnancy. A portion of pregnant women with BZD use disorder are unable to discontinue BZDs despite the knowledge of their associated risk on the developing brain. Pregnant women and women of childbearing age in general with BZD SUD (which usually includes polysubstance use disorder) tend to be very impaired and emotionally challenged with high impulsivity, frequent relapses, and trust issues, including nonadherence with treatment recommendations. BZDs should never be prescribed to pregnant women with SUD as they promote impulsivity, by decreasing inhibition and memory, thus preventing learning more adaptive coping skills. In addition, behaviors associated with BZD use increase risks of assaults and victimization further complicating the pregnancy and risks of harm to mother and fetus. When BZDs are continued into the late pregnancy, sedative neonatal abstinence syndrome (NAS) may occur. In the experience of one of the authors (MV) BZD NAS can be prolonged and protracted, with the newborn displaying major physiological and behavioral difficulties including high sensitivity to internal and external stimuli. The newborn cries easily, has difficulty with feeding, and has major difficulties tolerating regular touch, sounds, movement, visual stimuli, or internal stressors. Indeed, the child's uncontrollable crying and irritability may complicate the care and the mother/infant interaction, given the preexisting emotional vulnerabilities of the mother, as she may internalize the child's behaviors as rejection or overwhelmingly stressful. Given the high developmental stakes, alternative approaches to treating anxiety, anxiety sensitivity, stress, and distress intolerance during

pregnancy are desperately needed. Funding should target efforts to validate the effectiveness of integrative interventions to improve self-regulation and reduce stress during pregnancy. If successful, such interventions would have positive intergenerational impacts.

11.8.4 Polysubstance Users

The prevalence of BZD use reaches up to 50% individuals with OUD, including those on medication treatment (methadone, buprenorphine). BZD use in opioid-dependent populations is a predictor of overdose, lethality, and poor treatment outcome including cocaine and other drug use, self-harm behaviors, and poor psychosocial functioning. Methadone fatalities include BZDs in 75% of cases as do almost all buprenorphine fatalities. Benzodiazepines are frequently abused in combination with alcohol or other drugs (mainly opiates) to enhance the subjective reward of the primary substance, offset their adverse effects (e.g., irritability induced by stimulants), or alleviate withdrawal symptoms including insomnia. The risk of overdose death is greater when opioids and benzodiazepines are used in combination with alcohol due to the sedating and respiratory depression properties of all three substances.

The rehabilitation of patients who abuse BZDs in combination to other drugs is very challenging as they represent a treatment-resistant population. This phenomenon could have several explanations: the concurrent dependence on BZDs and opioids could lead to more severe withdrawal symptoms than opioid withdrawal alone, resulting in higher treatment attrition rates. Comorbid anxiety disorders are associated with avoidant behaviors, fears of discomfort, anxiety sensitivity resulting in lack of openness and flexibility, and resistance to alternative treatment modalities. The negative impact of BZDs on memory and cognition prevents learning more effective coping strategies that are indispensable to achieve abstinence.

11.8.5 Drug-Facilitated Sexual Assault (DFSA)

DFSA is a term used to describe sexual crimes that involve the surreptitious administration of psychoactive substances to compromise an unsuspecting individual's ability to consent to sexual activity. Although alcohol remains the most frequent substance used by perpetrators of sexual assault crimes, sedative drugs such as flunitrazepam (Rohypnol®), a fast-acting BZD, and other BZDs, ketamine, and gamma-hydroxybutyrate (GHB) are known to be slipped in a victim's beverage. Perpetrators choose these drugs because they act rapidly, produce disinhibition followed by deep sedation and relaxation of voluntary muscles, and cause the victim to have lasting anterograde amnesia for events that occurred under the influence of the drug. Many drugs associated with rape are given via alcohol to potentiate the drug effects [22]. The victim is left with a profound sense of betrayal, devastating powerlessness, and shame, in addition to the disorientation caused by the amnesia. The destructive emotions resulting from these assaults may derail a person's life goals and create vulnerabilities to resort to substance use to manage the emotional and physical pain.

11.9 Treatment of BZD Use Disorders

The management of patients with BZD use disorders includes several concurrent aspects: (1) management of the acute withdrawal phase, (2) treatment of underlying condition(s), (3) relapse prevention, and (4) crisis management, if needed. Clinicians need to work closely with patients showing empathy in helping managing distress, while providing choices of integrative or supportive therapies. Educational materials and tips regarding insomnia (sleep hygiene, sleep diary) and anxiety (CBT programs, self-help materials, referrals to mindfulness resources, breathing retraining) should be provided.

11.9.1 Intervention and BZD Detoxification

For some long-term BZD user patients, minimal interventions such as brief consultation or a letter with information about risks of long-term use of BZDs and the recommendation for their discontinuation can be effective and do not produce adverse effects [34].

The management of BZD withdrawal includes, either independently or in combination, (1) gradual tapering of the BZD, (2) switching to an equivalent dose of a long half-life BZD before gradual tapering of the latter, (3) the use of adjuvant medications, (4) treatment of the underlying conditions (e.g., SSRIs for anxiety) prior to detoxification and continuing these medications after BZD discontinuation, and (5) nonpharmacologic treatments of underlying conditions [25, 24]).

Although the rate of BZD taper needs to be individualized, there are some common recommendations as a function of the pattern of BZD use. A common recommendation is a reduction by 10–15% every 1–2 weeks, leaving some decision power to the patient. There is evidence that most patients will be able to complete a taper in 6–10 weeks.

For patients dependent on the more potent BZDs or those with higher abuse liability due to their short onset of action (lorazepam, clonazepam) or on those with short duration of action (alprazolam, triazolam, zaleplon, zolpidem), it is recommended to switch to a diazepam equivalent (https://clincalc.com/Benzodiazepine/default.aspx) for a few days and then rapidly taper off diazepam by 25% weekly over 4 weeks. This ensures a smooth detoxification as the drug long half-life and active metabolites will continue to taper itself for another 3–4 weeks after discontinuation. For heavy BZD-dependent polysubstance abusers, the availability of BZD from illegal sources may jeopardize outpatient detoxification, and residential treatment may be necessary to complete the detoxification.

11.9.2 Adjuvant Medications for BZD Withdrawal Treatment

Antiepileptic medications such as carbamazepine, its safer metabolite oxcarbazepine [11], and valproic acid are useful adjunct medications for attenuating BZD withdrawal symptoms especially for those coming off higher BZD doses, exceeding 20 mg diazepam equivalent daily. The newer antiepileptic zonisamide, which acts as both GABA enhancer and glutamate inhibitor, should also be investigated as it was found superior to diazepam on symptoms of craving, withdrawal, and depression for alcohol withdrawal [37].

Other GABA medications, such as pregabalin [8] and gabapentin, have been evaluated for BZD detoxification, but their benefits have not been confirmed [47]. Antiepileptic medications should not be considered for long-term BZD substitution because of their negative effects on cognition and potential risk of abuse (gabapentin).

11.9.3 Pharmacologic Treatment of Underlying Conditions

It is important to treat underlying condition(s) before, during, and after BZD withdrawal treatment. SSRIs and other antidepressant with low stimulating potential (sertraline, paroxetine, citalopram, escitalopram, mirtazapine, trazodone) are recommended for underlying anxiety disorders, especially with concurrent depressive symptomatology. Melatonin is recommended for insomnia, concurrently to adequate sleep hygiene. The recently approved orexin receptor antagonist, suvorexant, which was FDA approved in 2014 for the treatment of insomnia, should be evaluated for its potential in treating rebound insomnia in the setting of BZD and Z-drug withdrawal.

11.9.4 Non-pharmacologic Treatment of BZD Use Disorders

Maximizing the use of non-pharmacologic interventions is critically important, and a multidisciplinary approach is recommended. Although the review of non-pharmacologic interventions for anxiety and sleep disorders is beyond the scope of this chapter, clinicians will benefit their patients in developing familiarity with self-empowering strategies aimed at improving vagal tone and self-regulation as these practices lead to improved quality of life and better health by reducing stress reactivity, while minimizing risks associated with polypharmacy. Effective target-oriented short-term psychotherapy, cognitive behavioral therapy (CBT), exposure therapy, and mindfulness-based stress reduction are but a few examples.

Several promising therapies target anxiety: Creating Opportunities for Personal Empowerment (COPE) is a brief group CBT-based intervention that can be delivered to teens in school settings. Adolescents who received this therapy scored significantly lower in depression and anxiety on the Beck Youth Inventories and showed increases in self-reported confidence in managing negative emotions. Evaluations showed that the COPE intervention was well received by the teens [30].

A 12-session program of mindfulness-based stress reduction (MBSR) in seventh and eighth graders at a small school for low-income urban boys resulted in less anxiety, improved coping, and a trend to attenuation of cortisol response to academic stress, when compared with health education participants [38].

Pathological worry is considered a central symptom of GAD but can be seen in other types of anxiety (e.g., excessive worry over future panic attacks). A meta-analysis found that CBT for GAD is highly effective treatment for reducing pathological worry, including younger adults and geriatric patients, and the improvement was sustained at long term [10]. Tolin demonstrated that a 4-week breathing training aimed to correct hypocapnia in three anxiety clinics resulted in reduction of at least 40% of symptoms among 85% of completers and remission in 56% [45]. Battery-powered transcranial brain stimulation has been shown to stimulate vagal tone and found in uncontrolled trials to help with anxiety and insomnia. Recordings of imagery for insomnia or anxiety can help with sleep initiation and symptom reductions. The regular use of the recordings nudges the listener via metaphors to change usual ruminations toward more hopeful and restorative inner dialogues and is a cost-effective tool for change that one of us (AU) has found to be very well received by patients and effective. A collection of such recordings by B. Naparsteck and others can be found at https://www.healthjourneys.com/.

Avoidance of the discomfort of the withdrawal or rebound reactions during BZD tapering is a major difficulty in interrupting the vicious cycle of BZDs use to combat painful subjective states during the recovery from BZD misuse and dependence. To break this cycle, it is essential for individuals with co-occurring disorders to learn strategies to self-regulate anxiety symptoms as well as alternative coping strategies. Psychological support is required during and after BZD withdrawal as patients remain extremely vulnerable for several months after discontinuation. CBTs are among the most efficacious psychosocial interventions to treat individuals with co-occurring disorders and SUDs. The CB model of relapse is based on linear progression of responses in high-risk situations. Increase in self-efficacy leads to increased coping with anxiety and stress and less substance use. Combination of CBT with contingency management and relapse prevention combined with pharmacotherapy are among the most successful treatments [14].

Acceptance commitment therapy (ACT) [6] is a third-wave CBT intervention focusing on methods such as acceptance, mindfulness, cognitive defusion, decentering, and metaphors meant to reduce the impact of negative thoughts and feelings. ACT has also found wide acceptance as effective treatment for avoidance and anxiety disorders.

Physical exercise may enhance sleep and contribute to an increased quality of life in older adults [33], and increased physical activity also helps with insomnia [26]. CBT for insomnia is as effective for improving sleep quality, while decreasing depression and improving mental health.

11.10 Prevention of BZD UD

11.10.1 Awareness of Professional Guidelines

Countries have created guidelines aimed at curbing the chronic use of BZD to prevent the risks of misuse and abuse. Several health organizations (American Psychiatric Association (APA), the National Institute for Health and Care Excellence (NICE), The Royal Australian and New Zealand College of Psychiatrists (RANZCP), the UK Committee on Safety of Medicines (1988)) and governmental agencies (US Department of Veterans Affairs (VA) and the US Department of Defense (DoD), the UK Department of Health via the Chief Medical Officer (2004)) have created evidence-based guidelines describing indications and recommended length of time for BZD use. Most of these guidelines emphasize selective serotonin reuptake inhibitors (SSRI) as first-line treatment for GAD, panic attacks, and post-traumatic stress disorder and generally discourage the use of BZDs. However, primary and mental health-care providers frequently continue prescribing BZDs outside indications included in the guidelines [1]. Clinicians should avoid prescribing sedatives to children, as studies have documented that adolescents who received a medical prescription for sedatives are more likely to use nonprescribed medications of this type. Receiving a prescription reinforces the belief among adolescents that sedatives are "low risk" and that medications are the answers to life's challenges or unpleasant emotions.

11.10.2 Screening

Due to the strong association between anxiety disorders and SUDs, it is imperative to include screening questions regarding alcohol, smoking, and substance use histories when evaluating patients presenting with anxiety or insomnia complaints. A history of chronic lung disease or obstructive sleep apnea is relative contraindication to BZDs due to increased lethality. Identifying and counseling at-risk individuals, promoting alternative treatments where appropriate, and education on the safe and effective use of BZDs or Z-drugs may all decrease BZD diversion and misuse [31]. If in the last resort BZDs or Z-drug treatment is considered, it should be done with clear expectation of short duration and with education. To this effect, developing an explicit treatment contract with the patient and obtaining patient's signature to limit and monitor the duration of therapy for 2–6 weeks maximum are other ways of preventing BZD-related problems.

11.10.3 Patient Education

Education needs to highlight:

1. The side effects of BZDs, including their potential for physical dependence, symptom rebound upon discontinuation, and adverse effects on memory, cognition, and mood, including increased risk of dementia and increased risk of falls and accidents when operating vehicles or machinery within 24 hours of taking the medication
2. Risks of diversion, including ensuring safe keeping of medication in locked cabinets or boxes in order to prevent use of the medication by other persons living in the household
3. Safe handling of leftover medications which should be disposed appropriately by returning them to the pharmacist for environmentally safe disposal

More education is needed regarding the importance of sleep requirements, especially in

children and adolescents, and the timely recognition of poor sleep habits and/or sleep problems. Observing regular sleep hygiene behaviors is universally beneficial in improving sleep quality and for optimal mental health. Combination of sleep hygiene intervention, CBT, and stress reduction has been used to improve sleep and decrease the risk of relapse among adolescents with substance abuse problems [9].

11.10.4 Monitoring Patients Receiving BZD Prescriptions

An office policy should be in place to prevent BZD or Z-drug medication refill beyond 4–6 weeks. Depression should be addressed with antidepressant medications indicated for mood disorders, or patients should be referred to mental health providers. Inform patients in writing of the risks of BZDs if prescriptions for BZDs exceed 3 months, requesting patient signature acknowledging reception of the information, via certified letter if needed.

Pharmacies should be engaged in patient monitoring, informing practitioners when prescriptions are obtained from multiple providers and preventing duplication.

Programs treating OUD, such as opiate detoxification, need to screen for concurrent benzodiazepine dependence and modify the detoxification protocol accordingly and assess underlying psychiatric issues given their high prevalence in this population.

11.11 Conclusions

- While the true extent of BZD and Z-drug use/misuse and diversion is unknown, it is well known that they are among the most frequently prescribed medications and that they are prescribed chronically for insomnia, anxiety, and as muscle relaxants, which is against professional guidelines.
- BZD-related problems are found in all ages from adolescence to seniors and widely different populations such as war veterans and women.
- Due to their adverse effects on memory and cognition, BZDs impact daily activities such as driving or taking care of children.
- BZD use disorder is a common and costly comorbidity in patients with anxiety disorders or other SUDs complicating treatment outcome. In the last two decades, BZD use increase has contributed to the current epidemic of lethal drug overdose in the USA.
- BDZ discontinuation is a challenging process and needs to be closely monitored with compassion and encouragement given the severe discomfort and underlying distress, while knowing that improved quality of life lies ahead.
- Non-pharmacologic therapies, sleep hygiene, exercise, outdoor activities, CBT, mindfulness-based stress reduction, yoga, breathing retraining, or other relaxation interventions have been shown to be more efficacious than BZDs for insomnia and anxiety. These interventions have the benefits of long-term stress reduction, improvement of cognition and life satisfaction, and decrease in disease burden.
- Health-care providers and society in general need to be aware of BZD intrinsic abuse liability but also of individual vulnerabilities in risk for misuse and diversion.

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Cannabis Use Disorder and Its Treatment

12

Alan J. Budney and Michael J. Sofis

Contents

Abstract

Scientific advances and clinical epidemiology provide clear evidence of cannabis' potential for addiction and adverse psychosocial and health consequences, yet skepticism about its addictive potential remains, and perceived risk of its potential for harm continues to decrease. Indeed, treatment seeking for cannabis use disorder (CUD) comprises a substantial proportion of all substance use treatment admissions. This chapter is focused on cannabis' potential for misuse and addiction and reviews what is known about behavioral and pharmacological interventions for cannabis use reduction or cessation. Behavioral treatments, brief interventions, and digital health interventions have demonstrated efficacy, although there remains much room for continued improvement in outcomes. Unfortunately, a growing body of research has yet to identify an effective pharmacotherapy, and no medications are currently approved by the FDA for treating CUD. Continued efforts to identify and increase access to effective interventions for misuse and CUD are imperative to the public health considering the loosening of cannabis laws for both therapeutic and recreational use, the burgeoning of cannabis industry, and societal and cultural trends toward acceptance of cannabis use. The field will continue to benefit

A. J. Budney (✉) · M. J. Sofis
Center for Technology and Behavioral Health, Department of Psychiatry, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
e-mail: alan.j.budney@dartmouth.edu

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from efforts to develop innovative treatments that leverage scientific and technological advances and that better tailor interventions to individuals or subgroups of cannabis users.

Keywords

Cannabis · Cannabis use disorder · Marijuana Treatment · Medication

12.1 Introduction

Cannabis remains one of the most widely used regulated psychoactive substances in the United States and other developed countries, and the prevalence of cannabis use continues to rise. Debate about its addictive potential, health consequences, legal status, and therapeutic use has troubled governments, scientists, and the general public for more than a century. Advances in clinical and basic science have provided clear evidence of cannabis' potential for addiction and adverse psychosocial and health consequences, yet skepticism remains, and perceived risk of its potential for harm continues to decrease.

The discovery of the endogenous cannabinoid system in the late 1980s triggered a plethora of scientific investigation exploring the biological underpinnings of cannabis use and its effects and the potential mechanisms by which it impacts physical health and psychiatric disorders. Clear similarities were observed in the neurobiological processes involved in cannabis use and the development of cannabis use disorder (CUD) and those involved with other types of substance use and addictions. A withdrawal syndrome was identified, and increased concern about CUD and its treatment began to pervade the scientific literature. Clinical epidemiological studies and clinical studies of behavioral and pharmacotherapy interventions for CUD increased in numbers and unfortunately demonstrated that CUD was relatively common and, like other substance use disorders, not easy to treat [14].

The growing awareness of these clinical concerns related to cannabis misuse has been paralleled by an escalation of attention on the potential therapeutic use of cannabis and its constituent compounds, the acceleration of legalization of cannabis possession and use, and a flourishing cannabis industry, all of which contribute to a cultural context of reduced concern about the personal risks and public health consequences of cannabis use. Notably, lower perceived risk of harm in the general population corresponds with increases in prevalence. Such cultural changes raise concern about increased risk for CUD and the risk of harm related to cannabis misuse.

This chapter will focus solely on cannabis use and its potential for misuse and addiction and on what is known about interventions for helping those who develop problems with cannabis. Because we will not be focusing on therapeutic use of cannabis, it is important to clarify what we are referring to when we use the word "cannabis" in this chapter. Cannabis will refer only to cannabis plant material or extracts from the cannabis plant *that contain substantial amounts of delta-9-tetrahydrocannabinol (THC). THC* is the compound that produces the euphoric-like effects or the high experienced when cannabis is consumed [32]. Hence it is the THC in cannabis that relates most closely to its addictive potential. In this chapter, "cannabis" will *not* be referring to cannabidiol (CBD) products that contain no or only trace amounts of THC. CBD is the compound in the cannabis plant that has garnered much attention for its potential therapeutic effects, but CBD does not produce a high when ingested [25]. Given the current cultural climate, discussions of treatment for CUD or cannabis misuse need to distinguish between use of substances with THC and those with primarily CBD and little to no THC. Below, we provide a brief overview of the pharmacology, phenomenology, and epidemiology of cannabis and CUD, followed by an update and review of the current evidence base for effective treatments for those seeking to reduce or quit cannabis use.

12.2 Pharmacology and Phenomenology

12.2.1 Cannabis Use

Cannabis is the generic and most appropriate scientific term for the psychoactive compounds that comprise *Cannabis sativa* or *indica* plants that have been used by humans to alter consciousness or to enhance physical and mental well-being for thousands of years. The cannabis plant contains well over 100 compounds; however, the compound of most relevance to the development of problematic use or addiction is delta-9-tetrahydrocannabinol (hereafter referred to as THC). Ingestion of THC is the primary mediator of the *positive reinforcing effects of cannabis use* (i.e., pleasurable feelings or sensations) via its interaction with the endogenous cannabinoid system and, in particular, activation of CB1 cannabinoid receptors located in abundance throughout the brain [26]. The common positive effects of cannabis use include euphoria or "high"; sense of relaxation, calm, or stress reduction; increased propensity for laughter; a slowed time perception; and increased creativity and appreciation for music or other art mediums. Common adverse or negative effects of cannabis use include feelings of paranoia, anxiety, and mild to moderate impairment in attention, memory, learning, and judgment. Of note, the contribution of cannabinoids (other than THC) and other compounds in the cannabis plant in producing these positive and negative effects and putative therapeutic effects is not clear but continues to be an important focus of current research [55].

12.2.2 Cannabis Use Disorder

The accumulated body of neurobiological, behavioral, clinical, epidemiological, and health services data collected over the past 30 years should render the debate over cannabis' addictive potential obsolete [12]. Nonetheless skepticism remains; hence, here we provide a brief overview of this body of work and the clinical epidemiological data that illustrate the significant public health issues that arise related to cannabis misuse and CUD.

Neurobiological and behavioral research As alluded to above, preclinical nonhuman and human laboratory research has characterized the endogenous cannabinoid system and identified how exogenous cannabinoids, like THC, interact with CB1 receptors, stimulate dopamine production in the brain's reward pathways, and produce the psychoactive and reinforcing effects of cannabis, which are the common neurobiological features of mostly all substances with addictive potential [78]. Human laboratory studies have demonstrated positive subjective reinforcing effects of THC, with higher doses preferred over lower doses among current cannabis users, and a preference for THC over placebo [32].

Withdrawal Experimental research has demonstrated another key marker of cannabis' addictive potential, a withdrawal syndrome that can occur when regular cannabis use is discontinued, i.e., a person is deprived of THC. Human and animal research has clearly demonstrated how THC deprivation can precipitate withdrawal, CB1 agonists such as THC can relieve such withdrawal (pharmacological specificity), and CB1 antagonists can precipitate withdrawal in animals that have been regularly administered CB1 agonists. Numerous human clinical studies have now identified the common signs and symptoms of a cannabis withdrawal syndrome: irritability/anger/aggression, restlessness, anxiety, sleep difficulty, strange dreams, decreased appetite, weight loss, and depressed mood [11]. Physical symptoms are reported less frequently but include chills, headaches, physical tension, sweating, and stomach pain. The time course of this withdrawal syndrome is like most other types of substance withdrawal with onset within the first 24–48 hours of cessation, peaking within the first week, with a duration of approximately 1–2 weeks [11, 13].

Cannabis withdrawal is now included as a substance withdrawal disorder and a CUD criterion item in the DSM-5 and the ICD-11 (see below for CUD definitions). The syndrome can play a part in the development and maintenance CUD by contributing to the continuation of problematic cannabis use patterns and by precipitating relapse (i.e., negative reinforcement

processes). Of note, this withdrawal syndrome [3], although clinically important, does not typically precipitate serious medical or psychiatric risk [3]. In summary, the behavioral and neural processes observed related to cannabis administration and withdrawal parallel those of most substances that carry risk for development of an addiction.

Genetics As would be expected, genetic contributions to the development of CUD have been observed. Heritable risk factor studies suggest that genetic risk comprises 30–80% of the total variance in risk of developing a CUD, and genetic linkage studies strongly suggest a genetic link to CUD [1]. Cannabis-specific genes, i.e., those that impact vulnerability to the addictive potential of cannabis; genes that are related to a general vulnerability to mostly all SUDs, i.e., those that increase or decrease vulnerability to externalizing behavior problems; and genes that impact reactivity to environmental variables such as stress, have all been linked to cannabis use, misuse, and CUD.

Diagnosis and definition The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [3] and the *International Statistical Classification of Diseases and Related Health Problems (ICD-10 or 11)* provide clear operational definitions of *CUD*. Both classification systems describe a syndrome that develops from excessive use of cannabis and which includes all the same generic criteria for diagnosis as for most other substance use disorders [77]. The DSM-5 criteria denote 11 criteria that relate to impaired control over one's consumption, social impairment, risky use, and physical dependence, i.e., tolerance or withdrawal. Severity can range from mild (2–3 criteria), to moderate (4–6 criteria), to severe (7 or more criteria). The ICD operationalizes CUD somewhat differently by including two distinct disorders: *harmful use* and a *dependence syndrome* (which are highly similar to previous DSM versions of abuse and dependence diagnoses). *Harmful use* entails a pattern of psychoactive substance use causing damage to physical or mental health. The *dependence syndrome* entails a cluster of physiological, behavioral, and cognitive phenomena, which operationalize patterns of substance use that reflect increasing value of such use over other prosocial behaviors that previously had greater value. The *dependence syndrome* requires 3 of 6 specified criteria. Inclusion of CUD in the DSM and ICD taxonomies imparts the clear message that medical experts and scientists deem CUD to be a valid and clinically important substance use disorder that is not rare and is experienced in much the same way as other substance use disorders [3, 12].

Prevalence Cannabis remains the most commonly used psychoactive and regulated substance in the world after alcohol and tobacco. Globally, prevalence of its *use* has trended slightly upward since 2009, stabilizing over the past few years at approximately 4% (~190,000,000) of the adult and adolescent population who report using cannabis in the past year [69]. Greater increases over the past decade have been observed in the United States and Canada. Of note, in the United States, self-reported past-month cannabis use among pregnant women was approximately 7% in 2017, which reflects an increase from 3.4% in 2002. Reports of daily use among pregnant women also increased from 0.9% to 3.4% [72]. In Canada, a recent report also indicated an increase in cannabis use among pregnant women but at an overall lower prevalence rate (1.2–1.8% from 2012 to 2017) and reported a much higher rate of use (>6%) among younger women (15–24 years) [18]. Cannabis use during pregnancy, particularly during the first two trimesters, has been associated with effects on fetal growth and later childhood outcomes.

Global estimates of CUD indicate that over 13 million individuals meet criteria for a current diagnosis (~0.2% of the population or ~6% of those who use cannabis) [22]. In the United States, prevalence of current CUD appears substantially higher (1.5–3%) based on estimates provided by two general population surveys from the United States [37, 56]. Other high-income countries have also reported relatively high prevalence of CUD compared with the global population (e.g., Germany, 0.5%;

Australia, 1%). Conditional prevalence, or the percentage of those who use cannabis who develop CUD, has been estimated at 11.6% and 30% for past-year cannabis users across two US population studies [31, 36]. Of relevance to assessing the "addictive potential" of cannabis use, the conditional prevalence of CUD (30%) among past-year users observed in the US NESARC study appears higher than for alcohol (17.5%) but lower than for tobacco (80%) [17]. Like with other SUDs, the most prominent demographic risk factors associated with CUD are male gender and younger age (i.e., 18–25 or 18–29) [37, 59]. The relative risk of CUD among younger individuals is unique to CUD compared with other SUDs [59]. Overall, it is evident that CUD is not a rare disorder, and its prevalence appears to be increasing, leading the WHO to conclude that CUD is a clear public health problem, particularly among higher-income nations [74].

Phenomenology The estimated distribution of lifetime severity levels of CUD in the United States using DSM criteria is approximately 2.85% mild, 1.42% moderate, and 2.0% severe [37]. Severity level shows robust positive relationship with other mental health and substance use problems and a negative relationship to social, emotional, and cognitive functioning. Hence, like other SUDs, the more severe the CUD diagnosis, the greater the increase in the risk of physical and psychological symptoms that can negatively impact one's life. Those with CUD report greater disability [37] and are more likely to report inpatient and emergency room visits than those without CUD [16]. Additional consequences that have been associated with CUD relate to the pharmacological effects of cannabis intoxication and chronic use (e.g., driving accidents, risky sex behavior).

Treatment-seeking adults and adolescents identify multiple problems associated with their cannabis misuse. For adults these include procrastination/low productivity, memory issues, low energy, financial or employment difficulties, guilt about use, cannabis withdrawal, low self-confidence/self-esteem, insomnia, and distressed personal relationships [66]; and for adolescents these include neglected responsibilities, inability to do homework or study, missed school or work, went to school high, missed out on things because they spent too much money on cannabis, arguments with family, continued using despite promising oneself not to, and noticing unpleasant changes in personality [43].

Additionally, approximately 35% of those 12 years and older who are seeking treatment for CUD also report at least one additional psychiatric disorder [58]. Moreover, estimates from a general population study suggest that those with past-year CUD are more likely than those without CUD to have one or more additional SUDs (OR = 9.3) and to suffer from anxiety (OR = 2.8), personality (OR = 4.8), mood (OR = 3.8), and post-traumatic stress disorders (OR = 4.3) [37]. Importantly, those with CUD and another psychiatric disorder or another SUD demonstrate worse cannabis cessation outcomes and worse outcomes related to specific psychiatric conditions [6]. Given the notable prevalence of co-occurring CUD and psychiatric disorders, such findings indicate a clear need for services that provide integrated treatments.

Treatment seeking Across most parts of the globe, treatment admissions for CUD substantially increased in proportion to treatment for all SUDs from 2003 to 2016 (e.g., 8–15% in Eastern/Southeastern Europe, 19–30% in Western/Central Europe, 9–16% in Asia, 28–33% in North America) [68]. In the United States, treatment admissions for SUDs in general declined 18.6% from 2002 to 2015, with CUD admissions declining at an even higher rate (26%) perhaps related to escalating legalization policies [58]. Nonetheless, the number of CUD admissions remains substantial. In the United States, admissions for CUD make up approximately 13% of all SUD admissions, behind only alcohol and opioid use disorders as the primary substances reported by those entering treatment [57]. For those aged 15–17 years, the proportion of all SUD admissions for primary CUD is exponentially higher, comprising about 73% all admissions for these youth [57]. Notably, the

percentage of admissions of cases for CUD decreases by age: 12–17 years, 77%; 18–19 years, 44%; 20–24 years, 22.5%; and 25–34 years, 12%.

Although substantial numbers of those with CUD seek treatment, just as with all other SUDs, the great majority does not utilize treatment services. Estimates from the United States suggest that only 7–8% of those with CUD engage in treatment related to their cannabis use during the past year [37], which is even lower than the estimated 13.5% of those with any past-year SUD who sought treatment [5]. Postulated reasons for this lack of utilization include perception that treatment is not necessary, lack of problem awareness, stigma, and self-reliance [27, 70]. Overall these statistics suggest a strong need for effective treatment services for CUD, increased treatment access, and interventions that motivate treatment seeking.

12.3 Treatment for Cannabis Misuse and CUD

The CUD treatment research literature parallels that of most other SUDs. Pharmacotherapy laboratory studies and clinical trials testing a wide range of medications have proliferated over the past 10–15 years. Psychosocial treatment studies have primarily focused on evaluating motivational enhancement, cognitive-behavioral or coping skills, and contingency management interventions and their combinations. Research on treatments for adolescents with CUD or cannabis misuse comprises multiple types of family-based interventions in addition to similar approaches to those used with adults. Most recently, multiple studies have focused on the development of digital or mHealth approaches that can increase access to effective CUD interventions and perhaps enhance outcomes when integrated with standard treatments. Below we provide a brief overview of this clinical literature highlighting promising approaches, current trends, and future directions.

Behavioral/psychosocial treatments Multiple reviews and book chapters summarizing the CUD treatment literature have appeared over the past decade (e.g., [14, 28, 62]). The most frequently evaluated interventions and those that have been deemed efficacious have been motivational enhancement therapy (MET), cognitive behavioral therapy (CBT), and contingency management (CM).

MET, the briefest (1–4 sessions) of the interventions, focuses on the individual's ambivalence toward quitting or reducing use, as well as targeting increased motivation and commitment to change. Counseling skills, such as empathy, reflective listening, summarizing, and affirmation, to engender motivation and action toward change are strategically employed. CBT is a skills training-based approach focused on enhancing cannabis abstinence/reduction, coping, and relapse prevention skills. Skills training is taught and practiced in session and assigned for practice in-between sessions. Group and individual delivery of CBT of varying length session (6–14 sessions) has been evaluated. Typical CM interventions systematically arrange a program of reinforcement (rewards or incentives) to elicit behavior change related to therapeutic targets, which in most cases is cannabis abstinence but also can be attendance at sessions, completion of homework, or engagement in prosocial activities. In most cases, CM has been evaluated as part of an intervention that includes MET or CBT.

The published reviews of the CUD treatment literature generally converge on several key conclusions [14, 28]. For adults, CBT, MET, combined MET/CBT, and combined MET/CBT/CM have each demonstrated efficacy for reducing cannabis use and decreasing CUD severity. CBT or the combination of MET and CBT appears to engender greater effects on cannabis use than MET alone. The integration of abstinence-based CM with MET, CBT, or MET/CBT optimizes short-term treatment abstinence outcomes, and frequency of cannabis use, abstinence, and severity of dependence are enhanced out to 12 months

posttreatment. Overall, longer behavioral treatments (4 or more sessions) have shown more robust outcomes than brief MET motivational approaches, although threshold or optimal durations of treatment have not been identified.

As observed with controlled outpatient clinical trials of behavioral treatments for other substance use disorders, the outcomes observed in these CUD trials leave much room for improvement. The majority of participants does not achieve abstinence or substantial reduction in cannabis use indicative of significant clinical improvement. Moreover, of those who do achieve a positive response, a substantial number relapse either during outpatient treatment or shortly posttreatment.

Behavioral interventions for adolescents Although many clinical trials evaluating interventions for adolescents with SUDs include youth who use and misuse various substances, cannabis is typically the primary substance used by the adolescents and CUD the primary SUD diagnosis. Multiple reviews of this literature have appeared in the last 10 years (e.g., [39, 64, 67, 76]).

The largest clinical trial for youth with CUD, the Cannabis Youth Treatment (CYT), was a multi-site study ($N = 600$) comparing five outpatient treatments: individual MET/CBT, individual adolescent community reinforcement approach, group MET/CBT, the MET/CBT with family support network, and multidimensional family therapy [23]. Results indicated that the efficacy of these five approaches was not significantly different. That is, adolescents across conditions evidenced significant improvement in days of abstinence and recovery rates at the 1-year follow-up, and no one treatment outperformed the other. Most youth, however, did not achieve abstinence, with the great majority relapsing during treatment or during the 12-month follow-up period.

Most reviews have concluded that several family-based therapies, including functional family therapy, multidimensional family therapy, and brief strategic family therapy, have clear support for their efficacy, as do individual- and group-delivered CBT. The evidence-based family approaches likely have significantly larger effects on substance use than MET and CBT interventions. As concluded for adult CUD treatments, integrated models that increase the scope and intensity of treatments by combining evidence-based approaches can enhance outcomes [39]. A notable example of successful integration is the combination of CM with MET/CBT and behavioral parent training [65]. The youth CM program included abstinence-based rewards delivered by both the clinic and guardians. This integrative model optimized during treatment cannabis reduction and abstinence, but unfortunately longer-term effects for youth with CUD remain elusive. The most favorable combinations, duration, and CM reward parameters have yet to be identified, and alternative approaches are clearly needed to enhance maintenance of treatment effects.

12.4 Digital Health Interventions

Digital health interventions (DHIs) hold substantial promise to extend reach and enhance outcomes for those with cannabis-related problems and CUD [7]. DHIs can increase access to evidence-based CUD interventions by reducing the need for highly trained personnel, lessening burden associated with attending the treatment clinic, allowing treatment to be provided in non-specialty clinics, and reducing provider and patient costs. Some DHIs may improve treatment outcomes by making therapeutic tools available 24/7 via smartphone apps or web-based programs [7]. Moreover, new mobile technologies can potentially monitor risk factors for substance use in real time and provide individualized and automated approaches to dealing with high-risk situations. Readily available therapeutic tools (e.g., self-monitoring programs, skills training modules, social support platforms) hold promise for enhancing engagement with these evidence-

based clinical interventions and maximizing outcomes and long-term maintenance of change.

DHIs for adults with CUD have been tested in multiple, controlled clinical trials. The early DHIs for CUD adapted face-to-face evidence-based MET/CBT interventions for delivery in community clinics using a computer or mobile devices. Initial controlled trials indicated a positive impact on treatment outcomes comparable to or exceeding therapist-delivered interventions, and some data suggest that these outcomes were achieved at lower cost and that community clinicians are open to using these DHIs [15, 41, 42, 48].

DHIs targeting cannabis use and related problems have also been applied and evaluated outside traditional healthcare settings. A meta-analysis of four controlled trials (n = 1928) conducted in three different countries assessed the effectiveness of online-delivered DHIs that combined MET/CBT for reducing problematic cannabis use and showed evidence of positive small effects at 3-month follow-up [38]. Another trial from Switzerland evaluated an eight-session web-based MET/CBT self-help program for the general population of cannabis users and tested it with vs. without 1–2 internet-delivered "chat" counseling sessions [60]. Program retention and completion were not high, but those who received the program with the chat counseling reported greater cannabis reduction outcomes than those who received only the web-based program or those assigned to a waitlist control group. Other DHIs for cannabis use have focused on college students. For example, a one-session web-based MET-personalized feedback intervention for cannabis-using students transitioning to college did not show treatment effects, but positive effects were observed among those with higher motivation to change and those with family histories of substance use problems [44].

A more recent systematic review and meta-analysis of diverse DHIs for reducing cannabis use identified 20 controlled treatment studies and concluded that these types of interventions significantly reduced cannabis use, but the posttreatment effects tended not to maintain during the year following these interventions [7]. As with in-person interventions, combination approaches appear to provide increased efficacy.

DHIs for youth have received less attention and have primarily been assessed with youth who are using cannabis but who are not seeking or enrolled in treatment [47]. One innovative study integrated ecological momentary assessments (EMA) via mobile phones with MET with cannabis-using youth [63]. After two in-person MET sessions, youth reported triggers, cravings, and cannabis use via their mobile phone for 2 weeks. Youth also received text messages to help them cope with the identified triggers. The use of this program reduced frequency of cannabis use and was acceptable to youth. Another small trial with youth entering an SUD treatment program replaced in-person sessions with CBT-based digitally delivered modules and achieved similar reductions in substance use and mental health outcomes compared with the therapist-delivered intervention; youth rated the DHI as highly acceptable [47]. Last, a pilot study targeting enhanced recovery support tested the use of daily collection of risk factors via an EMA mobile program and 24/7 availability of automated ecological momentary interventions (i.e., automated coping skills interventions) for youth recently discharged from residential treatment [24]. Youth readily used the intervention, particularly those at high risk, and the use of the EMIs was associated with less substance use; note that a large randomized trial of this DHI for youth is in progress.

In summary, digital interventions have the potential to reduce problematic cannabis use when used as part of in-person interventions in traditional treatment settings, as primary interventions in non-healthcare settings, and as stand-alone, online interventions for the general population. Although having at least minimal in-person contact appears to increase the efficacy of DHIs, significant effects can be achieved even with no clinical contact. Future technological innovations will most certainly increase the possibilities for DHI provision, which will have substantial impact on reducing barriers to treatment, increasing access for at-risk cannabis users, and hopefully increasing the potency of interventions for CUD.

12.5 Brief Interventions

Another treatment modality for CUD and cannabis misuse is the brief intervention (BI). BIs for CUD usually comprise 1–2 sessions and primarily utilize interviewing and counseling strategies drawn from the MET literature. These have been tested in specialty and non-specialty treatment settings and demonstrated small to moderate effects [53]. As with DHIs, the availability of BIs can increase access to treatment and decrease burden, which can help reach a larger proportion of those with CUD or cannabis-related problems who might benefit from the intervention.

Opportunistic settings such as schools or medical settings offer the ability to identify and reach more persons experiencing problems related to their use of cannabis. Several brief interventions aimed at youth have been developed to facilitate intervention efforts in these settings. Two brief interventions for youth were developed for use in primary care or the emergency department, one with a focus on substance abuse generally [19] and the other for cannabis specifically [4]. Both used MET counseling principles and delivered the intervention via a 15–20-minute session plus a 10-minute booster phone call and reported significant reductions in cannabis use indicating that primary care and emergency room settings can be utilized effectively to identify and intervene on cannabis use.

Schools, both high school and college, provide advantageous environments for reaching youth who misuse cannabis. Several BI studies have recruited and delivered the intervention in school settings and shown positive effects. Two sessions of an MET-based BI reduced cannabis use and CUD symptoms assessed at a 1-year follow-up [75]. Findings from two studies comprised of only one session of MET showed significant reductions in cigarettes, alcohol, and cannabis in one trial, but not in a second trial [51].

The most well-established school-based intervention is the *Teen Marijuana Check-Up (TMCU* [73]). This alternative school-based approach focuses on recruiting teens who are not necessarily interested or willing to go to treatment, those who may have questions about their cannabis use but do not identify as having a problem, and even those who are not thinking about changing their use. The TMCU is advertised in schools as a confidential meeting with a healthcare counselor and is not labeled as treatment. Three trials have shown that teens with cannabis use frequency levels comparable to that observed in outpatient treatment studies readily volunteer for the TMCU and show reliably greater decreases in cannabis use relative to teens in control conditions [73]. Of note, the TMCU has also been adapted and evaluated in Australia [49] and the Netherlands [21]. An ongoing implementation trial will evaluate different strategies for effectively translating the TMCU to community school systems [35].

Overall, BIs provide an important intervention modality that can reach cannabis users who are not likely to seek treatment. Initial evidence suggests that these interventions have significant positive impact on cannabis use, but this effect is not large.

12.6 Pharmacotherapies for CUD

The development of medications to use as adjuncts to behavioral interventions or as standalone treatment has the potential to enhance outcomes for those seeking to reduce or stop using cannabis. Increased understanding of the neurobiology of cannabis and the complexities of the endogenous cannabinoid system, together with a clearer characterization of the cannabis withdrawal syndrome, has led to an escalating number of human laboratory and clinical trials exploring the effects of a diverse cadre of medications. Reviews of this literature, including a most recent Cochrane review, have unfortunately yet to identify an effective pharmacotherapy (e.g., [9, 52, 62]), and no medications are currently approved by the FDA for treating CUD nor are there sufficient data to justify clear clinical recommendations. Below, we briefly summarize findings from the reviews and highlight a few more recently published studies.

Pharmacotherapy approaches explored to date include the following:

(a) Targeting of the withdrawal syndrome, either by use of CB1 agonists or intervening on specific withdrawal symptoms
(b) Use of CB1 receptor antagonists or inverse agonists to block the effects of THC and reduce the reinforcing effects of cannabis
(c) Targeting of mood, stress, or craving with diverse medications
(d) Opioid antagonists that block opioid receptors, which putatively contribute to the reinforcing effects of THC via interactions with the cannabinoid system
(e) Novel medications that directly target the endogenous cannabinoid system and directly manipulate brain levels of specific endocannabinoids, i.e., FAAH inhibitors
(f) Medications that target comorbid psychiatric conditions (e.g., depression, anxiety)

Agonist therapies such as dronabinol and nabilone have demonstrated clear efficacy for reducing cannabis withdrawal symptoms and self-administration in human laboratory studies when delivered alone and in combination with other medications; however, CUD outpatient treatment studies have failed to demonstrate the efficacy of dronabinol or a combination of lofexidine (an alpha-2 agonist) and dronabinol, although some data suggest that perhaps higher doses of dronabinol should be evaluated [46, 61]. Nabilone has yet to be tested in a clinical trial. Similarly, nabiximols (i.e., Sativex) an oramucosal preparation of THC combined with cannabidiol (CBD) reduced cannabis withdrawal symptoms but did not show an effect on cannabis use or abstinence [2]. An antagonist-like medication, i.e., rimonabant, a CB1 receptor inverse agonist, effectively blocked the intoxicating effects of smoked cannabis in a human study [40] but has not been tested in clinical trials because it was withdrawn from the European market because of psychiatric side effects. Unfortunately, no other antagonists or inverse agonists have received systematic study in humans. Zolpidem, a nonbenzodiazepine GABA-A receptor agonist used for the treatment of insomnia, reduced cannabis-withdrawal-related disruptions in sleep [71], and results from a clinical efficacy trial are pending. Guanfacine, an alpha-2a-adrenergic agonist, has also shown positive effects on multiple symptoms of cannabis withdrawal [33].

Multiple laboratory studies and clinical trials have evaluated medications targeting mood, stress, or craving and have undergone tests in the laboratory and research clinics (e.g., baclofen, buspirone, bupropion, divalproex, fluoxetine, lithium, mirtazapine, nefazodone, oxytocin, quetiapine, topiramate, venlafaxine; [9]). Results of these studies have generally been unremarkable in that no robust evidence for potential efficacy has been observed. A few initial small clinical studies have reported positive findings. For example, the GABAergic medication, gabapentin, showed reductions in withdrawal symptoms and days and amount of cannabis use and improved sleep [50], but replication of these outcomes has not appeared in the literature. A trial of the naturally occurring amino acid, N-acetylcysteine (NAC), showed positive effects in reducing cannabis use in treatment-seeking youth [29], but a subsequent multi-site trial targeting CUD in adults did not observe positive effects on cannabis use [30].

Naltrexone, an opioid antagonist, has been considered as medication for CUD because of the bidirectional modulatory effects of the endogenous cannabinoid and opioid systems and the potential for opioid receptor blockade to decrease the positive effects of cannabis. Laboratory studies indicate that chronic dosing can decrease the reinforcing effects of cannabis smoking and may impact use patterns in the home environment [34]; however, no CUD clinical trials have been reported.

A recent novel approach to CUD medication development is to directly manipulate brain levels of specific endocannabinoid, for example, potentiating signaling by inhibiting fatty acid amide hydrolase (FAAH), the enzyme that degrades the endocannabinoid, anandamide. A small initial controlled trial of a FAAH inhibitor supported the safety of the FAAH inhibitor, and findings indicated positive effects on cannabis withdrawal symptoms during the initial 5-day inpatient stay and indicators of reduced cannabis use during a short 3-week outpatient period [20]. A larger controlled trial of this FAAH inhibitor is in progress.

Because the majority of those with CUD also has a psychiatric disorder, there has been some interest in testing medications for these co-occurring disorders. A large multi-site trial evaluated methylphenidate for teens with attention deficit hyperactivity disorder (ADHD) and an SUD (over 90% had CUD) [54]. Medication effects on ADHD were minimal, and no difference was observed on days of substance use. A small significant effect was reported on abstinence verified by urine toxicology. Prior studies that evaluated atomoxetine for ADHD and CUD and venlafaxine or fluoxetine for depression and CUD reported similarly weak results. Observational studies have reported that clozapine reduced cannabis use in those with schizophrenia and CUD, and a small, controlled trial supported this observation, observing a small effect on reductions in cannabis use [10].

12.7 Conclusions and Future Directions

Cannabis use and CUD, like other psychoactive substances and substance use disorders, pose an important public health problem impacting a substantial number of individuals across the globe. The changing landscape of cannabis legalization and the parallel burgeoning of a multibillion cannabis industry strongly suggest that problems related to the misuse of cannabis and the development of CUD will continue and likely escalate. Existing evidence-based behavioral treatments for CUD produce positive outcomes, with combination interventions such as MET/CBT/CM showing the largest effects. However, at least half of those who seek treatment for CUD do not show a positive response to these interventions, and many relapse. The majority of those with CUD does not seek or receive treatment. Digital health approaches delivered online or via mobile technologies such as smartphones hold promise for both increasing access to efficacious interventions and enhancing treatment potency and outcome. Integration of in-person and digital treatment approaches warrants further investigation.

Identifying of pharmacotherapies for CUD remains an important goal and one that could greatly enhance intervention options and enhance efficacy for those seeking to reduce or quit cannabis use. Finding an efficacious medication continues to be elusive. Novel approaches that warrant continued study include modulation of the endocannabinoid system, alternative dosing with CB1 agonists, and combinations of medications targeting withdrawal and co-occurring symptoms and disorders that may interfere with cannabis reduction or prompt relapse.

Methodological variability, particularly the lack of uniform outcome measures across CUD intervention studies, causes difficulties not only in comparing treatment efficacy but also in determining clinically meaningful outcomes [45]. To date, most studies have focused on cannabis abstinence to assess treatment efficacy, but substantial reductions in cannabis are also likely to result in improvement in psychosocial functioning [8]. In lieu of the current loosening of cannabis laws for both therapeutic and recreational use and societal and cultural trends toward acceptance of such use, broadening the range of outcomes used to evaluate CUD and cannabis use interventions is rationale and in line with the goals of those interested in addressing perceived problems associated with patterns of use that vary on frequency and amount of consumption. Persons who misuse cannabis and develop a CUD are a diverse group, with various patterns of cannabis use (frequency and quantity), differing symptom profiles, a wide range of severity levels, and assorted co-occurring problems. Behavioral and pharmacological treatment approaches that tailor interventions and outcome goals to specific subgroups may prove beneficial for enhancing their efficacy and can help better identify effective treatments for those struggling with cannabis use-related problems.

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Cocaine Addiction and Treatment

13

David A. Gorelick

Contents

D. A. Gorelick (✉)
Department of Psychiatry, University of Maryland
School of Medicine, Baltimore, MD, USA
e-mail: dgorelick@som.umaryland.edu

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Abstract

Cocaine use disorder represents a substantial clinical and public health burden in many countries, yet there are no well-proven and broadly effective pharmacological treatments available and no medication approved for this indication by any national regulatory authority. Medications with efficacy in more than one controlled clinical trial include disulfiram, oral stimulants in sustained-release formulation, bupropion, and the anticonvulsant topiramate. Cocaine-metabolizing enzyme, an anti-cocaine vaccine, and repetitive transcranial magnetic stimulation (rTMS) have each shown promise in small clinical trials. In the absence of proven, broadly effective medications, the mainstay of treatment remains psychosocial interventions, such as contingency management and cognitive-behavioral therapy.

Keywords

Cocaine · Pharmacological treatment · Disulfiram · Agonist maintenance · Topiramate · rTMS · Anti-cocaine vaccine

13.1 Introduction

Cocaine is a plant alkaloid found in leaves of the coca bush, *Erythroxylon coca*, which grows in the Andes Mountains region of South America. Its psychoactive properties make cocaine one of the most widely used and abused illicit drugs in the world. There were an estimated 18 million cocaine users worldwide in 2014, representing 0.4% of the 15- to 64-year-old population [96]. Cocaine use is associated with a variety of psychological and physical health problems, resulting in a substantial clinical and public health burden in countries where use is prevalent. About one in six cocaine users (via the intravenous or smoked routes of administration) develop addiction (moderate-severe cocaine use disorder in DSM-5 terms) to the drug, with subsequent psychological and socioeconomic problems [14]. In 2010, cocaine use disorder was associated globally with an estimated 1.09 million years lived with disability (rate of 16 per 100,000 persons) [97], 1.1 million disability-adjusted life years (16 per 100,000 persons) [67], and 500 deaths (<0.05 per 100,000 persons) [54]. Data from longitudinal studies in five different countries (Brazil, Canada, Denmark, France, and Italy) suggest that addicted cocaine users have death rates four- to eightfold higher than those of the same age and sex in the general population [13].

Notwithstanding this substantial health burden, there are no widely used, broadly effective treatments for cocaine use disorder. No medication is approved for this indication by any national regulatory authority because no medication has met the scientifically rigorous standard of consistent, statistically significant efficacy in adequately powered, replicated, controlled clinical trials. The mainstay of treatment is psychosocial, with good-quality evidence from controlled clinical trials for the efficacy of contingency management, which may have enhanced effectiveness when used in conjunction with pharmacological treatment [87] and cognitive-behavioral therapy [44, 76]. This chapter reviews the current state of pharmacological treatment for cocaine use disorder.

13.2 Overview of Pharmacological Treatment

The goals of pharmacological treatment of cocaine use disorder are to reduce or eliminate the desire (craving) to take cocaine, reduce or eliminate the acute positive reinforcement (euphoria, "high") from taking cocaine, and reduce or eliminate the negative reinforcement from cocaine withdrawal. To achieve these goals in clinical practice, medication should be used in conjunction with some psychosocial treatment component, if only to enhance medication adherence. There are few data to guide the choice of optimum psychosocial treatment to combine with pharmacotherapy [6]. As no medication currently has national regulatory authority approval for treatment of cocaine use disorder, psychosocial modalities should be the mainstay of treatment [18].

Four pharmacologic approaches are potentially useful to achieve these treatment goals [28]: (1) substitution treatment with a cross-tolerant stimulant (analogous to methadone maintenance treatment of opioid use disorder), (2) treatment with an antagonist medication that blocks the binding of cocaine at its site of action (true pharmacologic antagonism, analogous to naltrexone treatment of opioid use disorder), (3) treatment with a medication that functionally antagonizes the effects of cocaine (as by reducing the reinforcing effects of or craving for cocaine), and (4) alteration of cocaine pharmacokinetics so that less drug reaches or remains at its site(s) of action in the brain.

Most current clinical and research attention focuses on the second and third approaches. The first approach has been evaluated in a small number of clinical trials, with mixed results. The fourth approach has shown promise in animal studies and early phase II clinical trials [27].

Cocaine has two major neuropharmacological actions: blockade of presynaptic neurotransmitter transporters (reuptake pumps), thereby inhibiting the uptake of previously released monoamine neurotransmitters and resulting in psychomotor stimulant effects, and blockade of sodium ion channels in nerve membranes, resulting in local anesthetic effects [29].

Cocaine's positively reinforcing effects derive from its blockade of the dopamine reuptake pump, causing presynaptically released dopamine to remain in the synapse and enhancing dopaminergic neurotransmission [36]. Cocaine's local anesthetic effects are believed to contribute to cocaine-induced kindling, the phenomenon by which previous exposure to cocaine sensitizes the individual so that later exposure to low doses produces an enhanced response.

13.3 Medication Options

13.3.1 Antidepressants

Antidepressants are the most studied class of medication for the treatment of cocaine use disorder, but evidence for their efficacy is weak. A meta-analysis of 28 published clinical trials that involved 2547 participants found that antidepressants as a class (including tricyclics, selective serotonin reuptake inhibitors, serotonin-norepinephrine uptake inhibitors, and the MAO inhibitor selegiline) were no more effective than placebo in terms of dropout from treatment (relative risk 1.03, 95% CI 0.92–1.16) or number of weeks of continuous abstinence (8 studies, 942 participants, mean difference 0.08, 95% CI −0.17 to 0.32) [73].

There is variation across types of antidepressants, with some evidence of efficacy in controlled clinical trials for desipramine and bupropion. A meta-analysis of 16 published clinical trials with desipramine (plus one trial using imipramine) that involved 1293 participants found a significant benefit from desipramine in proportion of participants achieving at least 3 weeks of continuous abstinence (relative risk 1.55, 95% CI 1.10–2.17), but no benefit in treatment retention (relative risk 1.00, 95% CI 0.85–1.18) [73]. However, the abstinence benefit was limited to participants with mild cocaine use disorder. There is weak evidence that patients with steady-state desipramine plasma concentrations above 200 ng/mL have poorer outcomes [43], with better outcomes at concentrations around 125 ng/mL [47]. A meta-analysis of two published controlled clinical trials that involved 176 participants found bupropion significantly better than placebo in promoting at least 3 weeks of sustained abstinence in participants with moderate-severe cocaine use disorder (risk ratio 1.63, 95% CI 1.03, 2.59) [8].

Several other antidepressants have shown efficacy in small, open-label trials, including reboxetine, maprotiline, and mirtazapine [28].

Heterocyclic antidepressants have not been associated with unexpected or medically serious side effects. While theoretically possible, there is no evidence that patients who relapse to cocaine use while still on medication are at increased risk of cardiovascular side effects [68].

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, and sertraline, have not been effective in controlled clinical trials [73, 98]. A meta-analysis of 8 published clinical trials involving 662 participants found no significant advantage over placebo in dropout

rate (relative risk 0.99, 95% CI 0.70–1.41) or craving for cocaine (standardized mean difference −0.22, 95% CI −0.52 to 0.54) [73]. One clinical trial found citalopram (20 mg/day) significantly better than placebo [63]. That study, unlike previous studies, used contingency management, in addition to cognitive-behavioral therapy, as the concomitant psychosocial treatment, suggesting the importance influence of psychosocial treatment on medication efficacy.

13.3.2 Dopamine Agonists (Antiparkinson Agents)

Direct and indirect dopamine agonist medications have not generally been found effective for the treatment of cocaine use disorder. A meta-analysis of 24 published clinical trials involving 2147 participants that evaluated both direct dopamine receptor agonists (bromocriptine, pergolide, pramipexole, cabergoline, hydergine) and indirect agonists (amantadine and the amino acid dopamine precursor L-dopa [sometimes combined with the peripheral dopa decarboxylase inhibitor carbidopa]) together as a class found no evidence of efficacy compared to placebo [61].

13.3.3 Disulfiram

Disulfiram increases dopamine concentrations by blocking the conversion of dopamine to norepinephrine by the enzyme dopamine-β-hydroxylase, so it can be considered a functional dopamine agonist [21]. A systematic review of seven published clinical trials involving 492 participants identified several trials in which disulfiram (250 mg daily) was significantly better than placebo in reducing dropout rate or cocaine use [72]. The trials could not be combined for meta-analysis because of high heterogeneity and differences in outcome measures. Only one [48] of five larger controlled clinical trials not included in the earlier review [28] found significant efficacy for disulfiram compared to placebo.

Some of the heterogeneity in treatment response to disulfiram may be due to genetic factors and gender. Three recent clinical trials found significant efficacy for disulfiram in genetically defined subgroup of patients: with dopamine-β-hydroxylase gene alleles associated with higher enzyme activity [48], with functional variants in the ankyrin repeat and kinase domain-containing 1 (*ANKK1*) and dopamine D_2 receptor (*DRD2*) genes [95], and in the α_{1A}-adrenoreceptor (*ADRA1A*) gene [91]. A review of five published controlled clinical trials involving 434 participants found that disulfiram was less effective in reducing cocaine use in women than in men [15]. There was no such gender difference in response to behavioral treatments. These findings suggest that disulfiram may be a promising treatment for cocaine use disorder in some subgroups of patients.

Although disulfiram is generally well tolerated in clinical trials, where subjects are carefully screened and closely monitored, it may be less safe in routine clinical practice [56].

13.3.4 Stimulants

Stimulant medications might be useful for the treatment of cocaine use disorder as a form of agonist maintenance treatment, conceptually similar to methadone maintenance treatment of opioid use disorder or nicotine replacement treatment of tobacco use disorder. The evidence to date is very promising, but not conclusive. A meta-analysis of 14 published clinical trials involving 1549 participants found that stimulants as a class (including dexamphetamine, mixed amphetamine salts, methamphetamine, lisdexamfetamine, methylphenidate, modafinil, and mazindol) were significantly better than placebo in promoting at least 3 weeks of sustained abstinence (risk ratio 1.36, 95% CI 1.05–1.77), but did not increase proportion of cocaine-free urine samples among those who did not achieve sustained abstinence (standardized mean difference 0.16, 95% CI −0.02 to 0.33) nor improve study retention (risk ratio 1.00, 95% CI 0.93–1.06) [8]. Among specific stimulants, only dexamphetamine (risk ratio 1.98, 95% CI 1.12–3.52) and mixed amphetamine salts (risk ratio 3.63,

95% CI 1.15–11.48) were significantly better than placebo in promoting at least 3 weeks of sustained abstinence. A recent 12-week, controlled clinical trial, not included in the earlier meta-analysis, found that sustained-release dexamphetamine significantly reduced frequency of cocaine use among 73 participants with cocaine use disorder who were also receiving heroin treatment for opioid use disorder (mean difference of 16.7 [95% CI 3.1–28.4] fewer days of cocaine use) compared to placebo [70]. None of these studies reported significant adverse effects, suggesting that stimulant substitution treatment might be safe in cocaine-using patients.

Cocaine itself could be used for agonist maintenance treatment in a slow-onset formulation or route of administration [26], conceptually similar to the use of slow-onset formulations of nicotine (transdermal or transbuccal) for the treatment of tobacco (nicotine) use disorder. Oral formulations of cocaine (cocaine salt capsules and coca leaf tea) substantially reduced coca paste smoking in two large case series of adult patients in Lima, Peru (where oral cocaine products are legal) [53]. Among a case series of 50 coca paste smokers in La Paz, Bolivia, coca leaf chewing (100–200 g of coca leaf per week for a mean of 2 years) substantially improved the mental health of one-third and improved the socioeconomic functioning of almost half (data on cocaine smoking were not reported) [37].

13.3.5 Antipsychotics

Neither the older so-called first-generation (typical) antipsychotics nor the newer second-generation (atypical) antipsychotics have shown consistent efficacy in the treatment of cocaine use disorder in patients without a comorbid psychotic disorder. A meta-analysis of 14 published clinical trials involving 719 participants found that antipsychotics as a class (aripiprazole, olanzapine, quetiapine, risperidone, and one study each with haloperidol or reserpine) reduced study dropout (risk ratio 0.75, 95% CI 0.57–0.97), but did not significantly reduce proportion of subjects achieving at least 3 weeks of continuous abstinence (risk ratio 1.30, 95% CI 0.73–2.32) or proportion of participants using cocaine during treatment (risk ratio 1.02, 95% CI 0.65–1.62) [38]. A recent controlled clinical trial of aripiprazole, not included in the earlier meta-analysis, in individuals who had achieved 2 weeks of continuous cocaine abstinence with contingency management, found no significant reduction in lapse or relapse rates, but a significant increase in cocaine craving [66].

Any antipsychotic should be prescribed with caution to cocaine users because of their potential vulnerability to the neuroleptic malignant syndrome [1]. Cocaine users may also be at elevated risk of antipsychotic-induced movement disorders [17, 34].

13.3.6 Anticonvulsants

Anticonvulsants might be effective in the treatment of cocaine use disorder because they increase inhibitory GABA activity and/or decrease excitatory glutamate activity in the brain, both actions that decrease the response to cocaine in the dopaminergic cortico-mesolimbic brain reward circuit [4]. However, controlled clinical trials show little or no effectiveness for anticonvulsants, except for topiramate. A meta-analysis of 20 published clinical trials involving 2068 participants found that anticonvulsants as a class (carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, and vigabatrin) had no significant effect on dropout rate (risk ratio 0.95, 95% CI 0.86–1.05), cocaine use (risk ratio 0.92, 95% CI 0.84–1.02), or cocaine craving (standardized mean difference −0.25, 95% CI −0.59 to 0.09) nor did any individual anticonvulsant show any significant benefit over placebo [62]. A separate meta-analysis of two topiramate trials involving 210 participants found a significant difference in the proportion of participants achieving sustained cocaine abstinence for at least 3 weeks (relative risk 2.43, 95% CI 1.31–4.53) [93]. A more recent controlled clinical trial involving 59 participants (not included in the meta-analyses) found topiramate significantly better than placebo in increasing cocaine-negative

urine samples (odds ratio 8.69, p <0.001) and reducing self-reported cocaine use (mean reduction −3.1 g [p <0.001] for amount; mean reduction −0.78 times per week [p <0.005] for frequency), but only during the first 4 weeks of the 12-week trial [2].

13.3.7 Serotonergic Medications

Serotonergic medications such as buspirone and gepirone, used to treat generalized anxiety disorder, and ritanserin, developed as an antidepressant, showed no efficacy in controlled clinical trials [28]. Ondansetron, approved for the treatment of nausea and vomiting, significantly reduced cocaine use in a small controlled clinical trial, but only at the highest dose (4 mg twice daily) [39].

13.3.8 Cholinergic Medications

Several cholinergic medications have shown mixed results in controlled clinical trials. Varenicline, a partial agonist at α4β2 nicotinic acetylcholine receptors approved for smoking cessation, significantly reduced cocaine use in one small controlled clinical trial [80]. Biperiden (2 mg tid), a muscarinic cholinergic receptor antagonist used to treat movement disorders, significantly reduced cocaine use in a small controlled clinical trial [16]. In contrast, mecamylamine, a nicotinic cholinergic receptor antagonist, and donepezil or galantamine, which nonspecifically increase brain cholinergic activity by inhibiting acetylcholinesterase activity, did not reduce cocaine use in small controlled clinical trials [28].

13.3.9 Opioid Medications

Mu-opiate receptor (mOR) antagonists have been evaluated as treatment for cocaine use disorder because of the role of brain mORs in cocaine use [22]. Three small controlled clinical trials (two placebo-controlled) found that naltrexone (50 mg daily) significantly reduced cocaine use compared to placebo [88, 90] or to cognitive-behavioral therapy without medication [31]. Buprenorphine (4 mg or 16 mg sl), a partial mOR agonist/kappa opioid antagonist used to treat opioid use disorder, combined with naloxone, was not effective in a controlled clinical trial of outpatients with moderate-severe cocaine use disorder [52].

13.3.10 Other Medications

A wide variety of other medications have been evaluated for the treatment of cocaine use disorder, often on the basis of promising case reports or animal studies suggesting that they reduce the reinforcing effects of cocaine. None of these medications has shown effectiveness in a large controlled clinical trial [28].

Doxazosin, an α_1-adrenergic receptor antagonist approved for treatment of hypertension, when rapidly titrated over 4 weeks to a daily dosage of 8 mg, significantly reduced cocaine use in one small, controlled clinical trial [92].

13.3.11 Medication Combinations

Concurrent use of two different medications, which might enhance efficacy while minimizing side effects, has been effective in several small clinical trials. Concurrent use of pergolide (a dopamine D_1/D_2 receptor agonist) and haloperidol (a dopamine D_2 receptor antagonist) and of amantadine (indirect dopamine agonist) and propranolol (beta-adrenergic antagonist) both showed efficacy in small clinical trials [41, 55]. The combination of extended-release mixed amphetamine salts and topiramate was significantly better than placebo in achieving three consecutive weeks of cocaine abstinence [57].

13.3.12 Nutritional Supplements and Herbal Products

The use of nutritional supplements (e.g., amino acids, vitamins, minerals) and herbal products is attractive because of their relative freedom from regulatory oversight and perceived safety and

absence of side effects, but there is no support for efficacy from controlled clinical trials [28]. Trials of tyrosine (amino acid precursor of L-DOPA) and tryptophan (amino acid precursor of serotonin) (1 gram of each daily), L-tryptophan coupled with contingency management treatment, L-carnitine (500 mg/d) plus coenzyme Q10 (200 mg/d), and magnesium L-aspartate (732 mg daily), an easily absorbed form of magnesium, found them no better than placebo in reducing cocaine craving or use.

One herbal product that has received substantial publicity, but not yet rigorous clinical evaluation, is ibogaine, an indole alkaloid found in the root bark of the West African shrub *Tabernanthe iboga*. This compound maintained cocaine abstinence for a median of 8 months in 70% of 66 patients with moderate-severe substance use disorder (83% cocaine) after abstinence was initiated in a residential treatment program [86]. However, clinical research with ibogaine has been suspended in the USA because of the risk of life-threatening cardiac arrhythmia [45]. *Ginkgo biloba* (120 mg/d for 8 weeks) was no better than placebo in a controlled clinical trial [40].

13.3.13 Other Physical Treatments

Acupuncture is an ancient Chinese treatment that involves mechanical (with needles), thermal (moxibustion), or electrical (electroacupuncture) stimulation of specific points on the body surface. The mechanism of action is unknown; speculation has included stimulation of endogenous opioid systems. Meta-analyses of nine published studies did not find a significant benefit of active acupuncture over sham treatment [20, 60].

Transcranial magnetic stimulation (TMS) involves activation of brain neurons by fluctuating magnetic fields generated by electromagnetic coils placed on the scalp. Single and multiple sessions of repetitive TMS (rTMS) applied to the prefrontal cortex reduced cocaine craving and reduced cocaine use in a small, open-label pilot study [3]. Controlled clinical trials are currently underway.

13.4 Special Treatment Situations

13.4.1 Mixed Addictions

Concurrent opioid use, including comorbid substance use disorder, is a common clinical problem among individuals with cocaine use disorder. Some individuals use cocaine and opioids simultaneously (as in the so-called speedball) to enhance the drugs' subjective effects. Up to 20% or more of patients with opioid use disorder in methadone maintenance treatment also use cocaine [50]. Three different pharmacologic approaches have been used for the treatment of dual cocaine and opioid use disorders: (1) adjustment of methadone dose, (2) maintenance with another opioid medication, and (3) addition of medication targeting the cocaine use disorder.

Higher daily methadone doses (60 mg or more) generally are associated with less opioid use by patients in methadone maintenance. This relationship also holds in general for cocaine use among patients in methadone maintenance [75], although exceptions have been reported. Increasing the methadone dose as a contingency in response to cocaine use can be effective in reducing such use (and more so than decreasing the methadone dose).

Buprenorphine is a partial opioid agonist (μ-receptor agonist/κ-receptor antagonist) used for the agonist substitution treatment of opioid dependence [58]. Some (but not all) studies in patients with concurrent opioid and cocaine use disorders suggest that cocaine use (as well as opioid use) is reduced at higher buprenorphine doses (16–32 mg sl daily) [65].

Non-opioid medications for the treatment of cocaine use disorder frequently are evaluated in methadone- or buprenorphine-maintained outpatients with concomitant opioid use disorder because the opioid agonist maintenance component substantially enhances treatment adherence, improving the internal validity of the trial. There is no evidence that such agonist maintenance treatment significantly influences medication efficacy, but no studies have directly addressed this issue.

Alcohol use disorder is a common problem among individuals with cocaine use disorder, both in the community and in treatment settings, with rates of comorbidity as high as 90% [24]. Two medications used in the treatment of alcohol use disorder are also effective in the treatment of outpatients with concurrent cocaine and alcohol use disorders. Disulfiram substantially decreased both cocaine and alcohol use in two clinical trials and a small case series, but not in a third clinical trial [28]. Naltrexone, a μ-opioid receptor antagonist approved for the treatment of both alcohol and opioid use disorders, substantially decreased both cocaine and alcohol use at 150 mg po daily, but not at 50 mg daily or 100 mg daily or when given as a monthly long-acting injection [79]. Combined treatment with both disulfiram (250 mg daily) and naltrexone (100 mg daily) significantly improved abstinence from cocaine and alcohol [77].

A controlled clinical trial found no significant effect of topiramate compared to placebo in reducing cocaine or alcohol use in outpatients with comorbid cocaine and alcohol use disorders [42].

13.4.2 Psychiatric Comorbidity

Treatment-seeking individuals with cocaine use disorder have high rates of psychiatric diagnoses other than substance use disorder, with rates as high as 65% for lifetime disorders and 50% for current disorders. The commonest comorbid disorders tend to be major depression, bipolar spectrum, phobias, and post-traumatic stress disorder [12]. Personality disorders are also common, with rates as high as 69%. The commonest is antisocial personality disorder [11].

Antidepressants vary in their efficacy for reducing cocaine use among patients with comorbid major depression, although there are few direct comparisons or controlled clinical trials [71, 83]. Desipramine, imipramine, and bupropion have usually, but not always, been found effective, whereas SSRIs and mirtazapine are usually not effective. Venlafaxine (150–300 mg daily) and nefazodone (200 mg twice daily) showed some efficacy in small clinical trials [28].

Both anticonvulsant "mood stabilizers" and antipsychotics are used to treat comorbid bipolar disorder and cocaine use disorder. Case series and small clinical trials suggest that anticonvulsants such as valproate and lamotrigine and antipsychotics such as quetiapine and risperidone have some efficacy in reducing cocaine use in dually diagnosed patients [10]. Combining lithium with an anticonvulsant may be helpful in treatment-resistant patients.

Up to one-fourth of adults with cocaine use disorder have either adult attention-deficit hyperactivity disorder (ADHD) or a history of childhood ADHD [46]. Stimulant and dopaminergic medications are the mainstay of treatment for ADHD, suggesting that some of these patients may be self-medicating their ADHD with cocaine. Case series and clinical trials generally find that such medications successfully treat ADHD symptoms and reduce cocaine use in adults: dextroamphetamine, methamphetamine, extended-release mixed amphetamine salts, and bupropion, but not methylphenidate and bupropion [28].

Schizophrenia is not a common comorbid psychiatric disorder among patients in treatment for cocaine use disorder (about 1% prevalence) [51], but cocaine use disorder is commoner among treatment-seeking patients with schizophrenia (8–10% prevalence) [85]. Clinical experience suggests that first-generation antipsychotics, at doses that are effective in the treatment of schizophrenia, do not significantly alter cocaine craving or use.

Several case series and open-label trials suggest that the second-generation antipsychotics, including clozapine, olanzapine, quetiapine, risperidone, and aripiprazole, may be more effective than older (first-generation) antipsychotics in reducing cocaine and other drug use among patients with schizophrenia [84]. However, three head-to-head controlled clinical trials found no difference between olanzapine and haloperidol or risperidone in reducing cocaine use, with each medication reducing cocaine craving in one of the trials [28].

The use of cocaine can exacerbate or provoke antipsychotic-induced movement disor-

ders [17, 34] and increase vulnerability to the neuroleptic malignant syndrome [1].

13.4.3 Medical Comorbidity

Few data are available to guide the pharmacotherapy of cocaine use disorder in medically ill patients, making this an important issue for future clinical research. Prudent clinical practice requires a careful medical evaluation of any patient before starting medication, with special attention to medical conditions common in individuals with cocaine use disorder. Such conditions would include viral hepatitis and alcoholic liver disease, which might alter the metabolism of prescribed medications, and HIV infection. The presence of the latter necessitates caution in prescribing medications with a known potential for inhibiting immune function. Clinical experience suggests that buprenorphine [5] and bupropion can be used safely in HIV-positive patients, although antiretroviral medications may decrease bupropion plasma concentrations [35].

13.4.4 Gender-Specific Issues

Women tend to be excluded from or underrepresented in many clinical trials of cocaine use disorder pharmacotherapy [30], in part because of concern over risk to the fetus and neonate should a female subject become pregnant. Thus, there is a substantial lack of information about gender-specific issues of pharmacotherapy in general and the pharmacotherapy of cocaine use disorder in particular [33]. Meanwhile, clinicians must deal on an *ad hoc* basis with the treatment implications of possible gender differences in medication pharmacokinetics (such as those resulting from differences in body mass and composition) and in pharmacodynamics (such as those related to the menstrual cycle or exogenous hormones such as oral contraceptives).

In the absence of directly relevant and systematically collected data, caution should be used when prescribing medications to pregnant women with cocaine use disorder and to those with pregnancy potential, keeping in mind both the risks of medication and the risks of continued cocaine use. Some medications proposed for the treatment of cocaine use disorder (such as tricyclic antidepressants, bupropion, and buprenorphine) have little potential for morphologic teratogenicity or disruption of pregnancy, although there are few or no data on behavioral teratogenicity [28]. Some medications do pose at least slight risk, such as amantadine (associated with pregnancy complications), lithium (associated with cardiac malformations and neonatal toxicity), anticonvulsants (associated with increased risk of congenital malformations), and antipsychotics (associated with nonspecific congenital anomalies and neonatal withdrawal).

Some medications (e.g., disulfiram, naltrexone) may generate different treatment responses in men versus women [7, 78]. The reasons for such gender differences are poorly understood but may include differences in medication pharmacokinetics, hormonal interactions, or subjects' psychological or socioeconomic status.

13.4.5 Age

Although adolescents make up a substantial minority of heavy cocaine users, they have been largely excluded from clinical trials of cocaine pharmacotherapies because of legal and informed consent considerations. On the basis of the scarcity of published case reports, it is likely that medication is not often used in the treatment of adolescent cocaine use disorder.

Similarly, we are not aware of any published studies on the pharmacological treatment of cocaine use disorder in elderly patients.

13.5 International Perspectives

The prevalence of cocaine use varies substantially by geographic region, based in part on the relative availability of cocaine [96]. In addition, national differences in modes of cocaine use result in variation in cocaine use disorder and

related problems. The acute psychological effects of cocaine, and therefore its abuse liability, depend greatly on the rate at which drug reaches the brain. The more rapid the onset of the effect, the more intense the psychological effect [69]. This is the so-called rate hypothesis of psychoactive drug effect [26]. Routes of administration that produce rapid onset of effect, such as intravenous and smoked, are associated with greater abuse liability than those with slower onset, such as intranasal and oral [9, 25]. Thus, the Andean countries in which oral cocaine ingestion is legal and common (e.g., by chewing the leaves, drinking coca tea) tend to have lower prevalence of cocaine use disorder than might be expected from their prevalence of cocaine use [64].

Treatment of cocaine addiction is generally comparable worldwide, with the exception of the Andean countries. The legal availability of oral forms of cocaine in those countries makes possible the agonist substitution approach using cocaine itself [37, 53]. However, such treatment has never been evaluated in controlled clinical trials.

13.6 Future Prospects

Future progress in pharmacologic treatment for cocaine use disorder is likely to come from development of new medications with novel or more selective mechanisms of action and from development of pharmacokinetic approaches and new physical treatments such as TMS (see Sect. 13.3.13 above). New medications should evolve from an improved understanding of the neuropharmacology of cocaine use disorder and animal studies of the interactions of cocaine with novel compounds.

Preclinical studies with compounds that bind to the same presynaptic dopamine transporter site as does cocaine (thereby keeping cocaine from acting), but which do not themselves produce robust reinforcing effects (because of slow onset of effect and tight, long-lasting binding), suggest that such compounds may be useful as functional cocaine "antagonists" [82]. Manipulation of brain dopamine activity with selective dopamine receptor ligands, especially for the D_3 type, attenuated the rewarding effects of cocaine in several animal studies [32] and awaits the development of compounds suitable for clinical trials. Medications that presynaptically release both dopamine and serotonin also show promise in animal studies [81].

Cocaine administration, like stress, activates the hypothalamic-pituitary-adrenal (HPA) axis, and stress may play a role in relapse to cocaine use after abstinence. These observations stimulated interest in corticotrophin-releasing factor receptor antagonists, some of which reduce cocaine self-administration in animals [94].

The endogenous cannabinoid (endocannabinoid) brain neurotransmitter system modulates the dopaminergic reward system [74], and blockade of cannabinoid CB_1 receptors inhibits relapse to cocaine self-administration after abstinence in animals [99]. Therefore, CB_1 receptor antagonists (or inverse agonists) and cannabinoids such as cannabidiol (which does not produce a subjective "high") [19] have promising therapeutic potential. The failure of existing medications to show consistent efficacy in the treatment of cocaine use disorder has prompted growing interest in pharmacokinetic approaches, that is, preventing ingested cocaine from entering the brain and/or enhancing its elimination from the body [27]. The former approach could be implemented by active or passive immunization to generate binding antibodies that keep cocaine from crossing the blood-brain barrier. The latter approach could be implemented by administration of an enzyme (e.g., butyrylcholinesterase [BChE]) that catalyzes cocaine hydrolysis or by passive or active immunization with a catalytic antibody. A 12-week controlled clinical trial found that weekly intramuscular injections of a mutated BChE with enhanced catalytic efficiency significantly increased the proportion of cocaine-negative urine samples (14.6% vs. 4.7%), although there was no significant difference in the proportion of participants achieving abstinence [23]. In a phase II controlled clinical trial, an anti-cocaine vaccine (i.e., active immunization to generate cocaine-binding antibodies) significantly reduced cocaine use among the

one-third of participants who mounted a substantial antibody response, but only during the first 8 weeks of treatment [49]. Further work is needed to increase the consistency of the antibody response and lengthen the duration that antibody concentrations remain high enough to block cocaine use.

13.7 Conclusion

The absence of any medication that meets national regulatory standards for efficacy and safety leaves physicians with little clear-cut guidance for pharmacologic treatment of cocaine use disorder. Among existing medications marketed for other indications, none has yet shown consistent efficacy in replicated controlled clinical trials. Disulfiram appears the most promising, especially for patients with comorbid alcohol use disorder. Tricyclic antidepressants such as desipramine and imipramine (but not SSRIs) may be of use in patients with mild cocaine use disorder or with comorbid depression. The anticonvulsant topiramate has shown promise in controlled clinical trials and warrants further evaluation. The stimulant maintenance approach also warrants further evaluation using medications with low abuse potential (e.g., sustained-release amphetamine) or perhaps even a slow-onset (e.g., oral or transdermal) form of cocaine itself.

More sophisticated patient-treatment matching could enhance the efficacy of current medications by taking into account both patient characteristics that can influence treatment response (e.g., severity, withdrawal status, psychiatric comorbidity, or concomitant medications) and characteristics of the psychosocial treatment accompanying the medication. For example, a few studies suggest that some medications (e.g., L-DOPA, SSRIs) that are not effective when used with drug abuse counseling or cognitive-behavioral therapy may be effective when combined with contingency management treatment [63, 89].

Improved understanding of the neurobiology of cocaine use disorder should lead to new and more effective medications in the future, possibly by manipulation of the glutamate or endocannabinoid systems or HPA axis or by a pharmacokinetic mechanism. Regardless of which medications show promise in the future, their adoption into clinical practice should be guided by acceptable scientific proof of efficacy and safety, based on data from replicated, well-designed, adequately powered controlled clinical trials. Clinicians should also keep in mind the distinctions between efficacy (treatment works in a research setting in a selected research population getting close attention) and effectiveness (treatment works in a heterogeneous population in a realistic clinical environment) and between a statistically significant and clinically meaningful treatment effect [59].

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Pharmacotherapy of Addiction to Amphetamine-Type Stimulants

14

Ahmed Elkashef and Jag H. Khalsa

Contents

Abstract

Amphetamine-like stimulants (ATS) use is second to marijuana as the most widely used illicit substances worldwide with an estimated 59 million people using these at least once a year. Their use is associated with significant morbidity including cardiovascular complications, psychosis, and mortality. A wide range of modalities including psychotherapeutic and pharmacologic interventions are available for the treatment of dependence to amphetamine-type stimulants. Although many clinical trials are currently in progress for treating addiction to ATS, there is no FDA-approved medication for the indication. In the meantime, it is highly recommended that the available treatment should be started early and should be comprehensive, integrated, and long term.

Keywords

Amphetamine · Methamphetamine · Treatment · Medication

14.1 Introduction

Amphetamine-like stimulants (ATS) include a group of other synthetic stimulants like amphetamine, methamphetamine, 3,4-methylenedioxym ethamphetamine (MDMA), and related

A. Elkashef · J. H. Khalsa (✉)
Division of Therapeutics and Medical Consequences, National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland, USA

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substances. These are highly addictive, and their chronic use may result in a series of mental and physical symptoms including anxiety, confusion, insomnia, mood disturbances, cognitive impairments, paranoia, hallucinations, and delusion. Though there is no specific FDA-approved drug to treat addiction to any of the amphetamines, there are behavioral and other pharmacotherapeutic modalities and agents that have used to treat ATS dependence. Currently, according to the 2017 World Drug Report [57], amphetamine-type stimulants use is second only to marijuana as the most widely used illicit substance worldwide. In 2015, an estimated 59 million people, aged 15–64 years, used amphetamines, prescription amphetamines, and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) at least once in the last year. Regions with highest prevalence are Oceania and North and Central America. Increases in seizure of methamphetamine are also being reported in East, Southeast, and Central Asia and Transcaucasia [57]. Incidentally, in the USA, in 2016, there were 20,203 methamphetamine-associated ER admissions [46]; and between 2003 and 2015, there were 1,292,300 weighted amphetamine-related hospitalizations with annual hospital costs increasing from $436 million in 2003 to $2.17 billion by 2015 [60].

14.2 Pharmacology

Methamphetamine and amphetamine have very similar pharmacodynamic effects; either can be metabolized to the other [2, 21, 43]. METH was first synthesized in the late 1800s by a Japanese pharmacologist [9], while amphetamine was originally synthesized by the German chemist Lazăr Edeleanu in 1887. Both were used during war to reduce fatigue and were available over the counter in Japan as *Philopon* and *Sedrin.*

Both amphetamine and methamphetamine are highly addictive stimulants that can be easily manufactured in clandestine labs. Common street names vary from country to country, e.g., “speed,” “meth,” “ice,” “crystal,” “crank,” “glass,” “Yaba,” and “Ceptagon” just to name few.

ATS are potent dopamine uptake as well as vesicular monoamine transporter (VMAT2) blockers. The latter action is unique to ATS and not shared by other addictive stimulants like cocaine. VMAT2 blockers inhibit the incorporation of synthesized monoamines into the neuronal vesicles which lead to high concentrations of dopamine and other amines in the presynaptic terminal. This leads to higher levels of dopamine release which can cause oxidative stress and damage to the presynaptic terminals.

14.3 Health Consequences

Amphetamine and methamphetamine are approved in the USA and other countries worldwide for the treatment of attention deficit hyperactivity disorder, narcolepsy, and obesity. The weak isomer L-methamphetamine is used in the over the counter Vicks inhaler. ATS are powerful stimulants, with short-term effects that include euphoria, alertness, wakefulness, increased energy, and loss of appetite. Methamphetamine use is significantly associated with cardiovascular and cerebrovascular events [25]; some of the cardiovascular effects include irregular heartbeat, increased heart rate and blood pressure, aortic dissection, acute coronary syndrome, pulmonary arterial hypertension, and methamphetamine-associated cardiomyopathy [40]. Hyperthermia, convulsions, and stroke have also been reported with ATS overdose and can result in death if not treated.

Long-term ATS abuse can lead to weight loss, paranoia, chronic sleep disturbance, addiction, dependence, and psychosis almost indistinguishable from schizophrenia. Other psychiatric symptoms may include chronic anxiety, confusion, insomnia, mood disturbances, and violent behavior. PET studies have shown significant changes in striatal dopamine in chronic methamphetamine users in the form of downregulation or degeneration; these changes were associated with cognitive impairment. Some of the effects of chronic methamphetamine abuse appear to be, at least partially, reversible. A recent neuroimaging study showed recovery in some brain regions following prolonged abstinence (2 years, but not 6 months). This was associated with improved performance on motor and verbal memory tests. However, function in other brain regions did not display recovery even

after 2 years of abstinence, indicating that some methamphetamine-induced changes are long-lasting [59]. Withdrawal symptoms have been reported in patients attempting to stop or entering treatment and include depression, anxiety, fatigue, and an increased craving for the drug. Other serious long-term effect of methamphetamine is tooth decay known as "meth mouth" [39].

Injection drug use and risky sexual behavior among methamphetamine users have been associated with increase in HIV, especially among men who have sex with men (MSMs) [54]. Methamphetamine abuse may also worsen the progression of HIV and its consequences including greater neuronal injury and cognitive impairment compared with nondrug abusers [33, 41].

Prenatal exposure to methamphetamine can lead to premature delivery, placental abruption, fetal growth retardation, and heart and brain abnormalities [14, 15, 30, 48, 61]. Ongoing research is continuing to study developmental outcomes such as cognition, social relationships, motor skills, and medical status of children exposed to methamphetamine before birth. However, the use of other substances or alcohol and maternal poor nutrition and health make the interpretation of these results difficult.

14.3.1 Treatment of Addiction to ATS

The treatment of addiction to amphetamines can be challenging because of the changes in brain structure that occur with chronic use of amphetamines. Research has shown that the treatment of ATS addiction, as any other addiction, should by integrated, comprehensive, individualized, and long term. Psychotherapeutic interventions like contingency management, cognitive behavioral therapy, relapse prevention, matrix, and 12-step-based therapy, which have shown effectiveness in the treatment of other addictions, have also shown efficacy in treating ATS addictions. These are detailed elsewhere in this book. Combining medications and psychotherapy like CM has been shown to have synergistic effect and should be the rule in any treatment plan depending on the treatment setting. Early intervention will also guarantee better outcomes as most addictions start in adolescence. To guarantee best care, treatment should be integrated to address the multiple comorbid mental and physical problems that ATS addicts usually suffer.

In this chapter we will focus on pharmacological interventions that have been tried so far in the treatment of addiction to ATS.

14.3.2 Agonist Medications

Methylphenidate A dopaminergic stimulant approved for the treatment of ADHD was tried in methamphetamine dependence. An initial report of efficacy of SR methylphenidate (54 mg) against placebo and aripiprazole for intravenous amphetamine dependence in a 20-week randomized trial was not replicated in the larger double-blind study of 79 patients [56, 35].

Dextroamphetamine Another dopaminergic stimulant approved for weight loss, narcolepsy, and ADHD was tried in two double-blind studies in meth-dependent patients. The first trial used 110 mg of sustained release d-amphetamine daily for 12 weeks with gradual reduction over an additional 4 weeks. Medications were administered daily under supervision. The primary outcome was meth concentration in hair samples at baseline compared to follow-up using hair analysis. Although there was no significant effect for the primary outcomes, there was significantly greater reduction in meth withdrawal symptoms and craving compared to placebo [32]. Another double-blind study [19] of 60 mg sustained release d-amphetamine for 8 weeks showed no effect for the primary outcome of reducing meth use as evidenced by negative urines. Similar to the first study, this study also reported significant effect on craving and meth withdrawal symptoms for the d-amphetamine group.

Bupropion The safety of co-administering bupropion and methamphetamine was assessed in a clinical pharmacology study with no evidence of cardiovascular adverse events of PK interaction [38]. Three double-blind controlled outpatient studies investigated the effects of bupropion SR 150 mg BID in methamphetamine-

dependent patients. Significantly a positive effect in reducing meth use was reported in light users. The effect was not seen in heavy users defined as >18 days of use in a month or more than two positive urine samples per week on screening [18, 53]. Another study [24] did not report an effect for bupropion as measured by abstinence in the last 2 weeks of the trial; however the group that showed compliance with medication as measured by plasma showed a significant effect highlighting the very important issue of medication adherence as a factor in many failed addiction medication trials.

Modafinil Modafinil is a weak stimulant approved for the treatment of narcolepsy and obstructive sleep apnea. It is proposed to exert its action on the glutamate and hypocretin system. However, recent PET study suggests that it may also bind to the dopamine transporter. Clinical trials in cocaine suggest that it may have a role in treating addiction to other stimulants [39–41]. Modafinil at a dose of 200 mg/day was tested in a double-blind, placebo-controlled trial for 10 weeks in 80 methamphetamine-dependent patients. The trial outcomes were negative except for a trend of reducing methamphetamine use in those who were medication compliant and attended counseling sessions [49]. In another single-blind study, modafinil combined with cognitive behavioral therapy (CBT) was tested in 13 HIV+ gay men with methamphetamine dependence. Six of the 10 patients completed the study with reduction of their methamphetamine use by over 50% [34]. In a more recent multisite trial [1, 23], 71 methamphetamine-dependent treatment seeking patients were randomized to placebo or 400 mg of daily modafinil for 12 weeks. The primary outcome was weeks of negative methamphetamine in their urine. The patients provided three urine samples weekly. The trial was negative; however, a post hoc analysis showed a significant effect on duration of abstinence (23 days vs. 10 days) favoring modafinil among compliant patients.

A recent meta-analysis of the use of prescription amphetamines for the treatment of stimulant use disorders (SUD) reported that prescription psychostimulants increased the rates of sustained abstinence in SUD, specifically for cocaine use disorders ([55], CPDD 2019, poster presentation).

14.3.3 Antagonist Medications

Aripiprazole A partial agonist second-generation antipsychotic was studied in two human laboratory studies with significant effects on attenuation of subjective effects of orally administered d-amphetamine [50]. However, outpatient studies with aripiprazole have been negative. One double-blind randomized study of 15 mg daily had to be stopped prematurely because of high dropout rate and increased amphetamine use [56]. Another double-blind study of aripiprazole in 90 patients for12 weeks failed to show significant results [10].

14.3.4 Other Medications

GABA agonists Baclofen 60 mg and gabapentin 2400 mg daily were tried in a double-blind study of 25 meth-dependent patients in a 3-arm study for 16 weeks. Neither medication had an effect on reducing meth use compared to placebo. A post hoc analysis suggests a positive effect in patients who took higher doses of baclofen [22]. Topiramate interaction with meth and effect on its subjective effects were studied in a human lab double-blind study which showed that topiramate enhanced some of the positive effects of methamphetamine. This was attributed to possible PK interaction on meth metabolism [27]. A multisite outpatient trial of topiramate 200 mg for reducing meth use was negative for the primary outcome. However, there was a positive effect in the subgroup of patients that had negative urines at randomization suggesting a role in relapse prevention [17]. Vigabatrin was tried in an open-label study of 30 patients for 9 weeks. 18/30 subjects completed the study, and 16/18 tested negative for

methamphetamine and cocaine during the last 6 weeks of the trial [8]. A safety clinical pharmacology interaction study was conducted in nontreatment-seeking methamphetamine-dependent patients given 15 and 30 mg i.v. doses of methamphetamine and doses of GVG up to 5 mg [13]. There were no reports of cardiovascular interactions and no effects of GVG on methamphetamine subjective effects. No published reports currently exist of follow-up outpatient trials of GVG for the treatment of addition to methamphetamine.

Antidepressants Mirtazapine was tried in a double-blind controlled study in 60 methamphetamine-dependent patients for 12 weeks with significant effect in reducing methamphetamine-positive urines [11]. The SSRIs, fluoxetine, paroxetine, and sertraline were tried in double-blind controlled studies [3, 4, 42, 44, 52] with no effect on methamphetamine use.

Calcium channel blockers Two calcium channel blockers, isradipine and amlodipine, were tried in human laboratory studies [26, 6] and reported to reduce the subjective and physiological responses to methamphetamine. However, a controlled outpatient clinical trial of amlodipine failed to show any efficacy in reducing methamphetamine use [5].

Ondansetron A serotonin 5-HT3 receptor antagonist was postulated to reduce dopaminergic activity in the striatum. A double-blind multisite, randomized, trial of three doses of ondansetron (0.25, 1, or 4 mg twice daily) for 8 weeks combined with CBT failed to show an effect over placebo at decreasing methamphetamine use [28].

Naltrexone Naltrexone moderates the predictive relationship between cue-induced craving and positive subjective effects of methamphetamine [45], 49]. In a preliminary randomized clinical trial, using functional MRI, naltrexone significantly reduced methamphetamine use and striatal resting-state functional connectivity between the ventral striatum, amygdala, hippocampus, and midbrain in people with methamphetamine use disorder [29]. In a human lab study of abstinent meth-dependent patients, naltrexone 50 mg significantly reduced the subjective effects of d-amphetamine. In a double-blind placebo-controlled outpatient study, naltrexone 50 mg was effective in reducing amphetamine use [31].

Rivastigmine Acetyl cholinesterase inhibitors have been shown in animal studies to reduce methamphetamine-seeking behavior. Rivastigmine was tried in a 2-week double-blind placebo-controlled human laboratory study, to study its interactions with methamphetamine 30 mg given i.v. Rivastigmine reduced the cardiovascular and subjective effects of methamphetamine. The 3 mg dosage significantly reduced methamphetamine-induced increases in diastolic blood pressure and self-reports of craving and anxiety. In another controlled study, the same dosage reduced the positive subjective effects of intravenous meth self-administered in human volunteers [12]. Outpatient trials are underway to test its efficacy in reducing meth use.

Varenicline In a double-blind randomized phase II clinical trial, varenicline at 1 mg, bid, combined with cognitive behavioral therapy, was ineffective in treating methamphetamine dependence in methamphetamine-dependent subjects [7].

Combination therapy (1) Midazolam-droperidol combination versus droperidol alone or midazolam-droperidol versus olanzapine was tested in a multicenter, randomized, double-blind, controlled, clinical trial in 92 methamphetamine-affected subjects. The primary outcome was the proportion of patients sedated adequately at 10 min. Results showed that a midazolam-droperidol combination provided more rapid sedation of patients with methamphetamine-related acute agitation than droperidol or olanzapine alone [58]. (2) Another

combination therapy with naltrexone and N-acetyl-cysteine failed to show a significant effect on methamphetamine use in methamphetamine users [20]. (3) Two combinations trails of naltrexone and bupropion are published; the first is a human lab study [51] of 50 mg naltrexone and 300 mg of bupropion alone and in combination that failed to show an effect for the combination in reducing subjective effects of methamphetamine. An outpatient study of depot naltrexone monthly injection and 300 mg of bupropion SR daily showed a higher response in the medication group vs. placebo as defined by at least 6 negative urine tests out of 8 collected in the last 4 weeks of the trial [36].

14.4 Future Medication Options

VMAT2-inhibitors are being developed as methamphetamine antagonists to block its action on the VMAT receptors. Lobeline, a nicotinic alkaloid, has been shown in animal studies to decrease self-administration of methamphetamine and block meth-induced dopamine release [16, 37]. Tetrabenazine, another VMAT2 inhibitor recently approved in the USA for the treatment of Huntington's disease and other hyperkinetic disorders, is being studied in animal models of addiction. Research is also ongoing for more selective VMAT2 compounds.

CRF-1 antagonists have been shown in preclinical data to block stress-induced relapse to alcohol, cocaine, and heroin. The search for a safe CRF-1 antagonist to advance to clinical trials is underway.

D3 antagonists have been shown to block priming, cues, and stress-induced self-administration of nicotine, cocaine, and heroin, suggesting a role in relapse prevention in humans.

Cannabinoid-1 (CB-1) receptor antagonists have been reported to reduce or block self-administration and conditioned cue relapses in preclinical models of THC, nicotine, cocaine, MA, opiates, and ethanol.

Other compounds of interest are group I and group II metabotropic glutamate receptors. mGluR5 antagonists and AMPA receptor antagonists have been shown to block cue-induced relapse to cocaine and heroin.

The CRF-1antagonists, dopamine D3receptor antagonists, cannabinoid CB1 antagonists, and glutamate site modulators, data in animal models of addiction, show nonselectivity. Further development of these compounds in man will have far-reaching application in treating substance use disorders particularly polysubstance use.

Cognitive enhancers like D-1agonists, 5-HT 6 antagonists, and D-cycloserine may have a role in strengthening the frontal lobe's inhibitory controls on impulsive behavior. They are also expected to improve cognition in methamphetamine-addicted patients.

Other area of therapeutic development for addiction is *immunotherapy*. Vaccines and monoclonal antibodies are in early development for nicotine, cocaine, methamphetamine, and heroin, details of which are highlighted in another chapter.

Global impact ATS is a global public health problem with severe comorbidities and economic burdens that are in the billions of dollars. The global trends of use seem unchanged since the last decade according to the WHO drug reports. This is indicative of ineffective, inefficient, or insufficient application of prevention and treatment approaches across the globe. It is time for an international task force on the issue lead by the WHO, involving all countries affected. Effective approaches need to be shared across countries, e.g., contingency management coupled with medications, with consideration of unique and cultural issues for each. Programs like training the trainers and cross-training are vital for proper application of treatment programs especially ones that focus on vulnerable populations, e.g., adolescents and pregnant women. The cost of implementing such a global intervention should be figured out and shared among the members if they are serious about tackling the problem. Programs that proved successful in other areas of addiction, e.g., screening, brief intervention, and referral to treatment (SBIRT) and drug courts, should be adapted to ATS.

14.5 In Summary

- ATS addiction ranks second to cannabis globally and contributes greatly to the total burden of the disease of addiction.
- ATS addiction is associated with multiple health problems like HIV and psychiatric diseases like psychosis.
- ATS addiction treatment like other addiction treatment should be started early and should be comprehensive, integrated, and long term.
- Psychotherapeutic interventions like CM, MI, CBT, matrix, RP, and 12 steps are equally effective for the treatment of ATS addiction and should be utilized as appropriate.
- Agonist medications like d-amphetamine and methylphenidate may have a role in treating ATS withdrawal symptoms and craving, particularly in patients with comorbid ADHD/ADD.
- Other medications that may be helpful are bupropion and modafinil for low to moderate users.
- Naltrexone and topiramate are also promising especially for ATS addicts who are also addicted to other substances like nicotine, alcohol, or opiates.
- There are many trials that are currently in progress for treating addiction to ATS. It is highly recommended that clinicians search the literature periodically for updates prior to initiating medication treatment for their patients.

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Nicotine and Tobacco

15

Julia Sasiadek, Nicole Durham, and Tony P. George

Contents

Abstract

Although rates of tobacco use and tobacco use disorder have reduced substantially over the past 40 years, one in (six) Americans continue to smoke. The prevalence of smoking appears to be substantially higher in persons with psychiatric and substance use disorders and has remained unchanged, as these smokers have less success in quitting smoking. The epidemiology of tobacco use disorder and the pharmacological effects of nicotine and tobacco are reviewed followed by a discussion of the clinical assessment of tobacco users. The increasingly popular electronic cigarette will be examined as a possible form of treatment for tobacco use disorder. We then review psychosocial and pharmacological treatments, including the FDA-approved pharmacotherapies:

J. Sasiadek · N. Durham
Addictions Division, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

T. P. George (✉)
Addictions Division, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

Department of Psychiatry, University of Toronto, Toronto, ON, Canada
e-mail: tony.george@camh.ca

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nicotine replacement therapies (NRTs), sustained-release bupropion, and varenicline. Finally, integration of tobacco use disorder treatment into mental health settings is discussed with the view that tobacco use disorder is a chronic medical disorder and that more effective treatment of this comorbidity in psychiatric disorders may require targeted treatments based on a better understanding of the pathophysiology of individual psychiatric disorders.

15.1 Introduction: Epidemiology of Tobacco Use

Tobacco smoking is the leading preventable cause of morbidity and mortality in the Western world [5]. In the USA, approximately 14% of the population are currently tobacco users, which translates to roughly 34 million people. Worldwide, approximately 1.1 billion people use tobacco on a regular basis [17]. Around 33% of those who try cigarettes will become addicted, and 70% of those people will go on to want to quit completely. Most smokers who begin smoking in adolescence have difficulty quitting, with almost 2% of current 12th graders using cigarettes daily and, increasingly, 20% of 12th graders vaping nicotine [48, 81]. Since the release of the Surgeon General's report in 1965, however, smoking prevalence has been steadily declining, but this reduction appears to have slowed in recent years. Cigarette smoking remains the most common (>90%) method of tobacco use. In addition to cigarette smoking, pipe tobacco, cigars, hookah, and smokeless tobacco (e.g., chewing tobacco, snuff) are also common forms of tobacco use. Each year, approximately 480,000 people in the USA die as a result of smoking-attributable medical illnesses such as lung cancer, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and stroke, including 41,000 people dying as a result of secondhand smoke. Additionally, roughly eight million people are sick or disabled because of their cigarette use, and smoking has been estimated to cost the USA $170 billion in smoking-related medical expenses, as well as $156 billion in lost productivity annually [5]. Smoking is now increasing rapidly throughout the developing world, and it is estimated that current cigarette smoking will cause about 450 million deaths worldwide in the next 50 years. Reducing current smoking by 50% would prevent 20–30 million premature deaths in the first quarter of this century and 150 million in the second quarter. For most smokers, quitting is the single most important thing they can do to improve their health, and the results of epidemiological studies in Norway suggest that even with sustained reductions (>50%) in smoking consumption, there is little if any reduction in cardiovascular disease and lung or other smoking-related cancer risk [79]. However, reducing the amount of cigarettes smoked for individuals who have no intention to quit smoking did increase the probability of a quit attempt [41]. Although reductions in smoking consumption may not reduce risks of morbidity in the short term, it will more likely lead to self-quitting in the future.

15.2 Biology of Nicotinic Receptors

Nicotine is the main psychoactive ingredient in tobacco smoke. When tobacco is smoked, the primary site of action of nicotine is the α4β2 nicotinic acetylcholine receptor (nAChR), which is also activated by the endogenous neurotransmitter acetylcholine. nAChRs in the CNS are pentameric ion channel complexes [11] comprised of two α and three β subunits. The seven α subunits are designated α2–α9 and the three β subunits are designated β2–β4. Due to this, there is considerable diversity in subunit combinations, which may explain some of the region-specific and functional selectivity of nicotinic effects throughout the CNS. These pentameric receptors are either homomerically or heteromerically arranged (e.g., $(\alpha4)_3(\beta2)_2$ or $(\alpha7)_5$). Activation of nAChRs leads to Na^+/Ca^{2+} ion channel fluxes and neuronal firing, and chronic exposure to nicotine results in desensitization of the receptors. nAChRs are situated presynaptically on several different neurotransmitter secreting neuron types due to their wide dispersement throughout the CNS. Of importance for nicotine addiction are the nAChRs

situated on mesolimbic dopamine (DA) neurons that project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Activation of nAChRs on mesolimbic DA neurons leads to DA release in the NAc, which helps to facilitate the addictive process involved in chronic tobacco use.

At low concentrations of nicotine, α4β2 nAChR stimulation of afferent GABAergic projections onto mesoaccumbal DA neurons predominates, leading to reduced mesolimbic DA neuron firing and DA release. At higher nicotine concentrations, α4β2 nAChRs desensitize, and activation of α7 nAChRs on glutamatergic projections predominates, leading to increased mesolimbic DA neuron firing and DA secretion. Subsequently, nAChRs desensitize within several millisecond of activation by nicotine; nAChRs then resensitize after overnight abstinence, which presumably explains why most smokers report that the first cigarette in the morning is the most satisfying. Interestingly, the nAChR saturation levels reached after smoking to satiety are similar to the saturation levels seen after smoking just a few puffs. Therefore, while binding to central nAChRs is an important first step in the effects of nicotine, it is not a complete explanation for continued smoking behaviors.

15.3 Clinical Effects of Nicotine and Tobacco

The majority of tobacco users (>90%) smoke cigarettes. Most of these individuals smoke daily and have some degree of physiological dependence [60]. However, smoking patterns have lowered in recent years, and non-daily smokers now constitute 14% of all adult smokers in the USA [5]. While these non-daily smokers seem dependence-resistant, they still show the same difficulty with quitting as daily smokers do [77]. Smokers typically describe a "rush" and feelings of alertness and relaxation when smoking, and it is well known that nicotine has both stimulating and anxiolytic effects depending on basal level of arousal. Stimulation of the airway is an aspect of smoking that many individuals will report as reinforcing, and additives such as menthol enhance the experience by increasing the taste and reducing the harshness of smoked tobacco. A diagnosis of tobacco use disorder is accomplished clinically by following the criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5). These include increased tobacco use for longer periods of time, tobacco cravings, evidence of tolerance (e.g., increased amounts of tobacco needed to achieve the desired effect), and the presence of symptoms of tobacco withdrawal upon smoking cessation. Withdrawal symptoms, which begin within 24 hours of cessation, peak at 2–3 days, and usually subside within 2–3 weeks, include irritability, anxiety, decreased heart rate, insomnia, increased appetite, difficulty concentrating, and restlessness. Additionally, most dependent smokers state that they smoke their first cigarette of the day within 30 minutes of awakening, smoke daily, and increase their use of cigarettes per day. Timeline follow-back procedures [71] and smoking diaries have been used successfully to monitor smoking consumption over time. Scales such as the Fagerstrom Test for Nicotine Dependence (FTND) [28] allow assessment of the level of nicotine dependence with scores of ≥4 on a scale of 0–10 consistent with physiological dependence to nicotine. Nicotine craving and withdrawal can be reliably monitored using validated scales such as the Tiffany Questionnaire for Smoking Urges [76] and the Minnesota Nicotine Withdrawal Scale [31].

Besides positive reinforcement, withdrawal, and craving, there are several secondary effects of nicotine and tobacco use that may contribute to both maintenance of smoking and to smoking relapse including mood modulation (e.g., reduction of negative affect), stress reduction, and weight control. In addition, conditioned cues can elicit the urge to smoke even after prolonged periods of abstinence [2]. Specific effects might be most relevant to individuals high on dietary restraint (weight reduction) and psychiatric disorders (mood modulation, cognitive enhancement, stress reduction). These secondary effects may present additional targets for pharmacological intervention in certain subgroups of smokers (e.g., smokers with schizophrenia, depression, or obesity; [17]).

15.4 Electronic Cigarettes

Electronic nicotine delivery systems (ENDS), also known as e-cigarettes, are an alternative and increasingly common method of consuming nicotine. From 2010 to 2013, e-cigarette use in the adult population has drastically risen from approximately 1.8% to 13.0% in the USA [50]. The rise of electronic cigarettes has also been increasingly popular specifically among the adolescent population. In fact, data from the National Youth Tobacco Survey reported that the number of high-school children reporting use of e-cigarettes rose from 11.7% to 20.8% and 3.3% to 4.9% in middle-school children between 2017 and 2018. This increase in children was likely a result of peer pressure, high impulsivity, and interest in the device as a nicotine delivery system. Individuals with mental disorders and particularly substance use disorders are another subpopulation with twice the prevalence rate compared to those without mental health conditions [10, 46, 57].

Unlike traditional cigarettes, e-cigarettes contain no tobacco and do not require a flame. E-cigarettes contain a cartridge that houses the liquid (e-liquid), a heating element, and a battery. The liquid is a solution comprised of additives such as propylene glycol or glycerol, nicotine, flavoring, distilled water, etc. A lithium battery that powers the e-cigarette is connected to a vaporization chamber which is a tube containing electronic controls and an atomizer. When the e-liquid solution is rapidly heated and then cooled, it vaporizes into an aerosol mist that allows for inhalation or "vaping" of the liquid through a mouthpiece. Inhalation activates the atomizer to heat the liquid in the cartridge, converting the liquid to vapor, delivering nicotine to the lungs. Simple inhalation or manual initiation of a switch/button can activate the vaporizer inside [16].

There are approximately 460 brands sold in the market with a variety of e-liquid flavors, concentrations of nicotine (ranging from 0 to 24 mg/mL to max of 36 mg/mL), and pH levels. The typical concentration of e-cigarettes is 18 mg/mL, which is higher in comparison to the traditional cigarette (6–13 mg). However, the concentration levels of nicotine that is delivered to the bloodstream is still lower in comparison to the tobacco-smoked cigarette. E-cigarettes are also being used for other purposes. For example, cannabis, a popular substance choice, has been vaporized due to its decreased amount of smoke and odor. However, cannabis consumption via e-cigarette poses a risk since THC levels can exceed combustion mechanisms by 4- to 30-fold [52].

Despite risk factors associated with their use, e-cigarettes have also been suggested to be beneficial. Advocates welcome e-cigarettes as a gateway to smoking cessation or reduction of tobacco use [90]. Nicotine in an aerosol contains fewer tobacco toxicants compared to tobacco smoke and are thus considered less harmful and a less addictive alternative to tobacco cigarettes [12]. E-cigarettes have become the topic of a public health dispute as their popularity increased. The most significant barrier to e-cigarette regulation is the current lack of experimental evidence regarding their use. Although the evidence is limited and contested, some studies suggest that the majority of e-cigarette users treat them as cessation aides and report that they have been key to quitting smoking. For example, e-cigarettes compared favorably to nicotine replacement therapies (NRTs) in terms of the likelihood of having returned to smoking 6 months after a cessation attempt and have been perceived to be more efficacious than NRTs overall [12, 16, 69].

15.5 Psychosocial Treatments (See Table 15.1)

Several non-pharmacological interventions for smoking cessation are available. These include telephone quit lines, group and individual counseling, and self-help techniques ranging from the community to the individual domain. Behavioral treatments for tobacco use disorder can facilitate motivation to quit, provide an emphasis on the social and contextual aspects of smoking, and enhance overall success at smoking cessation [55]. Six-month quit rates with behavior thera-

Table 15.1 Pharmacological and behavioral treatments for tobacco use disorder

Treatment (*FDA-approved)	Mechanism of action	Rating
*Nicotine replacement therapies**		
Gum (OTC)	Slow nicotine absorption gradually reduces nicotine craving and withdrawal	1
Transdermal nicotine patch (OTC)	Slow nicotine absorption gradually reduces nicotine craving and withdrawal	1
Lozenge (OTC)	Slow nicotine absorption gradually reduces nicotine craving and withdrawal	1
Vapor inhaler (prescription)	Fast nicotine absorption leads to stimulation of nAChR which rapidly reduces nicotine craving and withdrawal	1
Nasal spray (prescription)	Fast nicotine absorption leads to stimulation of nAChR which reduces craving and withdrawal	1
Non-nicotine pharmacotherapies		
Bupropion SR*	Blocks reuptake of DA and NA; high-affinity, noncompetitive nAChR antagonism reduces nicotine reinforcement, withdrawal, and craving	1
Varenicline*	Acts as a partial agonist of $\alpha_4\beta_2$ nAChRs	1
Nortriptyline	Blocks reuptake of NA and 5-HT; probably reduces withdrawal symptoms and comorbid depressive symptoms; side effects limit utility	1–2
Clonidine	α_2-Adrenoreceptor agonist reduces nicotine withdrawal symptoms	2
Mecamylamine Cytisine	Noncompetitive, high-affinity nAChR antagonist combined with TNP reduces nicotine reinforcement, craving, and withdrawal Acts as a partial agonist of $\alpha_4\beta_2$ nAChRs but might have limited efficacy at dose necessary for cessation	2 2
Naltrexone	Endogenous μ-opioid peptide receptor antagonist reduces nicotine craving and withdrawal in combination with TNP, may reduce alcohol use, and obviate cessation-induced weight gain	3
Nicotine vaccine	Limited evidence of efficacy for smoking cessation in early human trials and may also have utility in relapse prevention	2
Psychosocial treatments		
Brief interventions	Increase motivation to quit and impart cessation skills (e.g., community support, telephone counseling, self-help materials)	2
Cognitive-behavioral therapy	Behavioral strategies are developed to manage triggers; cognitive coping strategies target maladaptive thoughts to prevent relapse	1
Motivational interventions	Promotes patient's self-motivational statements, and in turn, patient gains greater awareness of the problems with smoking; increases intention for smoking cessation	2
Relapse prevention	A specified cognitive-behavioral approach that focuses on relapse prevention skills (e.g., recognizing high-risk situations and coping with lapses)	1
Contingency management	Uses positive reinforcement through tangible rewards to increase positive behaviors such as abstinence	2
Exposure therapy	Behavioral technique used to expose smokers to situational cues that induce cravings	2
Internet-based intervention	Strategies used via internet- or mobile-based platforms targeting adolescents, young adults, and adults	1

Effectiveness rating 1 strong evidence to support efficacy. *2* moderate evidence to support efficacy, *3* little evidence to support efficacy

*Indicates FDA-approved medications for tobacco use disorder

pies are 20–25%, and behavior therapy typically increases quit rates up to twofold over control groups. Additionally, providing behavioral support in addition to pharmacotherapy can increase the chance of a successful quit attempt by approximately 10–25% [73]. The primary goals of behavioral therapies in treatment of tobacco use disorder include (1) providing necessary skills to smokers to aid them to initiate smoking cessation and (2) teaching skills to avoid smoking in

high-risk situations and smoking-related cues. Overall, studies have shown how more intensive counseling intervention approaches for smoking cessation have been more effective than less intensive interventions [45]. Although there is no sufficient evidence that suggests groups are more effective compared to individual interventions, group therapy seems to be a more effective intervention compared to self-help and less intensive interventions [72].

(a) *Brief interventions.* Brief advice has been found to increase the rate of smoking cessation (USPHS Guidelines, [14]); therefore it is recommended that doctors use the 5 A's with all patients (*ask* patients if they smoke, *advise* patients to quit, *assess* patients' motivation level for quitting, *assist* with quit attempts, and *arrange* follow-up contacts). Similar forms of smoking education in school settings have shown to reduce tobacco use as well as increase quit attempts in adolescent smokers [65]. Providing self-help material is a form of brief intervention used to increase motivation to quit and impart smoking cessation skills. Several studies have documented that minimal behavioral interventions such as community support groups, telephone counseling, and computer-generated tailored self-help materials can augment smoking cessation rates in controlled settings [73]. Additionally, the greatest quitting success rates may be seen when adding some support (at least 4 therapy sessions) compared to no support at all [73].

(b) *Motivational interventions.* The goal of motivational interviewing (MI) interventions is to elicit change through addressing ambivalence, increasing intrinsic motivation for change, and creating an atmosphere of acceptance in which patients take responsibility for making changes happen. Brief MI interventions have been developed for smoking cessation, and there is some evidence for increased smoking cessation using MI techniques [4]. MI interventions can also be especially effective for adolescents [29], possibly making MI useful for preventative efforts. Rollnick and colleagues [61] reported that clinicians found MI interventions to be feasible and acceptable due to the brief nature of the intervention and the focus on patient responsibility and enhancement of the clinician-patient relationship.

(c) *Cognitive-behavioral therapies.* In CBT (cognitive-behavioral therapy), patients learn strategies to anticipate and cope with situations in which they are likely to relapse to smoking**.** Some degree of efficacy of cognitive-behavioral therapies in smokers with and without psychiatric and substance use disorders has been observed for both individual [45] and group [72] counseling formats. Additionally, work by Brody et al. [3] has shown that reduced smoking with CBT (without pharmacotherapies) can reduce nAChR densities to normal receptor levels.

(d) *Relapse prevention.* A large number of smokers relapse within 6 months of quitting, with the majority of smokers relapsing within the first week after a quit attempt [32]. Focusing on relapse prevention skills including recognizing high-risk situations and coping with lapses can be included in initial smoking cessation treatment or following a quit attempt. However, some studies have not found an overall benefit for including relapse prevention with smokers after a quit attempt and suggest that more work is needed in this area of treatment research [44].

(e) *Contingency management.* CM (contingency management) is a type of behavioral therapy in which external reinforcers are used to change behavior. By using tangible rewards, smokers are conditioned to reinforce positive behaviors such as abstinence or a negative CO screen. Voucher-based reinforcement therapy (VBRT) uses vouchers or other monetary incentives, whereas prize incentive CM uses chances to win cash prizes to reinforce positive behaviors. These methods have been increasingly proven to be one of the more effective ways to minimize tobacco use and strengthen motivation to quit [75]. Studies have evaluated the strong positive correlation

CM has on tobacco abstinence in adolescent smokers, although treatment adherence and posttreatment efficacy seem to be poor [42]. Additionally, more recent studies have shown increasing reductions in smoking when incorporating delay discounting into a contingency management approach [26].

(f) *Exposure therapy.* Most cravings smokers experience are induced by situational cues. Cue-exposure treatment addresses cue-induced cravings and coping responses to avoid relapse [13]. This method has been shown to decrease cue-related cravings in individuals, especially those who have displayed initial cue reactivity [80]. Virtual reality has been an increasingly common type of cue-exposure therapy method along with photographs, video, auditory, and in vivo and imagery scripts. Evidence has shown that VR is a great way to produce strong cue-reactivity effects and cue-induced craving in real-world settings, however, may increase risks of relapse [56]. Overall, exposure therapy has been more promising when used to enhance other support interventions such as CBT [9].

(g) *Internet-based interventions.* Increasingly, methods such as mobile applications (MapMySmoke), social media platforms, and mobile text messages are being used, especially among adolescents. Website-delivered programs, such as 1-2-3 Smokefree, have shown to help maintain smoking abstinence in the short term. Wangberg et al. [82] have reported that tailored interventions delivered on a website and via email have shown to be almost twice as effective than nontailored internet interventions only in the short term. Both web-based and mobile-based approaches had shown to increase smoking cessation over a short term, suggesting this method would not be sufficient to aid in long-term tobacco abstinence.

(h) By using both a psychosocial and pharmacological approach, both biological and psychological dependence can be addressed. Providing behavioral support in addition to pharmacotherapy can increase the chance of a successful quit attempt by approximately 10–25%, with more intensive behavioral support increasing abstinence.

15.6 Pharmacological Treatments (See Table 15.1)

There are three FDA-approved classes of smoking cessation pharmacotherapies – nicotine replacement therapies (NRTs), sustained-release bupropion, and varenicline. According to the 2008 update to the Public Health Service *Treating Tobacco Use and Dependence Clinical Practice Guideline* [14], five NRTs, as well as bupropion SR and varenicline, all reliably increase cessation rates in comparison to placebo. Several other off-label and novel medications are also discussed in this section.

15.6.1 Nicotine Replacement Therapies

The goal of nicotine replacement therapy (NRT) is to relieve tobacco withdrawal, by providing nicotine without the harmful effects of cigarette additives, which allows smokers to focus on habit and conditioning factors when attempting cessation. After the acute withdrawal period, nicotine replacement therapy is gradually reduced so that little withdrawal should occur. NRTs rely on systemic venous absorption and so do not produce the rapid high levels of arterial nicotine achieved when cigarette smoke is inhaled. All commercially available forms of NRT are effective and increase quit rates by approximately 1.5–2.5-fold compared to placebo [68]. The transdermal patch, gum, and lozenge are over the counter (OTC), while the nasal spray and inhaler are by prescription.

(a) *Nicotine gum:* Nicotine ingested orally is extensively metabolized on first pass through the liver. Nicotine polacrilex gum avoids this problem via buccal absorption. Nicotine gum contains 2 or 4 mg of nicotine that can be released from a resin by chewing. The original recommended duration of treatment was

3 months though many experts believe longer treatment is more effective. Nicotine absorption from the gum peaks 30 minutes after beginning to use the gum. Venous nicotine levels from 2 and 4 mg gum are about one-thirds and two-thirds, respectively, of the steady-state (i.e., between cigarettes) levels of nicotine achieved with cigarette smoking. Nicotine via cigarettes is absorbed directly into the arterial circulation; thus, arterial levels from smoking are 5–10 times higher than those from the 2 and 4 mg gums.

Several placebo-controlled trials established the safety and efficacy of nicotine gum for smoking cessation [68]. There appears to be some evidence to support using higher doses of nicotine gum (4 mg pieces) in more highly dependent cigarette smokers (≥25 cpd), which supports the idea of matching nicotine gum dose to dependence level of the smoker [74].

Side effects from nicotine gum are rare and are mostly limited to those of mechanical origin (e.g., difficulty chewing, sore jaw) or of local pharmacological origin (e.g., burning in mouth, throat irritation) and most minimize over the course of 1 week.

(b) *Nicotine polacrilex lozenges*. Nicotine lozenges deliver nicotine (2 and 4 mg preparations) by buccal absorption. A 6-week double-blind, placebo-controlled RCT of 2 and 4 mg nicotine lozenges has shown their superiority to placebo lozenge [66], with significant reduction in nicotine craving and withdrawal. Furthermore, high doses of lozenge may be more efficacious in heavily dependent smokers suggesting that lozenge dose can be matched with dependence level. Just as with nicotine gum, mild throat and mouth irritation have been reported in preliminary trials [66].

(c) *Nicotine transdermal patch*. The four transdermal nicotine formulations take advantage of ready absorption of nicotine across the skin. Three of the patches are for 24-hour use and one is for 16-hour use. Starting doses are 21–22 mg/24-hour patch and 15 mg/16-hour patch. Nicotine via patches is slowly absorbed so that on the first day venous nicotine levels peak 6–10 hours after administration. Thereafter, nicotine levels remain fairly steady with a decline from peak to trough of 25% to 40% with 24-hour patches. Nicotine levels obtained with the use of patches are typically half those obtained by smoking. After 4–6 weeks on high-dose patch (21 or 22 mg/24 h, and 15 mg/16 h), smokers are tapered to a middle dose (e.g., 14 mg/24 hours or 10 mg/16 hours) and then to the lowest dose after 2–4 more weeks (7 mg/24 hours or 5 mg/16 hours). Most studies suggest that abrupt cessation of the use of patches often causes no significant withdrawal; thus, tapering does not appear to be necessary [68]. The recommended total duration of treatment is usually 6–12 weeks.

The overall efficacy of the nicotine transdermal patch (NTP) for smoking cessation has been well documented [68]. A meta-analysis of 17 RCTs in 1994 [15] reported end of treatment abstinence rates for NTP of 27% versus 13% for placebo patch (OR 2.6) and 22% vs. 9% at 6-month follow-up (OR 3.0). The effects of active NTP were independent of patch type, treatment duration, tapering procedures, and behavioral therapy format or intensity, though it should be noted that behavioral treatment enhanced outcomes with patch compared to patch alone. Additionally, combining the patch with nicotine lozenge has been shown to produce the greatest benefit for smoking cessation relative to placebo (above that of lozenge alone, patch alone, bupropion SR, and bupropion + nicotine lozenge relative to placebo) [58].

Significant adverse events with nicotine patches have not been found, with the most common minor side effects being skin reactions (50%), insomnia and increased or vivid dreams (15% with 24-hour patches), and nausea (5–10%). Tolerance to these side effects usually develops within a week of use. There appears to be little dependence liability associated with patch use as only 2% of patch users continue to use this product for an extended period after a cessation trial

[84], and this continued abstinence may be due to the desire to maintain abstinence.

(d) *Nicotine nasal spray.* Nicotine nasal spray is a prescribed NRT that is formulated as a nicotine solution in a nasal spray bottle similar to those used with saline sprays. Nasal spray delivers droplets that average about 1 mg per administration and is administered (10 mg/ml) to each nostril every 4–6 hours. The nicotine spray produces a more rapid rise in nicotine levels than that of nicotine gum but falls below the levels achieved by cigarettes. Peak nicotine levels occur within 10 minutes, and venous nicotine levels are about two-thirds those of between-cigarette levels. Smokers may use the nasal spray ad-lib up to 30 times/day for 12 weeks, including a tapering period.

Randomized, double-blind, placebo-controlled trials of nasal spray versus placebo spray [68] have established the safety and efficacy of the nasal spray for smoking cessation. Both trials employed treatment for 3–6 months, and active nasal spray led to a doubling of quit rates during active use relative to placebo use. Differences were reduced or absent with extended follow-up suggesting the need for maintenance use of this agent.

The major side effects associated with the use of nicotine nasal spray are nasal and throat irritation, rhinitis, sneezing, coughing, and watering eyes. Nicotine nasal spray may have some dependence liability; in a controlled study by West et al. [85], prolonged use of nasal spray was determined to be the case in 10% of smokers using the nasal spray, so follow-up of smokers using nasal spray is recommended.

(e) *Nicotine vapor inhalers (NVI).* NVI are cartridges (plugs) of nicotine (containing about 1 mg of nicotine each) placed inside hollow cigarette-like plastic rods. When warm air is passed through the cartridges, a nicotine vapor is produced, which is then inhaled. Absorption from nicotine inhaler is primarily buccal rather than respiratory. More recent versions of inhalers produce a rise in venous nicotine levels more rapidly than with nicotine gum but less rapidly than with nicotine nasal spray, with nicotine blood levels of about one-third that of between-cigarette levels. Smokers are instructed to puff continuously on the inhaler (0.013 mg/puff) during the day, and recommended dosing is 6–16 cartridges daily. The inhaler is to be used ad-lib for about 12 weeks.

No serious medical side effects have been reported with nicotine inhalers. Fifty percent of subjects report throat irritation or coughing. Double-blind, placebo-controlled RCTs [68] have demonstrated the superiority of NVI to placebo inhalers for smoking cessation. Results revealed a two- to threefold increase in quit rates (17–26%) at trial endpoint compared to placebo inhalers and smaller differences at follow-up periods of 1-year or longer. These data support the short-term efficacy of NVI in cigarette smokers, but longer-term trials with the inhaler are needed, and there is some modest concern about abuse liability, due to long-term use of the product in less than 10% of smokers [85].

15.6.2 Sustained-Release Bupropion

The phenylaminoketone, atypical antidepressant agent bupropion, in the sustained-release (SR) formulation (Zyban®), is a non-nicotine first-line pharmacological treatment for nicotine-dependent smokers who want to quit smoking. The mechanism of action of this antidepressant agent in the treatment of nicotine use disorder likely involves dopamine and norepinephrine reuptake blockade [1], as well as antagonism of high-affinity nAChRs [70]. The exact mechanism for bupropion's anti-smoking effects is unclear. The goals of bupropion therapy are (1) smoking cessation, (2) reduction of nicotine craving and withdrawal symptoms, and (3) prevention of cessation-induced weight gain.

The target dose of this agent in nicotine use disorder is 300 mg daily (150 mg bid), and it is typically started 7 days prior to the target quit date (TQD) at 150 mg daily, then increased to

150 mg bid after 3–4 days. Unlike the NRTs, there is no absolute requirement that smokers completely cease smoking by the TQD, though many smokers report a significant reduction in urges to smoke and craving, which facilitates cessation at the time of the TQD when drug levels reach steady-state plasma levels. Some smokers gradually reduce their cigarette smoking over several weeks prior to quitting. Smokers who are faster metabolizers of nicotine (as determined by genetic variation at the CYP2A6 allele) may benefit more from bupropion therapy, as opposed to NRT or counseling [59].

A pivotal multicenter study by Hurt and colleagues [34] established the efficacy and safety of sustained-release (SR) bupropion for treatment of nicotine use disorder which led to its FDA approval in the USA in 1998. In a 7-week double-blind, placebo-controlled multicenter trial, three doses of bupropion SR (100, 150, and 300 mg/day in BID dosing), in combination with weekly individual cessation counseling, were given to 615 cigarette smokers using at least 15 cigarettes per day. The end of trial 7-day point prevalence cessation rates for each of the bupropion doses, placebo, 100 mg/day, 150 mg/day, and 300 mg/day, were 19.0%, 28.8%, 38.6%, and 44.2%, respectively. At 1-year follow-up, cessation rates were 12.4%, 19.6%, 22.9%, and 23.1%, respectively. Bupropion treatment also dose-dependently reduced weight gain associated with smoking cessation and significantly reduced nicotine withdrawal symptoms at the 150 and 300 mg/day doses.

The primary side effects reported with bupropion administration in cigarette smokers are headache, nausea and vomiting, dry mouth, insomnia, and activation. Many of these side effects are observed in the first week of treatment. The main contraindication for the use of bupropion is a past history of seizures of any etiology. The rates of de novo seizures are low with this agent (<0.5%) at doses of 300 mg daily or less but have been observed when daily dosing exceeds 450 mg/day.

The combination of bupropion SR with nicotine transdermal patch (NTP) was evaluated in a double-blind, placebo-controlled, randomized multicenter trial [36]. A total of 893 cigarette smokers, using at least 15 cigarettes per day (cpd), were randomized to one of four experimental groups: (1) placebo bupropion (0 mg/day) + placebo patch; (2) bupropion (300 mg/day) + placebo patch; (3) placebo bupropion + nicotine patch (21 mg/day for 4 weeks, with 2 weeks of 14 mg/day and 2 weeks of 7 mg/day); and (4) bupropion + patch. Bupropion was administered 1 week prior to the target quit date (Day 15) at which time patch treatment was initiated for a total of 8 weeks. All subjects received weekly individual smoking cessation counseling. Cessation rates at the 1-year follow-up assessment were 15.6% for placebo, 16.4% for active NTP alone, 30.3% for bupropion alone, and 35.5% for the combination of patch and bupropion. Both bupropion + patch and bupropion alone groups were significantly better than the placebo and patch alone conditions, but the combination was not significantly better than bupropion alone. Weight suppression after cessation was most robust in the combination therapy group. Side effects were consistent with the profiles of patch and bupropion, and the combination was well tolerated. However, a higher than expected rate of treatment-emergent hypertension (4–5%) was noted with the combination of bupropion and patch [36]. Of note, patch alone treatment was significantly different from placebo at the end of the trial, but not at the follow-up assessments.

Hays et al. [27] examined the effects of bupropion versus placebo on the prevention of smoking relapse in 784 cigarette smokers who achieved smoking abstinence after a 7-week open-label trial of bupropion (300 mg/day). Abstinent smokers were then randomized to bupropion (300 mg/day) or placebo for a total of 45 weeks. Fifty-nine percent of smokers enrolled in the open-label phase of the trial quit smoking. Significantly more smokers were abstinent at the end of the 52-week treatment period in bupropion vs. placebo groups (55.1 vs. 42.3%, p <0.01), but not at the 1-year follow-up assessment. In addition, days to smoking relapse were higher in the bupropion vs. placebo group (156 vs. 65 days, p <0.05).

Weight gain was significantly less in the bupropion group at both the end of treatment and 1-year follow-up. The results of this study suggest the efficacy of bupropion in preventing smoking relapse. Data regarding the optimal duration of bupropion therapy for maintenance treatment requires further study.

15.6.3 Varenicline

Varenicline tartrate (Chantix® in the USA, Champix® in Europe and Canada), an $\alpha_4\beta_2$ nAChR partial agonist and weak α7 agonist, was approved as a first-line smoking cessation agent by the US FDA in 2006. The results of two independent but identical 12-week phase III trials comparing varenicline (1 mg bid) to bupropion SR (150 mg bid) and placebo have been published [21, 35]. The quit rate for both studies were similar for continuous abstinence over the last 4 weeks (weeks 9–12) of the study: study 1 [35], varenicline 43.9%, bupropion SR 29.8%, and placebo 17.6%; study 2 [21], varenicline 44.0%, bupropion SR 29.5%, and placebo 17.7%. Quit rates were significantly higher for participants taking varenicline compared to bupropion SR (ps <0.0001), and both drugs resulted in significantly higher quit rates than placebo. Continuous abstinence over the follow-up period (week 9 to 52) was lower, and participants taking varenicline continued to show a higher rate of abstinence (study 1, 22.1%; study 2, 23.0%) than participants taking bupropion (study 1, 16.4%, p <0.001 compared to varenicline; study 2, 15.0%, p = 0.064 compared to varenicline) and placebo (study 1, 8.4%; study 2, 10.3%). A third study examining the efficacy of the drug on smoking relapse prevention used a 12-week open-label varenicline phase followed by randomization to12 weeks of varenicline or placebo [78]. These investigators found that participants taking varenicline versus placebo were more likely to be continuously abstinent during weeks 13–24 (70.5% vs. 49.6%, p <0.001) and weeks 13–52 (43.6% vs. 36.9%, p = 0.02). Varenicline was found to reduce cravings and smoking satisfaction and to be safe and well tolerated. There were similar discontinuation rates for varenicline and bupropion, and the most common adverse event reported by the varenicline group was nausea (study 1, 28.1%; study 2, 29.4%).

There have been significant concerns about treatment emergent neuropsychiatric adverse events such as suicidal and homicidal ideation, psychosis, mania, and aggression with the use of varenicline for smoking cessation. However, evidence from controlled smoking cessation clinical trials in psychiatric populations such as schizophrenia [87] and bipolar disorder [89] suggest the safety of this agent for smoking cessation including in high-risk psychiatric populations. Further research on the safety and utility of these agents in psychiatric and addicted populations is clearly warranted.

15.6.4 Off-Label Medications

(a) *Cytisine.* Cytisine (Tabex® in Europe) is a nicotinic partial agonist that binds with high affinity to the $\alpha4\beta_2$ nicotinic acetylcholine receptor. West et al. [86] assessed the safety and efficacy of cytisine in the first randomized, placebo-controlled trial for the drug and found that it was significantly more effective for smoking cessation than placebo.

(b) *Nortriptyline*. Nortriptyline is a tricyclic antidepressant which has been shown in several double-blind, placebo-controlled trials to be superior to placebo [24] and to have comparable efficacy to bupropion [23]. Higher-intensity behavioral therapies may help to improve its efficacy. The mechanism of action is thought to relate to norepinephrine and serotonin reuptake blockade. Side effects include dry mouth, blurred vision, constipation, and orthostatic hypotension. It appears to have some utility in smokers with past histories of major depression, but its potential for fatal overdose has likely limited its utilization in smokers. However, nortriptyline can be recommended as a second-line agent after nicotine replacement therapies and bupropion, though more study of this agent is necessary.

(c) *Clonidine***.** Clonidine is a presynaptic alpha-2 receptor agonist that dampens sympathetic activity originating at the locus coeruleus. It appears to have efficacy for treating opioid withdrawal and thus was tested with nicotine withdrawal during smoking cessation trials. The most common side effects of clonidine are dry mouth, sedation, and constipation. Postural hypotension, rebound hypertension, and depression are rare with smoking cessation treatment. Several clinical trials tested oral or transdermal clonidine in doses of 0.1–0.4 mg/day for 2–6 weeks with and without behavior therapy and have suggested clonidine is more effective in women than in men. In general, the effects of clonidine have not proven to be as robust as NRTs. A meta-analysis by Covey and Glassman [7] of 9 placebo-controlled studies and 813 patients found short-term quit rates of 39% on clonidine versus 21% on placebo (OR 2.4, 1.7–32.8) and suggested that clonidine was effective in the transdermal preparation and more helpful in female smokers. A subsequent meta-analysis by Gourlay and Benowitz [22] found long-term follow-up quit rates in 4 subsequent studies of 31% on clonidine and 17% on placebo (OR 2.0, 1.3–3.0). It appears to be useful in reducing nicotine withdrawal symptoms acutely and may have a role in smokers who have high levels of anxiety during early cessation [53]. This agent should be considered as a second-line therapy for smokers failing initial treatment with NRTs or bupropion.

(d) *Mecamylamine*. Mecamylamine (MEC) is a noncompetitive blocker at the ion channel site of both high-affinity central nervous system and peripheral nAChRs. When MEC is given to smokers who are not trying to stop smoking, they initially increase their smoking in an attempt to overcome the blockade produced by this drug. MEC does not precipitate withdrawal in humans perhaps because it is a noncompetitive nAChR antagonist. Common side effects included abdominal cramps, constipation, dry mouth, and headaches. Based on a theory that combined blockade and agonist therapy at the nAChR might be beneficial, similar to the nAChR partial agonist profile of varenicline, two randomized trials compared MEC in combination with nicotine patch to placebo and nicotine patch, with the rationale that MEC would reduce the rewarding effects of nicotine and patch would reduce nicotine withdrawal symptoms [62, 63]. In the first trial [63], MEC (up to 10 mg/day; 5 mg bid for 5 weeks) or placebo was given in combination with nicotine patch (21 mg/day) for up to 8 weeks, and cessation rates were significantly higher in the combination group than the patch alone group (12/24 [50.0%] vs. 4/24 [16.7%], p <0.05). Mecamylamine was reported to reduce cigarette craving and negative effect and appetite increases associated with tobacco withdrawal. In a subsequent study of 80 cigarette smokers [62], MEC at doses of up to 10 mg/day was given as a pre-treatment for 4 weeks prior to nicotine patch initiation at the TQD, and the combination of MEC and patch was continued for 6 weeks. Similar to the first study, the combination of MEC with NTP increased continuous abstinence rates after the TQD compared to NTP alone (19/40 [47.5%] vs. 11/40 [27.5%], p <0.05). These data suggest the efficacy of the combination of MEC with NTP, and this combination should be considered a second-line therapy.

(e) *Naltrexone*. Naltrexone is a long-acting congener of the μ-opioid receptor antagonist naloxone. The rationale for using naltrexone for smoking cessation is that the performance-enhancing and other positive effects of nicotine may be opioid-mediated. Early studies observed that naltrexone monotherapy increases smoking, presumably an attempt to overcome blockade; however, a study of naltrexone in heavy smoking alcoholics found that cigarette smoking was decreased modestly [64]. Adverse events include elevated liver enzymes, nausea, and vomiting. A trial

by Covey and colleagues [8] in 68 cigarette smokers using at least 20 cpd and highly motivated to quit compared naltrexone (up to 75 mg/day) initiated 3 days prior to the TQD to placebo for a total of 4 weeks. Cessation rates in the naltrexone group were nonsignificantly higher than placebo (46.7% vs. 26.3%, p <0.10), and at 6-month follow-up, there were no group differences.

Additional promising data with naltrexone was observed with the combination of naltrexone and NRT. A preliminary study by Krishnan-Sarin et al. [43] suggested that the combination of naltrexone and NTP is superior to NTP alone when NTP administration precedes that of naltrexone (presumably to decrease naltrexone-related withdrawal). In a larger trial of the combination of nicotine patch (21 mg/day) with four active doses of naltrexone (0, 25, 50, and 100 mg/day), it was shown that the highest dose of naltrexone with patch significantly improves continuous smoking abstinence rates compared to placebo [54], but these effects appeared to be confined to the first weeks of treatment. Further studies of naltrexone either alone or in combination with the patch are needed, including in patients with concurrent alcohol misuse.

(f) *Nicotine vaccines.* Nicotine vaccines are being developed by a number of companies, but they are not currently available for public use. A systematic review of smoking cessation trials conducted by pharmaceutical companies as part of the drug development process showed that nicotine vaccines, while well tolerated, did not enhance long-term cessation rates [25], and recent phase III trials of one nicotine vaccine preparation suggested that these agents did not increase rates of smoking cessation in nicotine-dependent smokers. However, the nicotine vaccine may have promise for the prevention of smoking relapse or initiation of smoking. Side effects include soreness at the injection site and hypersensitivity reactions to vaccine components.

15.7 Integration of Tobacco Use Disorder Treatment into Mental Healthcare Settings

High rates of tobacco use disorder and low rates of smoking cessation are becoming increasingly appreciated in psychiatric and addicted populations [38]. Individuals with substance use issues such as alcohol are two to four times more likely to be dependent on tobacco compared to the general population. It is increasingly evident that mental health and addiction clinics have done little to address the tobacco culture that permeates these institutional environments. However, smoking bans are becoming increasingly common in psychiatric hospitals and addiction treatment programs and appear to be successfully implemented in the majority of reported cases, but these developments have shown little uptake and application in community settings [47].

The utilization of standard tobacco use disorder treatments such as behavioral therapies, NRT, bupropion, and varenicline has been increasingly reported in psychiatric and substance-abusing smokers. For example, various formulations of NRT including nicotine patch [20] and nasal spray [88] and sustained-release bupropion [19] and varenicline [87] have been reported to be well-tolerated and efficacious in increasing rates of both smoking reduction and cessation in patients with schizophrenia, when combined with cognitive-behavioral and motivational enhancement therapies. Both NRTs and bupropion have also been studied in smokers with major depression [6, 39], post-traumatic stress disorder [30], and alcohol [33, 37] and opioid [67] use disorder and have been found to be well tolerated and effective; small trials with bupropion SR [83] and varenicline [89] have suggested their safety and effectiveness in smokers with bipolar illness. Interestingly, most effective treatments for polysubstance users are combinations of counseling and NRT or non-NRT. Moreover, interventions addressing all drugs for polysubstance users can be a more effective strategy for smoking cessation with concurrent cessation or sequentially. Furthermore, studies which com-

pared integration of behavioral and pharmacological treatments in a mental health setting for smokers with PTSD found enhanced quit rates compared to nonintegrated smoking cessation therapies [49], suggesting that provision of integrated mental health and tobacco treatment produces enhanced cessation outcomes.

Finally, a better understanding of the pathophysiology of mental disorders may lead to improved treatments for this population. There is increasing evidence that available pharmacological and behavioral treatments, modified for those with mental disorders, can be used safely and effectively in these populations [47]. For example, schizophrenia is associated with a broad range of cognitive deficits particularly those related to prefrontal lobe dysfunction, and atypical antipsychotic drugs (e.g., clozapine, olanzapine), which improve certain cognitive deficits associated with schizophrenia, may facilitate reduction of smoking [18] or smoking cessation with standard pharmacotherapies such as nicotine patch [20] or bupropion SR [19]. The development of novel medications which target the underlying pathophysiology of psychiatric or substance use disorders may well lead to important advances in the management of tobacco use disorder in these special populations of smokers.

15.8 Conclusions

Tobacco use disorder remains one of the leading preventable causes of morbidity and mortality in the Western world. Nonetheless, smoking cessation therapies are among the most cost-effective and proven therapies in psychiatry and medicine. Yet, most healthcare providers do not identify tobacco use in their patients. In fact, a survey of psychiatric practices found that only 9.1% of smokers under the care of psychiatrists received treatment for nicotine use disorder [51]. Nonetheless, the American Psychiatric Association has recently published an update of its clinical practice guidelines for nicotine dependence [40] which should provide standards for the field of psychiatry in the assessment and treatment of tobacco use disorder. Furthermore, while medication and behavioral treatments have documented efficacy in treating tobacco use disorder, it is important that these therapies be used in combination to achieve the best overall results and ensure adequate skill acquisition and treatment adherence. Future challenges include developing safer and more effective smoking cessation therapies and making these therapies available to all smokers who want to quit.

Key Points

- Rates of tobacco use disorder have decreased substantially, but many of the remaining smokers appear to have comorbidities that reduce their chance of quitting such as psychiatric and substance use disorders.
- Identification of smokers in clinical settings is of critical importance to the treatment of tobacco use disorder.
- There are effective pharmacological and behavioral therapies for tobacco use disorder, which work best when used in combination.
- E-cigarettes are an increasingly common smoking cessation aid, although may be misused by adolescents.
- A better understanding of the pathophysiology of mental health and addictive disorders may lead to improved treatment approaches for tobacco use disorder in these smoking populations.
- Smokers with psychiatric and substance use comorbidity may be best treated in settings which integrate smoking cessation treatments with mental health and addiction treatment.

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Addiction to Caffeine and Other Xanthines

16

Thierry Favrod-Coune and Barbara Broers

Contents

Abstract

Xanthine (3,7-dihydro-purine-2,6-dione) is a purine base that can naturally be found in human body tissues and fluids as well as in plants and other organisms. Methylated xanthines (methylxanthines) are phosphodiesterase inhibitors and adenosine receptor antagonists. Methylxanthines have thus different effects: reduce inflammation and immunity, reduce sleepiness, and increase alertness, but also stimulate the heart rate and contraction and dilate the bronchi. The most well-known methylxanthines are caffeine, methylbromine, and theophylline. Large observational studies suggest that caffeine may have long-term health benefits. Coffee and caffeine withdrawal symptoms exist and

T. Favrod-Coune (✉) · B. Broers
Unit for Dependencies, Division for Primary Care, Department for Primary Care Medicine, Geneva University Hospitals, Geneva, Switzerland
e-mail: thierry.favrod-coune@hcuge.ch; barbara.broers@hcuge.ch

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are often not recognized, especially in treatment settings, where caffeine withdrawal can be confounded with other symptoms. Caffeine intoxication and withdrawal are recognized clinical entities, but caffeine dependence is currently not. Caffeine withdrawal symptoms occur in half of regular coffee drinkers, even at moderate caffeine intake. The most common symptoms are headache, fatigue, and difficulty to concentrate. Health professionals and patients should be better informed about these symptoms and the risk of occurrence of caffeine withdrawal. There is little research on treatments for clinical problems associated with xanthine use or abuse.

16.1 Introduction

For professionals in the addiction field, discussing the issue of caffeine, in a private or professional context, is a pleasure. Finally there is a domain that allows us to have a sort of positive message: "drink your coffee, it's probably good for you, it's probably good for your patients."

Our image of "controllers" telling in general frightening stories about the risks of smoking, drinking, sniffing, or injecting different psychoactive substances can be slightly improved if we can enchant the benefits of a few cups of espresso in the morning. And it is even better if we can carefully formulate the recommendation not to forget the daily bit of dark chocolate, full of theobromine, another member of the methylxanthine group.

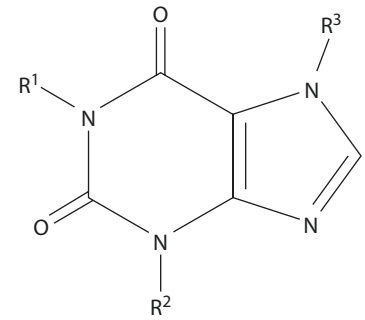
But is this really so? Are we sure there are no acute or long-term risks related to caffeine use? Is there a safe level of use? Should we talk about coffee or caffeine use? Are there subgroups of patients that should avoid xanthine use? And what about caffeine addiction or dependence, is it a clinical entity or a popular but misused term?

In this chapter we will focus mostly on caffeine and marginally on other methylxanthines. The objective of this chapter is to describe the effects, risks, and benefits of use of caffeine; discuss "caffeinism and chocoholism"; and provide some clinical recommendations.

16.2 Caffeine and Methylxanthines

Xanthine (3,7-dihydro-purine-2,6-dione) is a purine base that can naturally be found in human body tissues and fluids as well as in plants and other organisms. Methylated xanthines (methylxanthines; *see* Fig. 16.1 *for chemical structure*) are phosphodiesterase inhibitors (increasing intracellular cAMP, activating protein kinase A, inhibiting the synthesis of tumor necrosis factor (TNF)-alpha and leukotriene) and adenosine receptor antagonists (inhibiting sleepiness-inducing adenosine). Methylxanthines have thus different effects: reduce inflammation and immunity, reduce sleepiness, and increase alertness, but also stimulate the heart rate and contraction and dilate the bronchi. The most well-known methylxanthines are caffeine, methylbromine, and theophylline.

Caffeine can be found naturally in coffee beans but also in tea leaves, guarana, and mate plants or kola nuts. Theobromine and theophylline are found in cacao beans and mate plants; tea leaves contain some theophylline. Caffeine and other methylxan-



Caffeine: R1 = R2 = R3 = CH3

Theobromine: R1 = H, R2 = R3 = CH3

Theophylline: R1 = R2 = CH3, R3 = H

Fig. 16.1 Chemical structure of methylxanthines. (Source: https://en.wikipedia.org/wiki/Xanthine#/media/File:Methylxanthin_(R1,_R2,_R3).svg)

thines can be manufactured. Theophylline is a well-known asthma medication.

Caffeine is absorbed rapidly and completely through the gastrointestinal tract. After oral consumption the plasma peak is after 30–45 min, and the half-time elimination is around 3.5–6 h [16] with high variability related to age, hormones, use of nicotine or medications, etc. Metabolization takes essentially place in the liver through the cytochrome P450 pathway, especially through the cytochrome CYP1A2. The deficiency of CYP1A2 enzymes has been shown to impair caffeine metabolism and prolong caffeine half-life [9], as can certain medications, such as disulfiram [2] or quinolones, through CYL1A2 inhibition. Also during pregnancy, the half-life of caffeine increases, with one study suggesting that in the last month of pregnancy, half-life increases to 10.5 h on average [27]. Smokers seem to metabolize caffeine more quickly through acceleration of demethylation steps, with normalization of the enzyme-inducing effects of nicotine occurring after 4 days of abstinence [6].

Caffeine is metabolized in the liver into 10% theobromine, 4% theophylline, and 80% paraxanthine (Cornish and Christman 1957), so this means that theobromine can be found in the human body even without intake of chocolate.

Only 3% of non-metabolized caffeine is excreted through the urine.

16.3 Caffeine, Coffee, Tea, and Energy Drinks

Caffeine (1,3,7-trimethylxanthine) taken in coffee and tea can be considered the world's most widely consumed psychostimulant. About 90% of the adult population takes these beverages daily, with important regional differences [16]. Coffee is preferred to tea in most developed countries (except in England and Ireland) where 71.5% of the total amount of coffee is consumed. Tea is (until now) preferred in the developing countries, particularly in Asia, Argentina, Chile, Paraguay, and Uruguay. These countries count for over three quarters of the tea consumption in the world. The total quantity of tea consumed is much higher than coffee, and tea is thus the second beverage consumed after water.

The use of the so-called energy drinks seems to be on the rise especially among young people in the developed world [37, 43] and in the sports population, with between 50% and 70% of elite athletes taking these drinks [11]. In the USA the sale of energy drinks increased from 100 to 600 million dollars between 2002 and 2006 [37], with prevalence of use increasing significantly in adolescents and middle-aged adults between 2003 and 2016 [42].

It should be kept in mind that coffee and tea contain several other components that can be responsible for potential beneficial and adverse health effects, such as antioxidants (e.g., polyphenols, catechins, flavonoids). Also, the way the beverages are prepared (filtered or unfiltered coffee) and what is added (sugar, milk, creamer, flavors) will have a potential impact on health. Caffeine (mostly artificial) is also added in different soft and energy drinks, as well as in prescribed and over-the-counter medications.

In Europe, the typical dose of caffeine for a cup a coffee is around 60–70 mg; for a cup of tea, 35 mg; for a glass of Coca-Cola, 46 mg; and for an energy drink, about 80 mg [13].

In the USA, the average consumption of caffeine is 280 mg per day, which is the equivalent of two cups of filtered coffee per day. Soft drinks contain variable amounts of caffeine, but official FDA limits are 71 mg per drink of 12 oz. (355 mL). The so-called energy drinks can contain up to 300 mg of caffeine per drink of 250 mL and up to 500 mg for a bottle [37] (*see* Table 16.1 *for caffeine content of selected foods, beverages, and drugs*).

Individuals taking six or more cups of coffee per day (over 600–1000 mg of caffeine daily) are considered to be heavy coffee users [5]. In adults, caffeine consumption is considered to be safe at a dose up to 400 mg per day and for adolescents and children up to 2.5 mg/kg per day [10, 36].

With regard to chocolate consumption, inhabitants of Central Europe are considered the champions with over 5 kg of chocolate taken per year,

Table 16.1 Caffeine content in selected food, beverages, and drugs

Product	Serving size	Caffeine per serving (mg)	Caffeine (mg/L)
Percolated coffee	207 mL (7 US fl oz)	80–135	386–652
Drip coffee	207 mL (7 US fl oz)	115–175	555–845
Coffee, decaffeinated	207 mL (7 US fl oz)	5–15	24–72
Coffee, espresso	44–60 mL (1.5–2.0 US fl oz	100	1691–2254
Tea – black, green, and other types – steeped for 3 min	177 mL (6 US fl oz)	22–74	124–416
Guayakí yerba mate (loose leaf)	6 g (200 US fl oz)	85	Approx. 358
Hot cocoa	207 mL (7 US fl oz)	3–13	14–62
Hershey's special dark chocolate (45% cacao content)	1 bar (43 g or 1.5 oz)	31	–
Hershey's milk chocolate (11% cacao content)	1 bar (43 g or 1.5 oz)	10	–
Coca-Cola classic or diet	355 mL (12 US fl oz)	34	96
Mountain dew	355 mL (12 US fl oz)	54	154
Guaraná Antarctica	355 mL (12 US fl oz	30	100
Red bull	250 mL (8.5 US fl oz)	80	320
Cocaine energy drink	250 mL (8.5 US fl oz)	288	1152
Caffeine tablet (regular strength)	1 tablet	100	–
Caffeine tablet (extra strength)	1 tablet	200	–
Excedrin tablet	1 tablet	65	–

References: Bordeaux 2019 and http://en.wikipedia.org/wiki/Caffeine with different validated sources

with Swiss citizens as champions with 8.8 kg/year in 2017, whereas in most Asian countries the average citizen takes less than 200 g of chocolate per year (https://www.statista.com/statistics/819288/worldwide-chocolate-consumption-by-country/). According to the International Cocoa Organization (www.icco.org), the world per capita consumption of cocoa has increased over the last 10 years, from 0.54 kg in 2002/2003 to 0.61 kg in 2010/2011. No updated data are available, but the world cocoa production in 2016 was globally stable compared to 2010/2011.

16.4 Main Effects of Caffeine

Caffeine is mostly taken for its psychostimulating properties: it increases alertness, energy, and ability to concentrate, predominantly in sleep-deprived individuals and also in those working in night shifts and suffering from jet lags [24].

A normal portion of chocolate has also this "arousing" effect, probably through the combined effect of caffeine and theobromine [40]. The counter side of the stimulating effect of caffeine is the occurrence of sleeping difficulties, with little or no tolerance developing for this effect, and the risk of anxiety symptoms including panic attacks in sensitive individuals (Wikoff et al. 2017). Part of these symptoms, occurring after (in general high dose of) coffee intake, can be related to both the psychostimulating effect and tachycardia induced by caffeine [5].

Caffeine increases physical performance, with different studies suggesting that even at 1–2 mg of caffeine per kg of body weight (around one 250 mL serving of an energy drink), reaction time, alertness, and aerobic and anaerobic performance are improved. At higher dose (3 mg caffeine/kg body weight), the ability to repeatedly sprint and the distance covered at high intensity improve, and the jump height increases [11].

The cardiovascular effects of caffeine include mainly the acceleration of heart rate and increase of force of contraction, with heavy caffeine use

potentially triggering tachycardia and arrhythmia in susceptible persons. With regard to gastrointestinal effects, caffeine will increase gastric secretion and gastric acidity, possibly influencing absorption of different nutritional and pharmacological elements (e.g., iron), but most studies have been inconclusive. Caffeine stimulates the smooth muscles, thus impacting on bowel function and decreasing constipation [5].

Caffeine probably has a diuretic effect, an effect that is rapid and strong [4], but that has not been found in other study [1]. Probably both gastric and urinary discomforts contribute to spontaneous cessation of coffee intake in the elderly [16].

16.5 Risks of Caffeine Use

Acute Risks

Caffeine has a low-risk profile, but after intake of quantities over 250 mg, especially in non-tolerant subjects, an overstimulation of the central nervous and the cardiovascular system can occur, resulting in what is called a "caffeine intoxication." This clinical entity is mentioned in both the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and *International Classification of Diseases* (ICD).

In DSM-IV, the caffeine-related disorders were as follows:

- 292.89 – induced anxiety disorder
- 292.89 – induced sleep disorder
- 305.90 – intoxication
- 292.9 – related disorder NOS

The fifth edition of the DSM (DSM-V) includes the following diagnoses related to caffeine: caffeine intoxication, caffeine withdrawal, other caffeine-induced disorders (e.g., anxiety and sleep disorders), and unspecified caffeine-related disorder. "Caffeine use disorder" is not included in DSM-V, but is included in Sect. III (Emerging measures and models) in order to encourage further research on the issue (www.dsm5.org).

For the ICD-10 criteria of caffeine intoxication, please see Table 16.2.

The incidence of caffeine intoxication seems to be increasing; it occurs mainly in young patients, mainly due to the use of caffeine-containing medications or energy drinks (not due to coffee intake), and when hospitalization is necessary, there is in general co-occurring use of other psychoactive substances or pharmaceutical products [32]. Death from caffeine overdose has been described [19], but it is not clear if in these cases patients have taken medications or have genetic cytochrome abnormalities inhibiting caffeine metabolism. Based on animal studies, the median lethal dose was estimated to be 192 mg/kg; when extrapolating to humans, this should correspond to an intake of around 10 g of caffeine, corresponding to 80–100 cups of coffee [34], making the occurrence of overdose with regular coffee not very probable.

16.6 Chronic Risks of Caffeine Use

Caffeine Dependence and Addiction

"Caffeine dependence" and "caffeine abuse" were not included in the DSM-IV, even if these terms are frequently used in the lay and medical literature. In general, there are not sufficient criteria to establish the diagnosis of caffeine dependence, even if 50% of regular caffeine users will present with withdrawal symptoms in case of acute abstinence. In the DSM-V "caffeine use disorder" has been added as a research diagnosis only (see above).

As caffeine intoxication, the caffeine withdrawal syndrome is included in both DSM and ICD classifications. The ICD-10 criteria for the caffeine withdrawal state (F15.3) are found in Table 16.2. ICD-11, to be introduced in the coming years, also covers caffeine withdrawal (and different other caffeine-related symptoms) but not caffeine use disorder (https://icd.who.int/browse11/l-m/en).

The caffeine withdrawal syndrome is probably largely underdiagnosed. It can occur after sudden abstinence from regular caffeine even at rather low intake of 100 mg daily [21]. The most frequent symptoms are headache, fatigue, decreased energy/activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, and being foggy/not clearheaded. Symptoms occur after 12–24 h of abstinence and last for several days. The severity and duration of symptoms are related to the amount of regular caffeine intake. Juliano and Griffiths (2004) suggest that expectancies are not a prime determinant of caffeine withdrawal and that avoidance of withdrawal symptoms plays a central role in habitual caffeine consumption.

Patients who are hospitalized and depending on their state or inpatient regulations (decaffeinated coffee only in psychiatric settings) can find themselves in caffeine withdrawal with symptoms that can be misinterpreted or unrecognized. For instance, for a patient suffering from head trauma and not receiving his daily coffee, the severity of the headache can very well be influenced by the lack of caffeine.

The same misinterpretation can occur during expeditions at high altitude. For practical reasons or fear of increasing sleeplessness and risk of dehydration, caffeine intake is often stopped in this context. Several symptoms of altitude sickness and caffeine withdrawal are common, such as headache, fatigue, and lassitude [17]. Hackett suggests that during expeditions caffeine likely will have more beneficial than negative effects, especially in regular coffee drinkers.

Table 16.2 ICD 10 criteria for intoxication and withdrawal state of caffeine and other stimulants (other than cocaine, F 14.0)

F15.0 Acute intoxication due to use of other stimulants, including caffeine
A. The general criteria for acute intoxication (F1x.0) must be met
B. There must be dysfunctional behavior or perceptual abnormalities, as evidenced by at least one of the following:
1. Euphoria and sensation of increased energy
2. Hypervigilance
3. Grandiose beliefs or actions
4. Abusiveness or aggression
5. Argumentativeness
6. Lability of mood
7. Repetitive stereotyped behaviors
8. Auditory, visual, or tactile illusions
9. Hallucinations, usually with intact orientation
10. Paranoid ideation
11. Interference with personal functioning
C. At least two of the following signs must be present
1. Tachycardia (sometimes bradycardia)
2. Cardiac arrhythmias
3. Hypertension (sometimes hypotension)
4. Sweating and chills
5. Nausea and vomiting
6. Evidence of weight loss
7. Pupillary dilatation
8. Psychomotor agitation (sometimes retardation)
9. Muscular weakness
10. Chest pain
11. Convulsions
F15.3 Withdrawal state from other stimulants, including caffeine
A. The general criteria for withdrawal state (F1x.3) must be met
B. There is dysphoric mood (for instance, sadness or anhedonia)
C. Any two of the following signs must be present
1. Lethargy and fatigue
2. Psychomotor retardation or agitation
3. Craving for stimulant drugs
4. Increased appetite
5. Insomnia or hypersomnia
6. Bizarre or unpleasant dreams

From ICD-10 [20]

16.6.1 Other Chronic Risks

Heavy caffeine use is often associated with increased risk for other substance use or addictive disorders and mental health disorders such as adult hyperactivity syndrome. This correlation

does absolutely not mean causality, but different studies suggest a two- to threefold increase of prevalence of tobacco dependence or problematic alcohol use for those consuming more than six to seven cups of coffee per day compared to those taking one to two cups [5, 16]. The combined (and increasing) use of energy drinks with alcohol in adolescents and young adults deserves specific attention.

Caffeine can induce panic attacks in some individuals, but seems not be correlated to the occurrence of negative outcomes of chronic psychiatric problems. A link between heavy caffeine use and schizophrenic relapse has been suggested but not confirmed [16]. Generally speaking, no association between psychiatric disorders and caffeine has been found after controlling for genetic and environmental factors [23].

Several studies suggest a correlation between high caffeine intake (>5 cups of coffee daily) and risk of lower bone density and increased risk of fracture, especially in lean elderly women and/or those having low calcium intake, but with tea intake correlated to higher bone density [5, 28].

The use of unfiltered coffee has been associated with increased level of cholesterol, a major risk factor for cardiovascular disease [38]. Still, the effect of filtered and unfiltered coffee on other risk factors is not fully clear, and even if caffeine can induce tachycardia and arrhythmia, the available literature suggests that caffeine has more benefits than risks for cardiovascular disease. A recent study suggests that while energy drink consumption up to a dose of 200 mg is safe, some cardiovascular adverse effect (including QT prolongation) is possible at more than 320 mg [12].

The same seems to be true for the oncology field (see below).

16.7 Benefits of Methylxanthine

16.7.1 Caffeine

As said before, when considering the benefits of caffeine, we remind that there is a difference between the benefits of caffeine itself and the benefits of coffee or other caffeine-containing drinks. Coffee contains hundreds of other compounds that are antioxidants (polyphenols, flavonoids, catechins, melanoidins, etc.) that pass through coffee filters.

Moreover, it is globally difficult to speak only of caffeine because only few publications are about caffeine itself. Most scientific evidence is related to studies on coffee and do not consider the biologic effect of caffeine. In energy drinks, the consequences of caffeine are difficult to isolate from those due to the high content of sugar and other components like vitamins or the amino acid taurine.

First of all, there are strong suggestions that taking caffeine from coffee is associated with a diminution of the risk of total or specific mortality [14]. This study is based on the follow-up of more than 229,000 men and 173,000 women for 13 years. At inclusion, participants' age varied between 50 and 71 years. After adjustment for tobacco-smoking status and other possible biases, the risk of death was inversely correlated to coffee consumption. The benefit became significant at one cup of coffee per day for men (hazard ratio 0.94, 95% confidence interval 0.86–0.93) and at two or three cups of coffee for women (hazard ratio 0.87, 95% confidence interval 0.83–0.92). The benefit tended to rise with the amount of coffee taken, with a statistical inverse correlation between caffeine and mortality. An inverse correlation was also observed for death from respiratory disease, injuries, diabetes, and infection. No association was found between caffeine and cancer-related mortality. These results were confirmed in subgroups, including people in very good health at inclusion. In this study, the inverse correlation for heart disease and stroke was at the limit of statistical significance. An umbrella review of meta-analyses [36] comes to the same conclusions, with an optimal risk reduction for overall mortality at three to four cups of coffee per day. A recent meta-analysis, covering 40 studies and almost four million subjects [25], confirmed these findings and concluded that, compared to no coffee consumption, moderate coffee consumption (defined as two to four cups/day) was associated with reduced all-cause and cause-specific mortality. This inverse association between coffee and all-cause mortality was consistent by potential modifiers (age, overweight,

alcohol and tobacco use), except region. The lowest relative risks were 3.5 cups per day for all-cause mortality, 2.5 cups for cardiovascular mortality, and 2 cups for cancer-related mortality.

When searching specific potential benefits of coffee for specific diseases, the most impressive observed effect is on liver disease. A large cohort study [26] (more than 129,000 subjects) was conducted over 20 years, from the 1980s in the USA. A strong inverse correlation was found between cirrhosis and coffee drinking especially when the origin of the cirrhosis was alcohol. In this case, there was a 40% risk reduction in 16-year cirrhosis incidence when people drank one to three cups of coffee (relative risk 0.6, 95% confidence interval 0.4–0.8) and an 80% risk reduction for four or more cups (relative risk 0.2, 95% confidence interval 0.1–0.4). For nonalcoholic cirrhosis, there was no significant risk reduction of caffeine on mortality and a non-significant 30% risk reduction for people drinking four or more cups (relative risk 0.7, 95% confidence interval 0.4–1.3). This relation was not observed for tea drinkers. Other cohort and case-control studies found strong reduction in the risk of liver cancer in coffee drinkers, with an increase in consumption of two cups of coffee per day being associated with a 43% reduced risk of liver cancer (relative risk 0.57, 95% confidence interval 0.49–0.67) (Larsson and Wolk 2007).

Coffee use is also inversely correlated to progression of fibrosis in hepatitis C liver disease (Freedman et al. 2009). The relative risk of two-point increase in fibrosis was 0.70 (0.48–1.02) for one or two cups of coffee a day and 0.47 (0.27–0.85) for three or more cups per day (significant trend). Although these are observational data (for evident ethical reasons, randomized studies will be difficult to realize), it is probable that people suffering from chronic hepatitis C are partially protected from fibrosis progression if they drink coffee on a regular basis.

Furthermore, the same authors found later that drinking coffee was a predictor to improved response to hepatitis C treatment with pegylated interferon and ribavirin (Freedman et al. 2011). The probability to achieve sustained virological response was almost twice for coffee drinkers of three or more cups of coffee daily (odds ratio 1.8, 95% confidence interval 0.8–3.9).

Patients suffering from substance use disorders (legal or illegal) have a higher prevalence cardiovascular risk factors and disease than the general population. Tobacco smoking is more common in this population; one study suggests there is not a lower physical activity or unbalanced diet (Berg and Høstmark 1996), but this study included few and young participants (22-year-olds). Interventions promoting cardiovascular and heart health are important in the addicted population.

For the general population, caffeine consumption was considered to have a negative impact on the cardiovascular system until the 1990s. More recent studies suggest that coffee has no effect on the incidence of cardiovascular events and even suggest a small benefit for people without preexisting cardiac disease.

While people drinking coffee had a trend (at the limit of statistical significance) for beneficial cardiovascular effect in the first study discussed in this section [14], other studies show an inverse relation was mortality [25], and others detected no association concerning men and a reduction in the cardiovascular mortality for women (relative risk of death 0.83, confidence interval 0.73–0.95) [30]. For stroke, a 20% reduction of relative risk has been found in a cohort study of women (Larsson et al. 2011); this was consistent with the results of another study concerning men (Larsson et al. 2008).

The effect of caffeine on insulin resistance is controversial and probably depends on the source of caffeine and the duration of exposition. At short term, caffeine has been shown to diminish insulin sensitivity (Beaudoin and Graham 2011). In a randomized controlled study, a dosage from 400 mg caffeine per day for a week showed a decrease of 35% (95% confidence interval 7–62%) of insulin sensitivity [31]. In another study, sweet caffeinated beverages tended to increase type 2 diabetes (Malik et al. 2010). Still, it was not possible to separate the effect of sugar or caffeine. The long-term effect of pure caffeine from other sources than tea or coffee seems to

have the opposite effect in animal models, ameliorating the insulin sensitivity and neutralizing the negative metabolic of sucrose in rats [33], but this study was conducted not in humans but in type I diabetic rats. In humans, the regular consumption of coffee has been clearly linked to decrease the incidence of type 2 diabetes (Huxley et al. 2009). In this study, the relative risk was diminished by 7% for any additional cup of coffee or tea absorbed. This effect was not associated with certainty to caffeine as it was also observed with decaffeinated coffee.

Caffeine also influences the metabolism of uric acid and occurrence of gout [8]. In this large observational study, more than 50,000 men without former episode of gout were followed for 12 years. The relative risk of incidental gout was reduced by almost 60% (relative risk 0.41, 95% confidence interval 0.19–0.88) for the group consuming a large amount of coffee (six cups a day or more). The smallest efficient dose for gout protection was four to five cups of coffee a day with a 40% risk reduction (relative risk 0.60, 95% confidence interval 0.41–0.87). This was clearly linked to coffee and not caffeine, as this protective effect was not observed with tea or other sources of caffeine.

Tea and coffee (at a dosage of 300 mg caffeine per day) have been shown to protect against Parkinson's disease, with a risk reduction of 25% (relative risk 0.75, 95% confidence interval 0.68–0.82) (Costa et al. 2010), excluding women taking hormonal replacement after menopause.

A neuroprotective effect of coffee on Alzheimer's disease has been suggested, but this assumption is based on a small number of observational studies (Barranco Quintana 2007). The risk reduction could be 30% (relative risk 0.7, 95% confidence interval 0.55–0.9). Still, a more recent meta-analysis [29] suggested there was no link between caffeine intake and Alzheimer's disease or other forms of dementia.

A case-control study in Australia confirmed the potential benefit of caffeine to prevent road accidents (Sharwood et al. 2013). More than 500 professional drivers involved in crash accidents were compared to controls. After adjustment for confounding factors, drivers who consumed caffeine (from coffee, tea, energy drinks, or tablets) had a risk reduction of 63% of being involved in an accident (odds ratio 0.37, 95% confidence interval 0.27–0.50). This is probably due to the psychostimulant properties of caffeine (increase alertness, lessen fatigue, promote memory, prevent errors to people who are tired or working on night shift) [24]. Also in light drinkers, the accident reduction was found; this is an argument against that it was only an effect of the reversal of withdrawal (Childs and de Wit 2006).

Another well-established positive effect from caffeine is the enhancement of physical capacities [7]. The most effective dosage for this purpose seems to be around 3 mg caffeine per kilogram of weight. Positive impact was found on intermittent effort sports (e.g., soccer), continued effort sports lasting until 1 h (e.g., swimming), or endurance sports (e.g., running). The enhancing effect of caffeine is so significant that for a long time, caffeine was considered a doping substance controlled by the World Anti-Doping Agency (WADA). In 2004 caffeine was removed from the list (www.wada-ama.org).

The potential analgesic properties of caffeine are subject of debate. Caffeine is successfully used in the treatment of headache or migraine [15] and is a frequent component of combined analgesics or other medication (e.g., when mixed with paracetamol or salicylates or antihistamines). On the other hand, it can be the cause of headache [3] as caffeine withdrawal symptom.

Coffee and tea also seem to present benefit for mental health based on a data of a large cohort from the Nurses' Health Study. More than 50,000 women not suffering from depression at baseline were followed between 1996 and 2006 and stratified by their consumption of caffeine (Lucas et al. 2011). During the follow-up, women consuming four cups or more of coffee per day had a 0.80 relative risk of developing depression when compared to the group consuming one cup per week or less (95% confidence interval 0.68–0.95). This effect seems related to caffeine itself as it was not observed for women drinking decaffeinated coffee. These results are coherent with data from other studies showing an inverse correlation between coffee, depression, and suicide [22].

16.7.2 Theophylline

Theophylline, another methylxanthine (1,3-dimethylxanthine), is found in medication and in small quantity in tea, coffee, chocolate, mate, and guarana. Its principal indications are related to its bronchodilatative properties and immunomodulatory effects [41]. It is known to restore the sensitivity to corticosteroids in asthma. Consequently, theophylline is used in asthma and chronic obstructive pulmonary disease. It seems that it could also be useful for the prevention of acute kidney injury caused by radiologic contrast product (Dai et al. 2012). It is not as psychoactive as caffeine and not known to be a substance of abuse.

16.7.3 Theobromine

There is a popular belief that theobromine, a third methylxanthine, found principally in guarana, cacao, and chocolate, has a euphoric effect, but no studies can confirm this. The appetite for chocolate would be more linked to other methylxanthine such as caffeine and taste or cultural influences. So up to know, there are no proven benefits for theobromine [39].

16.7.4 Caffeine Abuse Treatment

In case of acute intoxication (Yew 2018), which necessitates more than 70 mg/kg of caffeine intake, (Bronstein et al. 2010), clinical management should be "supportive." The first action is to give standard protocols for cardiac life or other support (ABCs) [35], then give oxygen to the patient, and check the blood glucose. In case of extreme anxiety, agitation, or seizure and lack of effect of non-pharmacological interventions, give short-acting benzodiazepines (e.g., lorazepam orally when possible or intravenously/intramuscularly).

Activated charcoal is effective in reducing the absorption of methylxanthine and recommended early in the treatment. If needed, the patient should be transferred to an emergency unit where the care will also be supportive. Cardiovascular or neurologic toxicities are the most frequent. Sinus tachycardia occurs but does, in general, not require any intervention, but arrhythmia does. In case of extremely high caffeine levels, a dialysis or hemofiltration may be necessary.

Gastric lavage is rarely done because of aspiration risk. Caffeine is rapidly absorbed, and gastric lavage should not be considered unless in less than one hour after intake.

In case of withdrawal, no specific treatment or intervention was found in scientific publications. Anyway, caffeine withdrawal is not dangerous and self-limited, so no intervention is needed and a wait-and-see approach privileged. Nevertheless, the main problems during caffeine withdrawal are fatigue, lack of concentration, or headache. We can recommend general interventions such as rest, physical activity, and good fluid and electrolyte supply. In case of severe headaches, simple analgesia (e.g., paracetamol) could be used. If the time to go through withdrawal is really not adequate, for example, in case of professional or familial obligations, caffeine (in a limited dose) could be taken in the form of coffee, a caffeine-containing drink, or a tablet, and complete and slow withdrawal conducted later. For regular caffeine users who will be exposed to a period of caffeine abstinence (e.g., planned medical intervention), a decrease of daily caffeine intake days before is recommended [13]. Currently, no effective interventions to reduce excessive energy drink consumption exist [42].

16.8 International Perspectives

Currently, coffee, tea, and other caffeine-containing drinks are legally available in all countries and not subjected to regulation. Based on our review of benefits and risks of methylxanthines, we believe that there is no rationale to change this. This seems neither necessary nor useful in a public health or cultural perspective,

as prohibition certainly will have a number of unwanted side effects. Nevertheless, information and warning (on package of food or drinks) are probably warranted, indicating the risk of high doses of caffeine and when mixed with alcohol and when relevant the risk of sugar, calories, or other compounds.

The FDA has warned four companies about adding caffeine to alcoholic beverages in 2010 [18] and stated that a further action, including the seizure of products, is possible under federal law. The FDA stated that caffeine is an "unsafe food additive" when mixed with alcohol.

Another international measure that we consider useful would be a limitation of the amount of caffeine in energy drinks. It seems difficult to reach toxic levels of caffeine when a drink contains 50–100 mg of caffeine. Nevertheless, content of 500 mg caffeine in one drink can represent a real danger, especially for children or teenagers, given their lower body weight and the propensity to like those drinks.

16.9 Conclusion

Safe caffeine use is possible and moderate coffee use (200–400 mg of caffeine per day) probably has more physical and psychological benefits than risks. Relative contraindications for caffeine intake are uncompensated heart disease, anxiety, and sleeping problems. Since most studies on caffeine use are observational, we can of course not recommend the use of caffeine or other methylxanthines for medical reasons to those who do not drink. The studies are merely based on cohorts of individuals drinking coffee and tea, so the use of these beverages should be privileged and not of energy drinks. Energy drinks lack several compounds found in coffee or tea (antioxidants) and contain others that possibly have a negative impact on health (sugar). In case of liver disease, especially if related to alcohol and HCV, a daily intake of at least five cups of coffee can be reasonably recommended to diminish the progression of the disease.

Coffee and caffeine withdrawal symptoms exist and are often not recognized, especially in treatment settings, where caffeine withdrawal can be confounded with other symptoms. Caffeine withdrawal occurs in half of regular coffee drinkers, even at moderate caffeine intake. The most common symptoms are headache, fatigue, and difficulty to concentrate. Health professionals and patients should be better informed about these symptoms and the risk of occurrence of caffeine withdrawal.

Caffeine intoxication and withdrawal are recognized clinical entities, but caffeine dependence, nor caffeine use disorder, is currently not. Some individuals can meet difficulties in controlling their caffeine intake and present withdrawal symptoms in case of abstinence, but most often other criteria of dependence are lacking. In some cases, such behavior seems close to an obsessive-compulsive or eating disorder.

In psychiatric inpatient settings, often only decaffeinated coffee is available. We recommend, for the reasons mentioned above, and a probable positive effect of caffeine in depressive symptoms, that both caffeinated and decaffeinated coffee be at the disposition of the patients, with restriction for those who suffer from anxiety or insomnia. Caffeine taken from coffee seems to be without risk for most psychiatric patients. Personalized recommendations (maximum daily quantity of caffeine, time limit) are probably more appropriate than constraining all patients to abstain from coffee consumption.

Finally, we highly recommend more and better information to the population about the risk of acute intoxication of caffeine, the nutritional and metabolic risks of energy drinks, and the problems of mixing these with alcohol. Warning messages on caffeine-containing food or drinks as well as a legal limitation of the content of caffeine (e.g., maximum 200 mg per unit) are certainly justified. They should be promoted in all countries.

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Khat Addiction

17

Michael Odenwald, Axel Klein, and Nasir Warfa

Contents

Abstract

Khat leaves are traditionally consumed in African and Arab countries around the Horn of Africa. The central and peripheral stimulant alkaloid cathinone (S-(-)-a-aminopropiophenone) is considered to be the main psychoactive compound in the khat leaves. The leaves and tender stems are usually chewed and kept in a tight wad in the cheek pocket. Within about 15–30 minutes, the user experiences physiological excitability, euphoria, talkativeness, and flow of ideas. While khat production and consumption is popular in traditional user countries and use patterns swiftly change to excessive usage, particularly in East Africa, the substance is treated as illegal in the rest of the world. Today, cathinone is listed in Schedule I of the 1971 International Convention on Psychotropic Substances, although the leaves

M. Odenwald (✉)
Department of Psychology, Konstanz University, Konstanz, Germany
e-mail: michael.odenwald@uni-konstanz.de

A. Klein
Global Drug Policy Observatory, University of Swansea, Swansea, UK

N. Warfa
Maltepe University, Maltepe/İstanbul, Turkey

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of khat are not internationally controlled. Khat use is associated with a number of mental health problems. A problem with diagnosis of khat use disorders is that established criteria are not easily applicable. Since the first edition of this textbook, some research has been done on khat; however, the current empirical knowledge base is still limited on prevalence and use patterns; most studies that associate khat use with mental and physical health problems have weak designs and treatment studies are rare. There is a need to build up research and treatment capacities in the main khat use countries. There is also a need to develop adequate legal regulations, monitoring systems, and public health responses that moderate between economic, cultural, and health viewpoints.

Keywords

Khat · Qat · Miraa · *Catha edulis* · Cathinone

17.1 Introduction

Khat refers to the young and tender leaves and shoots of the khat tree (*Catha edulis*). It is an evergreen tree of the Celastraceae family. It grows to 6 m in height, and 25 m under warm equatorial climate. *Catha edulis* can be found in the Abyssinian highlands, East Africa and in the southern Arab peninsula [64]. Khat has many names including *qat* (Yemen), *jad/chat* (Ethiopia, Somalia), *miraa* (Kenya), and *marungi* (Kenya, Uganda). The leaves and twigs of khat have been consumed for centuries for their mildly stimulating properties. Khat has several alkaloids and more than 40 known different chemical compounds. The alkaloid cathinone (S-(-)-a-aminopropiophenone) is considered to be the main psychoactive compound. It is unstable as it swiftly decomposes soon after harvesting. Cathinone resembles amphetamine in chemical structure and has a stimulating effect on the central and peripheral nervous system and behavior similarly [33]. In the anthropological literature, the effect of khat as well as its cultural integration has often been compared to coffee and caffeine. Recently, synthetic cathinone derivates such as mephedrone constitute a large group among the "novel psychoactive substances" that are known as "legal highs" [24]. More stable compounds of the khat leaves are cathine (S,S-(+)-norpseudoephedrine) and other alkaloids which are at the same time metabolites of cathinone and less potent central and peripheral stimulants.

While consumers prefer chewing fresh leaves, dried leaves are used when no fresh khat is available or is too expensive. Soon after harvesting, the fresh twigs, leaves, and shoots of khat are artfully rolled into bundles and wrapped into banana leaves to retain their moisture. Such bundles form the standard unit of consumption, though leaves of lower quality are also sold in plastic bags. Traditionally, khat is used in group sessions in private homes and at specific khat establishments ("marfrish") that start from early afternoon and finish evening hours. During these chewing hours, some users accompany khat with cigarettes, water pipe, carbonated soft drinks, and sometimes chewing gums. Consumers pick off leaves and tender stems and form a tight wad in their cheek pocket where they are slowly chewed over hours. Within the first 15–30 minutes, the effects reach the "mirqaan" (high), a psychological state marked by euphoria, talkativeness, and a flow of ideas. This is followed by a quieter and introvert phase, often accompanied by irritability, anxiousness or depression, and then a gradual come-down. The experience may disturb sleeping patterns in the following night and is liable to produce hangover the next morning. In order to balance off these unwanted feelings, some khat chewers carry on chewing for prolonged longer sessions.

The khat research field is still in its infancy. Although scientific literature on khat is steeply increasing, the quantity of peer-reviewed papers, however, is small compared to the use prevalence [69]. The quality of the research, methods, and methodologies is not consistent, and key khat studies have not yet been replicated. One impor-

tant challenge for the external validity of khat research is that main user populations are deprived, and studies need to control for potential confounding factors. There is a great need to build up research capacity in the traditional khat use countries.

17.2 The Khat Controversy

The legal, economic, social, and religious controversies around khat, and the question of whether it is a drug or a part of cultural heritage, are as old as the existence of khat itself [42]. Medieval writings and ancient legend anecdotes narrate the ambivalent attitudes toward its effects that are sometimes described as helpful and joyful, noxious, and damaging at other times [42]. It has been condemned by the Ethiopian Orthodox Church and Islamic Scholars who consider it to be harmful or "haram." On the other hand, some moderate Islamic scholars in Somalia and Ethiopia integrated khat use into religious rituals. For moderate Sufi Muslims, the justification made is to stay awake at night time in order to cite religious texts, particularly during the month of Ramadan in order to stay awake until late in the evening. The use of khat is controversial as it regularly stirs emotions across diverse secular, religious, cultural, and economic groups (e.g., [13, 64]). During the colonial era, arguments about moral degeneration, falling economic productivity, and the association of khat use with political unrest motivated officials to ban khat in countries like Somalia or Yemen, but these attempts led to political opposition and were largely unsuccessful (Klein, Beckerleg and Hailu 2009; [25, 39]). Likewise, strong pro-khat movements prevented the introduction of legal restrictions in the traditional khat-producing and khat-consuming countries.

Similarly, the scientific discourse on khat is dominated by disagreements along the lines of various competing academic disciplines [55]. Medical and pharmacological research approach khat from the underlying assumption that it is analogous to other harmful psychoactive drugs. Consequently, these studies focus on the pharmacology of psychoactive compounds, as well as the mental and physical health problems linked with khat use. Since the current khat studies lack rigorous study designs, some social scientists warn against the medicalization of khat-related problems. Overall, the negative and positive roles khat play in social, cultural, and economic factors are much debated. One aspect of the literature highlights how khat is consumed for sustaining cultural functions and traditional values [10]. There is an ongoing international debate that these cultural and traditional functions of khat are often overlooked or not fully taken into account by medical research. Others argued that such concepts as addiction are Western and that these do not grasp the philosophy of the mostly non-Western khat users.

This ambiguity is also found in the way khat is seen from a legal perspective. Attempts have been made to include khat leaves and its psychoactive compounds in international and national drug legislation. Cathinone is listed in Schedule I and cathine in Schedule III of the 1971 International Convention on Psychotropic Substances. Fresh khat leaves and twigs, however, are not controlled under the Convention. On national levels, most producer countries allow khat production, use, and trade, e.g. Ethiopia, Kenya, and Yemen. While these countries have put in place some restrictions and taxation schemes, in recent time the official classification of khat has gradually moved from a psychoactive substance to a cash crop. Some of the neighboring countries (e.g., Tanzania) and most of the Western countries, however, have imposed legal restrictions and treat khat as illegal drug [27]. Recently, the UK and the Netherlands (two countries which had been used as transit ports for khat transportation to rest of EU countries and North America) prohibited khat. The objectives behind such prohibitions and the aims of public health protection were questioned from social scientific perspectives [40]. Several countries implemented ambiguous politics, e.g., Saudi Arabia, where khat is banned but its production and use are tolerated in Jazan region neighboring Yemen.

17.3 From a Niche Crop to a Cash Crop

Historically, khat use was confined to certain cultural or ethnic groups. It was used socially during cultural ceremonies and rituals. The elites were stated to chew khat for social purposes but also to get inspirations for artistic expressions in poetry and song composition. They would gather in dedicated rooms within private households and/or in communal places called Marfrish. Other groups who are known for khat use are khat farmers, distance travelers, and university students. These groups are reported to use khat for staying alert or to overcome tiredness. From these earlier times, khat misuse was rarely observed. Outside the few traditional producing areas, khat use was rare. Khat use for medical purposes was noticed by early European travelers, for example, the Swedish botanist Peter Forsskal (1732–1763). By 1900, new patterns of khat use and misuse begin to emerge, which was partly linked to increased availability. In countries like Somalia and Yemen, groups of men from all walks of life would meet to discuss politics, business, and social issues over khat sessions [65]. In the second part of the century, frequent and excessive use has become a regular part of social life for a large number of people in East Africa. With no or limited legal restrictions, the historical and cultural significance of usage gradually eroded, replaced by practices of khat misuse.

Transport innovations, the invention of fast railway networks, road haulages, and affordability of air cargo have facilitated greater commodification and branding. This has created a regional market with attractive conditions for the producers and the development of a whole new industry around khat. All these emerging developments have made khat a popular cash crop from its previous niche markets. To this date, khat is sold and consumed in several regions and countries beyond East Africa and Arabia. New varieties of khat have emerged in response to new khat markets, partly encouraged by immigrants living in the West and elsewhere. After decades of rapid production, the economic significance of the khat sector has dramatically increased. The khat economy provides significant employment and income to farmers, pickers, packers, sellers, and other associated traders in East Africa and the Arab Peninsula [10, 25]. It has been identified as an example of an economic success story for African agricultural producers without any support by development actors and involvement of multinational companies [39]. Consequently, the recent bans in the Netherlands and the UK had negative effects on incomes of khat farmers in Africa [41]. As production has risen in response to increasing demands, new social, health, and ecological challenges have emerged particularly over the use of finite resources. For example, water irrigation for khat production was identified as one of the major factors that contribute to the groundwater decline in Yemen, as well as a contributing factor to deforestation in Ethiopia.

17.4 Development from Traditional Use to Binge Patterns

Despite the growing scientific data on khat, only limited population surveys are available. It is estimated that more than ten million globally use khat for recreational purposes on any 1 day [56]. In Yemen, the pre-civil war estimates vary between 60% and 90% of adult males and 10% and 50% of adult women [25]. Different surveys indicated that Yemeni households spent 9–10% of their income on khat (on average), with low-income groups spending as much as 40% [25]. In Ethiopia, two representative national surveys [30, 62] revealed a current prevalence use of 15–16%, with regional variations of 50% (khat production regions) and 1–3% (in a region where khat is traditionally not consumed); furthermore, male gender, Muslim faith, living in rural areas, wealth, and lower education were positively related to khat use. A recent meta-analysis [26] estimated a national prevalence rate of 23.2% among high school and university students, with considerable regional variations (18.1–31.6%). In Kenya, no prevalence data for the general population is available. A survey conducted from a khat-growing region put a prevalence estimate of 36.8% (lifetime 44.6%; [58]). Other studies of treatment-seeking patients revealed a lifetime

prevalence rate of 10.7–30% [48]. From the last population survey carried out in Somalia, regular (or current) khat use was estimated to be between 31% and 64% of adult males in the north of the country and 21% in the South, with excessive khat use patterns found among militia members [22]. In the West, khat use is almost exclusively limited to immigrant groups from khat-producing or khat-consuming countries.

The pattern of khat use has changed significantly over recent decades due in part to the combined consequences of urbanization, commodification, and rapid social changes [10]. The dissolution of traditional and cultural use of khat together with the lack of government regulations has led to the rise of more excessive and extensive use, including early morning use, prolonged binge sessions, as well as the emergency of new patterns of risky use, for example, khat chewing while taking other drugs and substances, e.g., alcohol or benzodiazepines [44, 58, 62]. This illustrates that like other stimulant users, the functional use of "downers," e.g., in order to be able to sleep, has become common among khat users which may be indicative of a shift in the patterns of use and integration into functional lifestyles. Furthermore, today khat chewers frequently smoke tobacco (cigarettes or shisha) during khat sessions [6]. The age in which people start chewing khat also changed. Traditionally, chewers were exposed to the habit from about the age of 20 years, whereas now children as young as 8 years old are reported to use it [56]. Furthermore, what has previously been considered an exclusively male habit is increasingly practiced by women, with a recent study showing significant evidence of khat use by pregnant women in Ethiopia [46].

17.5 What Is Known About Khat Addiction?

While there have been reports of excessive patterns of khat consumption and description of addictive behaviors since colonial times [28], experts consider the harm associated with khat use mild when compared to other psychoactive substances, i.e., similar to MDMA (3,4-methylenedioxy-methamphetamine; "Ecstasy") [51]. This is one of the reasons why the WHO Expert Committee on Drug Dependence has repeatedly decided that the misuse potential is too low to merit international controls [68], at least, on medical grounds.

Without firm database, it is believed that prolonged and excessive khat use can potentially produce psychological dependence comparable to amphetamine [68].

Mild and brief withdrawal symptoms upon discontinuation are reported, unless khat is used excessively for extended periods of time [68]. Withdrawal symptoms include profound lassitude, anergia, difficulty in initiating normal activity, mild trembling, and nightmares of paranoid nature, for example, vivid or unpleasant dreams of being attacked, strangled, or followed by strangers (e.g., [38]). Recent studies provided first data on the prevalence of withdrawal symptoms among chewers (any symptom 68.2%; [3]; 28% meeting core requirements for stimulant withdrawal, [21]) and about the course of withdrawal symptoms in the weeks after quit attempts [19].

In the same token, today it is generally believed that with regular consumption over extended periods of time khat chewers become habituated to the physical effect, a process described as "tolerance," often associated with increased levels of consumption [68]. It has been argued that the chewing mode of ingestion limits the possible amount to consume in a certain time, and, thus, tolerance development is usually prevented. This view can be criticized based on recent definitions of tolerance. Among stimulant users, tolerance development, the upward shift in the set point for reward, and the subsequent dysphoria ("opponent process") are closely related to the development of "binge" consumption patterns: Users need to increase the dose and the frequency of drug administration in order to experience the desired psychological effects. Thus, khat tolerance development might not only include increases in the amount of consumption per time unit but rather the extension of the time spent for consuming it which leads to an increase of the absolute amount ingested. Recent studies and personal observations indicate that a growing group of binge users consume khat for more than

24 h in a row in such large quantities a novice would never manage [45, 66, 67]. While the development of tolerance to physiological effects was reported [50], no study has ever directly targeted the topic of tolerance to desired psychological effects, e.g., euphoria. In contrast to the medical view of tolerance development, social scientists highlight that among khat-using populations who are frequently exposed to violence, deprivation, and injustice, increasing levels of khat use are mechanisms of coping with adverse living conditions and of strengthening social and cultural identity. Studies are needed to disentangle the social mechanisms from the pure somatic processes.

Other features of khat addiction that have been the focus of research are craving, the urge to consume khat, and the continuous need to use the substance despite harmful effects and unsuccessful attempts at reducing consumption (e.g., [62]). The dynamic around khat use is illustrated by typical scenes from khat markets where there are situations of heightened euphoria, nervousness, and aggressiveness during or before khat is delivered [29].

Furthermore, observational data confirm the existence of a specific nomenclature for psychological states experienced by Somali khat users, e.g., "jibane" ("eye opener," i.e., early morning use of khat in a group setting in order to reduce aversive symptoms) or "xaraaro" (feelings of urge to chew and nervousness), which point to use-specific reflection on shared experience and a cumulative learning.

A recent study reported that khat chewers enhance the experience of euphoria and other emotional benefits by stepping up consumption of tobacco [35], but studies on co-use of other psychoactives, particularly tea and sugar, are still missing.

17.6 Measurement and Diagnosis of Khat Addiction

A problem with diagnosis of khat use disorders is that established criteria are not easily applicable as is the case for other traditional substances. Besides the previously mentioned limited knowledge on withdrawal and tolerance, some of the other criteria outlined in DSM-5 (or ICD research criteria) might need further specification to adapt to societies where daily social khat use is rather the rule than the exception and where social khat use is the most widely practiced social and leisure activity, i.e., "… The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects… Important social, occupational, or recreational activities may be given up or reduced because of substance use" [11, p. 483]. In general, the adaption of criteria seems necessary in order to avoid overdiagnosis. Although research has started to address this problem [44], it needs more studies to understand khat-related cultural conventions that establish the range for socially acceptable consumption as well as sanctions for excess, including stigmatization and social exclusion. Recently, studies showed the applicability of the diagnostic criteria as defined by DSM and, at the same time, the skewed distribution highlighting the above-mentioned problem: in the UK, 31% of 204 khat users of Yemeni origin fulfilled the DSM-IV criteria for dependence [37]; in an Ethiopian university student convenience sample (N = 400), 10.5% were diagnosed with mild, 8.8% with moderate, and 54.5% with severe khat use disorder according to DSM-5 (using an adapted version of the AUDADIS-IV; [21]).

Limited evidence-based information is emerging from cross-sectional studies on the prevalence of khat use disorders as defined by ICD or DSM criteria. An Ethiopian study [12] used the WHO's Composite International Diagnostic Interview to measure the prevalence of khat dependence according to ICD-10 in a representative sample drawn in a traditional khat-producing area, reporting 5% among males and 1.3% females. Using a structured clinical interview, in a representative sample of 242 Somali refugees in Nairobi, the criteria for substance abuse according to DSM-IV were applied to khat and

were fulfilled in 15.3% of khat users [49]. In selected patient or user samples, khat dependence reached much higher levels (e.g., [66]). These studies should be interpreted with caution, because studies developed their own conventions to adapt diagnostic criteria to the reality of khat use.

Validated self-report instruments to screen for and to assess aspects of khat addiction are rare, and few standardized questionnaires have ever been applied in khat users. A general problem is the missing cross-cultural validation of instruments that originally had been developed in Western countries. A khat version of the Severity of Dependence Scale (SDS), a five-item instrument thought to measure the psychological component of dependence, was developed [34] and validated for the study of khat addiction in various languages, including Arab and Amharic [47]. The SDS score correlated with DSM-5 SUD symptoms [18], with more khat-related behaviors and higher khat alkaloid levels in saliva [36]. Furthermore, the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was adapted to khat use [67] as well as the Drug Abuse Screening Test-10 (DAST-10; [2]).

17.7 Neurocognitive Deficits and Comorbid Disorders

A common characteristic of chronic central stimulant use is a neurocognitive deficit syndrome. Several studies found poorer working memory among heavy khat users compared to controls [16, 31]. Other studies reported impaired memory functions [32], impaired executive functions, inhibitory control [15], cognitive inflexibility [16], lack of cognitive control [17], as well as problems with perception processing and motor speed [31, 32]. Cognitive deficits among khat chewers, however, were related to age and education [32], and in general, studies did not control for potential confounding factors, i.e., like chronicity of use, recent use, or withdrawal states.

17.8 Comorbid Disorders

Khat use has been associated with the presence of mental distress and psychiatric and physical disorders (for overview [57]) – with heterogeneous assumptions on the type of underlying association.

Comorbidities of khat use with depression, posttraumatic stress disorder, psychotic symptoms, and suicide ideas have been reported [64]. Recent cross-sectional studies found associations between khat use and occurrence of psychotic symptoms (e.g., [5, 21, 58]) as well as with measures of mental distress (e.g., [1]). Functional khat use to counteract symptoms of depression, posttraumatic stress disorder (e.g., [54]), and antipsychotic medication side effects has been described (e.g., [61]). While there is no evidence for a simple causal-effect relationship, khat use per se doesn't seem to be related to the development of psychiatric disorders in healthy individuals, in contrast to specific patters of use, e.g., excessive or prolonged use, but longitudinal studies are missing in order to quantify khat use patterns as specific risk factors. Several studies on brief khat-induced psychotic episodes (for overview, [53]) reported excessive khat use before the onset and violent behavior in the course of the acute psychiatric development; complete remission was observed after 2–4 weeks when abstinence is maintained, but such episodes tended to occur repeatedly. Also the exacerbation of psychotic symptoms and antipsychotic nonadherence in patients with preexisting psychotic disorders have been reported [14, 23, 61]. A few and weak studies found first support in favor of the hypothesis that early, chronic, and severe khat use might be a risk factor for the development of chronic psychotic disorders [52].

The problems of this literature are the cross-sectional design and the use of self-report measures and screening instruments instead of gold standard assessments and biological data.

Besides psychiatric sequelae, numerous physical health problems have been attributed to khat use (for review, see [7, 57]). Observed somatic consequences associated to khat use include mucosal problems, hypertension, cardiovascular complications, duodenal ulcers, sexual dysfunction, hepa-

toxicity, and problems related to pregnancy and birth (e.g., [9, 59, 60]). Efforts to establish khat consumption as risk factor for physical health problems remain inconclusive because it has not been possible to differentiate between the effects of khat itself, the pesticide contents in khat leaves, and comorbid tobacco smoking and because of other problems related to research design. As with mental health, moderate khat use seems not to be noxious in most users, and adverse effects are commonly linked with the currently growing excessive use. Additionally, some studies showed that khat users (like other substance users) have lower adherence to treatment of physical disorders and infectious diseases (e.g., HIV, [43]).

By the same token, the argument for possible medicinal uses has only been touched on, e.g., probiotic effects.

17.9 Treatment of Khat Addiction

According to the UNODC's annual World Drug Reports, khat users constitute the largest group of patients in substance treatment facilities in Ethiopia and the second largest group in Kenya [63]. However, the UNODC statistics have to be treated with caution, e.g., because the absolute numbers of provided treatments are very small in these countries. Treatment offered to individuals with khat use disorders in traditional khat use countries is usually nonspecific standard psychiatric treatment. Specialized khat addiction programs or treatment facilities are nonexistent. Additionally, some nongovernmental organizations offer counseling.

In Western countries, khat users almost exclusively belong to minority groups from the original khat use countries, and individuals with khat use disorder have been integrated into general treatment programs for illegal substances. Some local initiatives in Western countries (e.g., the UK, Sweden) gained experience in psychosocial support for khat users showing the multifaceted problems of khat-using individuals that seem to be similar to other groups of illegal substance users. Unique has been the building up of a specialized khat addiction treatment center in Stockholm; however, the utilization and acceptance of this service by the target group was weak.

A recent review [57] revealed the scarcity of scientific studies on psychiatric and psychological treatment offered to individuals with khat use disorders. A problem is the high mental health comorbidity of khat users due to violence in traditional khat use countries. One recent case series reported on a combined treatment of khat dependence according to DSM-IV and comorbid PTSD in Somali refugees with encouraging outcomes [4]. Several studies report on the reduction of khat use in nonclinical groups: In a retrospective study, former khat users reported reasons why they stopped using it [8]. Using the quit date paradigm, 60 healthy Ethiopian university students chewing khat at least three times per week for 2 years with high motivation to stop their use were followed up for 28 days: While 93.2% lapsed, only 6.8% achieved continuous abstinence [20]. One controlled study used Screening and Brief Intervention with 330 Somali khat users from the community (adapted version of the ASSIST-linked Brief Intervention; [67]): The intervention group showed decreased khat use time compared to a control group who just received assessment; among participants without comorbid psychopathology (depression, PTSD), khat use reduction was more pronounced.

17.10 Conclusion

The economic significance of khat production and its use are growing in one of the poorest regions of the world, barely noticed by international health policies, losing sight of the potential public health consequences. The topic of khat use and its related social, mental, and physical health complications urgently need empirical studies. The current empirical knowledge base is weak, while the use of khat is becoming widespread, and patterns of use are changing. Khat research capacities need to be built up in the traditional use countries. Future studies will have to get the full picture of current khat use and to disentangle

khat effects from confounding effects (e.g., psychosocial and socioeconomic, environmental effects) using strong methods and designs.

Current evidence supports the hypothesis that khat is used because of its euphorigenic effects and in order to alleviate symptoms of mental distress and that excessive and prolonged khat use can contribute to the development of a range of mental and physical health problems, including khat use disorder. The question of khat-related withdrawal and tolerance needs further studying as well as the neurocognitive consequences of chronic use. For the application of diagnostic criteria for khat use disorder, conventions are lacking plus the development of culturally validated psychodiagnostic measures. The current knowledge base about the treatment for khat use disorders is poor especially as its users rarely utilize or demand for addiction treatment services. The development of commonly accepted, effective, and culturally adequate treatment concepts to be applied in the traditional khat use countries and among khat-using immigrant communities is highly demanded.

It is time for a balanced approach to khat, overcoming the controversies of the past and the romanticized or sensationalist approaches to its use that too often had been deemed an exotic or peculiar habit. Instead, empirical evidence is needed to guide national and international policies and to support law and public health strategies in order to strike a balance between khat-related health and social issues and cultural and economic interests.

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Opioid Addiction and Treatment

18

Marta Torrens, Francina Fonseca,
Fernando Dinamarca, Esther Papaseit,
and Magi Farré

Contents

M. Torrens (✉) · F. Fonseca
Institut de Neuropsiquiatria i Addiccions,
Hospital del Mar, Barcelona, Spain

IMIM (Institut Hospital del Mar d'Investigacions
Mèdiques), Barcelona, Spain

Universitat Autònoma de Barcelona,
Barcelona, Spain
e-mail: mtorrens@parcdesalutmar.cat

F. Dinamarca
Institut de Neuropsiquiatria i Addiccions,
Hospital del Mar, Barcelona, Spain

IMIM (Institut Hospital del Mar d'Investigacions
Mèdiques), Barcelona, Spain

E. Papaseit · M. Farré
Universitat Autònoma de Barcelona,
Barcelona, Spain

Hospital Universitari Germans Trias i Pujol (IGTP),
Badalona, Spain

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Abstract

Opioid use disorder continues to be an important public health concern, reaching epidemic ranges in some countries as well as the consequences associated with consumption. A review of the pharmacology of different opioid drugs available is presented. Also, a current state of the art in the treatment of opioid-related disorders is reviewed. Opioid overdose is a potentially fatal medical emergency that can be reversed with naloxone, an antagonist of opioid receptors, in different doses and routes depending on the opioid that caused the intoxication. For opioid use disorders, the main pharmacological approach is substitution treatment (methadone, buprenorphine, slow-release oral morphine) with the objective of neurochemical stabilization, avoiding the reinforcing effect, and decreasing withdrawal symptoms and craving; there is also a naltrexone depot formulation approved for relapse prevention, associated with psychosocial interventions that seek to restore functionality and prevent relapse. In this chapter, the authors review the current state of knowledge in the field focused on clinical practice.

Keywords

Opioid · Dependence · Overdose · Methadone Buprenorphine · Naloxone

18.1 Introduction

Opioid use disorder (OUD) is a chronic relapsing disease with high costs to individuals and society. In this chapter the term opioids will include all-natural plant alkaloids from opium, such as morphine and codeine, and many semisynthetic derivatives as heroin and methadone as well as totally synthetic substances as fentanyl and others. OUD may involve the use of illicitly manufactured opioids, such as heroin or street fentanyl or the nonmedical use of prescribed opioid medications.

There were an estimated 34.3 million past-year users of opioids globally in 2016, corresponding to 0.7 per cent of the global population aged 15–64 years. The prevalence of past-year use of opioids among the population aged 15–64 years is high in North America (4.2 per cent) and Oceania (2.2 per cent). Among users of opioids, 19.4 million were past-year users of heroin or opium, corresponding to 0.4 per cent of the population aged 15–64 years, with high prevalence rates of past-year use of these opioids in Central Asia and Transcaucasia (0.9 per cent), Eastern and Southeastern Europe (0.7 per cent), and North America (0.8 per cent). WHO estimates that there were 167,750 deaths associated with drug use, with 76 per cent of deaths from drug use disorders related to the use of opioids. Also, it is important to take into account the deaths indirectly attributable to opioid use, such as those related to HIV and HCV acquired through unsafe injecting or from suicides [1].

The high level of misuse of pharmaceutical opioids remains a major concern in North America, where there is also resurgence in heroin use in the past 4 years, particularly in the USA. Together with the use of fentanyl and its analogues, the interlinked epidemic of prescription opioids and heroin has generated a high number of fatal overdoses associated with their use. There are also increasing signs of misuse of pharmaceutical opioids in Western and Central Europe. While not at the same level as in North America, overdose deaths related to fentanyl and its analogues have also been reported in Western and Central Europe [1]. The misuse of pharmaceutical opioids such as tramadol is reported in many countries in Africa (particularly West and North Africa) and in some countries of the Near and Middle East.

This chapter is aimed at updating knowledge about OUD. After a review of the main pharmacological characteristics of opioids, mainly focused in the new synthetic opioids, a state-of-the-art treatment of opioid-related disorders, including opioid intoxication, opioid withdrawal, and opioid use disorder including pharmacological and psychosocial interventions, is presented.

18.2 Pharmacology of Opioids

Opioids exert their pharmacological effects through the endogenous opioid system. The endogenous opioid system is constituted by opioid receptors, mu, kappa, and delta, which are widely distributed in the brain, and the endogenous opioids that include different peptides as endorphins, enkephalins, and dinorphins, which are the ligands of these receptors and play a central role in establishing habits and responses for survival and pain relief.

The opioid endogenous system plays an important role in opioid addiction [2], and also it has been implicated in the pathophysiology of dependence of alcohol and cocaine [3].

The three opioid receptors belong to the G protein receptor family. Depending on the capacity to promote changes in the G protein, ligands are classified into full opioid agonists, partial agonists, antagonists, and agonists–antagonists:

- An agonist or full agonist is a substance that is capable of binding to a receptor, producing their activation and causing a biochemical or cellular response.
- An antagonist is the opposite of an agonist in the sense that it also binds to a receptor, but does not activate the receptor and blocks its activation by agonists.
- A partial agonist binds and activates the receptor, but does not cause complete effect as a full agonist, and has a ceiling of maxim effect inferior than the agonist. They can display antagonism when used in conjunction with a full agonist.

Opioids can be classified according to their affinity on opioid receptors (Table 18.1) as:

- *Pure agonist or full agonist:* opioid agonists at receptor mu fundamentally, with high efficacy (intrinsic activity). This is the group of morphine, heroin, pethidine, methadone, fentanyl, and its derivatives.
- *Mixed agonist–antagonists:* act as agonists in one receptor (kappa) and as partial agonists or antagonists in another (mu). When administered together with a pure mu agonist, it may antagonize the effects and may reduce or eliminate their analgesic effect. In opioid-dependent subjects, agonists (heroin) cause withdrawal symptoms. This is the group of pentazocine, butorphanol, or nalorphine.
- *Partial agonists:* act on mu receptors with lower efficacy than pure agonists. They are analgesic when administered alone but antagonize the effects of a pure agonist. The most characteristic of this group is buprenorphine.
- *Pure antagonists:* possess affinity for the receptors but not exhibit intrinsic effect. Inhibit or reverse the action of the agonists and do not have analgesic effects. In subjects with opioid dependence, withdrawal symp-

Table 18.1 Classification of pharmacological opioid ligands based on their affinity for the opioid receptors (mu, delta, and kappa)

	Mu	Delta	Kappa	Others
Morphine	Ag+++	Ag+	Ag+	
Diacetylmorphine	Ag+++	Ag+	Ag+	
Methadone	Ag+++	Ag+	Ag++	NMDA antagonist
Codeine	Ag++			
Buprenorphine	PA	An+++	An+++	
Fentanyl	Ag+++			
Oxycodone	Ag+++			
Hydromorphone	Ag+++		Ag+	
Hydrocodone	Ag+++			
Meperidine (pethidine)	Ag+++	Ag+	Ag+	Serotonergic activity
Pentazocine	An+	Ag+	Ag+	Norepinephric and serotonergic activity
Tramadol	Ag+			Norepinephric activity
Tapentadol	Ag+			
Naloxone	An+++	An+	An++	
Naltrexone	An+++	An+	An+++	
Nalmefene	An+++	An+	PA	

The number of symbols "+" is an indication of potency
Ag agonist, *PA* partial agonist, *An* antagonist

toms occur. They are used in cases of poisoning or overdose by its ability to reverse the effects of exogenous opioids. They are naloxone and naltrexone.

In the brain, mu receptors are highly concentrated in regions that are part of the pain and reward networks and in brainstem regions that regulate breathing. Then the agonist actions at mu receptors are responsible for the rewarding effects of opioids and analgesia, and respiratory depression, which is the main cause of death from opioid overdoses.

The main pharmacodynamic effects of opioid agonists at the mu-opioid receptor are:

- Sedation: can produce drowsiness and cognitive impairment, and at higher doses, they could produce stupor, sleep, and coma. They worsen the psychomotor performance. At very high doses, convulsions can appear.
- Euphoria: feeling of euphoria, pleasure, and a well-being feeling and reduces anxiety. The euphoria has been linked to reinforcing, abuse potential, and addiction of opioids.
- Analgesia: reduction of the sensorial and affective components of pain. They can relieve and suppress acute and chronic pain. This action is mediated by with the mu agonist action; mu receptors control the pain pathways in the medulla. Also, it has actions in the limbic and cortical systems that reduce the negative perception of pain.
- Respiratory depression: reduction of the sensitivity to CO_2 and hypoxemia at the pontine respiratory center. It reduces the number of breaths per minute and can cause an apnea. This effect is dose dependent.
- Antitussive: depression of the cough reflex at least in part by a direct effect on the cough center in the medulla. This mechanism is not well known and has no relation with analgesia or respiratory depression.
- Miosis: the pupillary constriction is related with the disinhibition of the Edinger–Westphal nucleus at the oculomotor nerve. This effect does not show tolerance and could be adequate to detect recent use of opioids.
- Nausea and vomiting: they are observed more frequently after the first administrations. It is caused by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla.
- Neuroendocrine actions: morphine actions in the hypothalamus inhibit the release of gonadotropin-releasing hormone and corticotropin-releasing hormone, producing a decrease in the luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone (ACTH), and beta-endorphin. It also stimulated the secretion of the antidiuretic hormone (ADH). By its effects in the hypothalamus, also a central hypothermia is observed.
- Muscular tone: myoclonus is a rare side effect, ranging from mild twitching to generalized spasm. In anesthetic use muscular rigidity can be observed.

The main peripheral actions are a reduction in the gastrointestinal motility, which clinically is related with constipation; some hypotension by its action in the vasomotor center and by vasodilatation; histamine release in the face, neck, and upper thorax, with a feeling of heat, flushing, and pruritus; and an increase of the tone of the detrusor muscle of the bladder.

The pharmacokinetic properties of main opioids are summarized in Table 18.2; some of them present a low oral bioavailability. The pharmacokinetics varies, depending on the route of administration (oral, intravenous, intramuscular, cutaneous, etc.) and metabolization.

Opioids are biotransformed mainly by hepatic glucuronidation and through the CYP450. Genetic differences among CYP2D6 involved in the metabolization and also the activity of major metabolites must be taken into account for possible interactions of the different opioids with other drugs. Some opioids as tramadol or codeine are transformed to its active opioid metabolites (desmetramadol or O-desmethyltramadol and morphine, respectively) by the CYP2D6, and genetic polymorphisms in CYP2D6 produce inability to convert to the active metabolites, thus making these drugs ineffective as an analgesic for

Table 18.2 Pharmacokinetic properties of main opioids

					10 mg morphine equivalence (analgesia)	
Opioid	Oral bioavailability (%)	Elimination half-life (h)	Plasma protein binding (%)	Duration of action (h)	im	po
Morphine	35–75	2–3	35	4–6	10	30–60
Slow-release oral morphine	35–75	2–3	35	12–24 h		
Diacetylmorphine	20–50	0.1	35	3–6	5	20
Methadone	70–80	15–40	80	24	10	20
Codeine	50	2–4	7	4	130	75
Buprenorphine	50(sl)/90(td)	3–5	96	6–8	0.3	0.8 (sl)
Fentanyl	20–50(po)/90(td)	2–4	80–85	1–2(im)	0.002	
Oxycodone	60–87	3–4	45	12	–	6.7
Hydromorphone	30–40	5	8–19	3–5	1.5	7.5
Hydrocodone	25	4–6	20–50	4–8	–	30
Meperidine	50	3	60	1.5–3	100	300
Pentazocine	10	2–3	60	3–6	60	150
Tramadol	68	6	4	4–6	100	100
Tapentadol	32	4–5	20	4–6	–	100–200
Naloxone	5–10	1–2	NA	0.5–2	–	–
Naltrexone	5–20	4–13a	20	24–72	–	–
Nalmefene	41	13	30	24	–	–

Im intramuscular, *po* oral administration, *sl* sublingual, *td* transdermal
[a]Half-life for 6-β-naltrexol

about 7–10% of the Caucasian population. Table 18.3 summarizes the metabolism and interactions of main opioids.

Also, other medications that can be used in patients under opioid treatments are drugs for HIV and HCV infections. In relation to antiretroviral treatment (ART) for HIV, patients on nevirapine, efavirenz, and ritonavir (including lopinavir/ritonavir and darunavir/ritonavir combinations) may require higher methadone doses [4]. The combination regimen of paritaprevir/ombitasvir/ritonavir has many interactions with psychotropics drugs including opioids as buprenorphine, fentanyl, and hydrocodone that should be used with caution (probably because ritonavir is a strong inhibitor of CYP3A). The combination regimen voxilaprevir/velpatasvir/sofosbuvir also has a caution recommendation regarding the coadministration with buprenorphine, and finally there is a warning in relation to ledipasvir/sofosbuvir that could increase dose of buprenorphine because of mild/moderate inhibition of P-gp [5]. Because of the continued update of reports of new antivirals and other medications, we suggest checking interactions of prescriptions in webs as https://www.drugs.com.

Short- and long-term opioid use is also characterized by the development of different neuroadaptative processes including tolerance, physical dependence, and addiction. Physiological dependence is manifested with the emergence of withdrawal symptoms when use of opioids is abruptly discontinued or an antagonist is administered. Symptoms include insomnia, cramps, diarrhea, nausea, vomiting, and body aches, as well as dysphoria, anxiety, and irritability. The severity of these symptoms varies, depending on chronicity, the opioid drug in question (symptoms are stronger for more potent and shorter-acting drugs), and individual variability [2].

All patients treated with opioids or misusing them will develop physical dependence, and withdrawal symptoms usually resolve promptly

Table 18.3 Metabolism of main opioids

Opioid	Phase I metabolism	Phase II metabolism	Major metabolites	Clinical effects and drug interactions
Morphine	CYP3A	UGT2B7	Morphine-3-glucuronide (M3G) Morphine-6-glucuronide (M6G)[a]	Cimetidine reduces metabolism Increase of metformin (lactic acidosis risk) Caution in renal failure (accumulation)
Diacetylmorphine			6-Monoacetylmorphine (6-MAM)[a] Morphine[a]	
Methadone	CYP3A4 CYP2B6 CYP2D6		EDDP EMDP	QT prolongation Interactions with rifampin, carbamazepine, phenytoin (>metabolism) and fluconazole, voriconazole, ciprofloxacin, fluoxetine (<metabolism)
Codeine	CYP2D6 CYP3A	UGT2B7	Morphine[a]	Risk of accumulation in renal failure 7–10% are poor metabolizers
Buprenorphine	CYP3A4 CYP2C8	UGT1A1 UGT1A3 UGT2B7	Norbuprenorphine[a] Buprenorphine-3-glucuronide Norbuprenorphine-3-glucuronide	Could precipitate withdrawal symptoms if other agonist is present Higher dose of naloxone are required in respiratory depression
Fentanyl	CYP3A4		Noralfentanil *N*-Phenylpropionamide	Bradycardia and hypotension with amiodarone
Oxycodone	CYP2D6 CYP3A		Oxymorphone[a] Noroxycodone[a]	7–10% are poor metabolizers Risk of accumulation in renal failure
Hydromorphone		UGT2B7 UGT1A3	Hydromorphone-3-glucuronide	Risk of accumulation in renal failure
Hydrocodone	CYP3A4 CYP2D6		Norhydrocodone Hydromorphone[a]	Risk of accumulation in renal failure
Meperidine	CYP2D6 CYP3A CYP2C19		Normeperidine[a]	Neurotoxic metabolite, not indicated for chronic treatment Risk of accumulation in renal failure
Tramadol	CYP2D6 CYP3A4		Nortramadol *O*-Desmethyltramadol[a]	Risk of serotoninergic syndrome (antidepressants) 7–10% are poor metabolizers
Tapentadol	CYP2D6 CYP2C9 CYP2C19	UGT1A9 UGT2B7	Hydroxy tapentadol *N*-Desmethyltapentadol	Risk of interactions with other drugs that affect noradrenergic system
Naltrexone		UGT2B7	6-β-Naltrexol	Could increase liver enzymes (dose related) Theoretical interactions with zidovudine (AZT)

[a]*Active metabolite*

within a few days but can sometimes last weeks after use is discontinued. Dependence can lead to opioid seeking as individuals attempt to avoid withdrawal symptoms, contributing to addiction by perpetuating repeated exposures.

Pharmacologic characteristics of more used opioids in opioid addiction and their treatment are described with more detail.

18.2.1 Morphine

Morphine is a natural product of the seeds of the poppy plant and the most important compound found in opium. Morphine is the prototype for opioid agonist actions.

Slow-Release Oral Morphine (SROM) has been used in some countries as an alternative

maintenance pharmacotherapy for treatment of opioid dependence with retention rates similar to methadone, with a better safety profile and greater improvements in several patient-reported outcomes, including tolerability, treatment satisfaction, and mental symptoms, as well as alleviation of cravings and withdrawal symptoms [6].

18.2.2 Diacetylmorphine (Diamorphine, Heroin)

Heroin is synthesized from morphine and is twice more active than morphine at equivalent doses due to its higher lipophilic properties. Heroin is the world's most widely misused opioid, and frequently associated with intravenous administrations, with an increased risk of bloodborne disease transmission (such HIV and hepatitis B and C) and overdoses, because of the narrow margin between recreational and lethal doses and the variations in street drug purity [7].

There are several types of heroin in the market depending on its origin and characteristics:

(a) Base heroin or Tsao-ta: comes from Southeast Asia. Its color is white or dark and is used for injection or smoking.
(b) The brown sugar: is the heroin used to be smoked. It has been mixed with other substances as caffeine, strychnine, sugars, etc. Contents vary from 25% to 50%.
(c) White heroin or hydrochloride: is also known as the Thai heroin. Its use is predominantly intravenous. It has the higher active content, sometimes more than 90%.
(d) Black heroin or black tar heroin: as its name indicates, its aspect is similar to tar; it is a black and sticky substance. It comes from America and its purity is around 20%. It is used for injection.

Heroin itself has no intrinsic opioid activity; but it is a very effective prodrug and metabolized in humans to active opioid compounds first by deacetylation to the active 6-monoacetylmorphine (6-MAM) and then by further deacetylation to morphine, when administered by parenteral route [8]. Heroin has an average half-life in blood of 3 min after intravenous administration; the half-life of 6-monoacetylmorphine in humans appears to be 3–10 min. The use of intranasal, intramuscular, and subcutaneous heroin all produces peak blood levels of heroin or 6-monoacetylmorphine within 5 min; however, intranasal use has about half the relative potency [9].

Diacetylmorphine is also used for treatment in opioid users previously not responding adequately to methadone or other opioid treatments in some countries as Switzerland, the Netherlands, Germany, Canada, and England [10]. The prescription is under special programs.

18.2.3 Methadone

Methadone is a semisynthetic opioid agonist that is used in the chronic treatment of pain and in the OUD. It has been used as a maintenance treatment for heroin addiction since the first years of the 1960s [11]. Methadone is rapidly absorbed after an oral dose, it can be detected in the blood at 15–45 min after oral administration, and peak plasma concentrations occur at 2–4 h after dosing [12]. The oral bioavailability of methadone was found to be around 70–80% in a range of doses of 10–60 mg with great interindividual variability. Methadone is highly bound to plasma proteins. Enantiomeric differences are also relevant in protein binding (the unbound fraction for (*S*)-methadone is 10% while for the (*R*)-enantiomer is 14%) and its metabolic disposition [12]. All these variables might contribute to interindividual response differences to methadone treatment. Methadone undergoes N-demethylation by multiple cytochrome P450 (CYP) enzymes including CYP3A4, CYP2B6, CYP2C19, CYP2D6, CYP2C9, and CYP2C8 [13]. Its main metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)) is inactive. (*R*)-Methadone has a longer half-life than (*S*)-methadone (38 vs. 29 h, respectively). After chronic administration, a reduction in half-life (from 55 to 22 h) has been detected because it induces its own metabolism regulated by cytochrome P450 CYP3A4 [12, 14]. Also, many

studies have demonstrated genetic variability in the coding genes involved in the pharmacokinetics of methadone metabolism and transport. These genetic variables must be considered to improve the clinical management of methadone [15]. Chronic administration of methadone leads to the gradual development of tolerance to the effects on hypothalamic-releasing factors, with resumption of normal menses and return of plasma levels of testosterone to normal within 1 year as well as return to normal levels and activity of anterior pituitary-derived ACTH and beta-endorphin and normal ACTH stimulation in approximately 3 months. Prolactin levels still rise after oral methadone dosing; however, both peak plasma levels of methadone and also prolactin are found at 2–4 h after dosing; prolactin levels usually do not exceed the upper limit of normal [16].

There are two important adverse events related to methadone: the risk of respiratory depression and the risk of cardiac rhythm disorders related to QT interval prolongation. Methadone at high doses can increase the QT interval. A QT interval longer than 500 ms increases the risk of polymorphic ventricular tachycardia, such as torsade de pointes (TdP) [17]. The mechanism of this increase has been related to the inhibitory action of methadone on the hERG voltage-gated potassium channel and also could be related to the blockade of calcium channels in the cardiac myocyte membrane and the induction of bradycardia. Risk factors that increase prolonged QTc interval in patients on methadone maintenance are female gender, cardiac disease, high doses of methadone, HIV infection chronic, and hepatitis C-induced cirrhosis [18].

In order to detect and minimize the risk for cardiac adverse events related to methadone, clinicians should follow some recommendations: (a) to obtain a complete clinical history about background related to personal and familiar heart disease; (b) to inform patients of arrhythmia risk with methadone; (c) to obtain a basal electrocardiogram with QTc measure, to detect patients with a possible congenital long QTc syndrome, and also an annual electrocardiogram and additional if doses are above 100 mg/day with every dose change; (d) in cases with QTc interval between 450 and 499 ms, patients should be monitored more frequently; (e) in cases with QTc interval equal or above 500 ms, consider to switch to another opioid substitution treatment with reduced risk of QTc enlargement (slow-release morphine, buprenorphine); and (f) potential interactions should be always taken into account, with drugs that could prolong the QTc interval and those that increase methadone plasma concentrations [19].

18.2.4 Codeine

Codeine is one of several naturally occurring alkaloids found in opium. It is more lipophilic than morphine and thus crosses the blood–brain barrier faster. Its oral bioavailability is greater than that of morphine. Codeine has very low affinity for opioid receptors; it is active only because a 10% of it is metabolized to morphine, while other metabolites are mostly inactive and excreted in the urine. Codeine is commonly used in combination to non-opioid analgesics in moderate pain (before using strong opioids) and to suppress cough via a central mechanism, at doses lower than used for analgesia [14, 20].

18.2.5 Buprenorphine

Buprenorphine is a semisynthetic opioid that it is primarily mu-opioid receptor partial agonist and a kappa antagonist. Buprenorphine has high affinity for, but low intrinsic activity at, mu receptors and displaces some full opioid agonists from receptors. For this reason, and because of buprenorphine's higher affinity for the mu receptor, full agonists cannot displace it and therefore will not exert a dose-related opioid effect on the receptors already occupied by buprenorphine, and also it can induce a withdrawal syndrome in subjects using full opioid agonists. Owing to its ceiling effect, increasing doses in humans beyond 32 mg sublingually has no greater opioid agonist effect. Two important properties of buprenorphine are relevant: (a) its apparent lower severity

of withdrawal signs and symptoms on cessation, compared with heroin and methadone, and (b) its reduced potential to produce lethal overdose when used alone in opiate-naive or nontolerant persons because of its partial agonist properties. However, it is not clear whether there is a ceiling for this effect; the respiratory depression and other effects of buprenorphine can be prevented by prior administration of naloxone, but they are not readily reversed by high doses of naloxone once the effects have been produced [21]. This suggests that buprenorphine dissociates very slowly from opioid receptors. This very slow dissociation from mu-opioid receptor seems to be responsible for its long duration of action (24–48 h) when administered on a chronic basis. In relation to the antagonist properties at the kappa-opioid receptor of buprenorphine, and its important role in mood regulation, new clinical studies about the possible antidepressant effects of buprenorphine are in development [22].

Buprenorphine has poor oral bioavailability and fair sublingual bioavailability. FDA-approved formulations of the drug for the treatment of opioid addiction are in the form of sublingual tablets that are held under the tongue and absorbed through the sublingual mucosa. After the report in many countries of the buprenorphine diversion and the intravenous misuse, a formulation in combination with naloxone was developed. In this formulation, naloxone will not precipitate withdrawal when taken sublingually because of its limited oral bioavailability; however, it may block the initial euphoric effects of buprenorphine if abused by the intravenous route and may also then precipitate acute withdrawal [23]. In the last years, with the objective of diminishing the risk of misuse, sustained-release buprenorphine formulations (a 6-month subdermal implant and a monthly injectable sustained-release; already approved by the FDA) have been developed with apparently good efficacy and safety profile [24].

18.2.6 Fentanyl

Fentanyl is a synthetic opioid synthesized in 1974 by Paul Janssen. The actions of fentanyl and its congeners (sufentanil, remifentanil, and alfentanil) are similar to other mu-opioid receptor agonists, although its potency is 50–100 fold more potent than morphine and 24–40 than heroin. It produces analgesia, drowsiness, and euphoria, the last effect less than heroin and morphine. Its half-life is not affected significantly in the case of hepatic impairment, and in renal impairment, fentanyl excretion is less affected than other opioids [25]. There are several fentanyl formulations including sublingual tablets, nasal sprays, transmucosal lozenges, transdermal patches, and injectables, which are used as anesthetic agents but also as treatment for chronic pain and supplemental medications for breakthrough pain in oncologic patients [24]. In the last years there has been a growing concern in relation to the illicitly manufactured fentanyl in the USA being used as an adulterant to heroin (for the lower cost of production and transportation because it is so potent) with a rise in overdose deaths [26]. Fentanyl, fentanyl analogues, and other new synthetic opioids (NSO) have arrived onto the illegal drug market as new psychoactive substances (NPS). They are often sold as heroin. These derivatives are more potent than fentanyl and represent a third of the opioids causing acute intoxication in the USA (Opioid Overdose Crisis).

18.2.7 Oxycodone

Oxycodone is a semisynthetic opioid with agonist activity, primarily at mu receptors. It is combined with aspirin or acetaminophen for moderate pain and is available orally without co-analgesic for severe pain. It is a popular drug of abuse, especially in the controlled-release formulation, which can be crushed for a potentially toxic, rapid "high" comparable to the effects of the immediate-release formulation [27].

18.2.8 Tramadol

Tramadol is a synthetic codeine and morphine analogue that is a weak mu agonist. It also exerts

some capacity to inhibit the uptake of norepinephrine and serotonin [28]. It is more effective in the treatment of mild and moderate pain than in the treatment of severe and chronic pain [18]. Misuse, diversion, physical dependence, abuse, addiction, and withdrawal have been reported in conjunction with the use of tramadol. The pharmacological effects are similar to those of morphine, and the main adverse effects include nausea, vomiting, dizziness, dry mouth, sedation, and headache. Respiratory depression and constipation are mild compared to morphine. Tramadol can cause seizures and possibly exacerbate seizures in patients with predisposing factors; also there is a risk of serotoninergic syndrome, especially with the use of other serotoninergic medications [28]. Recent reports indicate that it is one of the most abused opioids in Africa.

18.2.9 Naloxone

Naloxone is competitive antagonist at all opioid receptors, but with great affinity for mu receptors. Naloxone is usually administered in the streets and emergency department to revert heroin overdoses and also as an aid to distinguish causes of coma (if patient does not respond to naloxone, a non-opioid cause should be considered) [29, 30].

Naloxone is widely distributed and rapidly achieves effective concentrations in the CNS after parenteral administration. Plasma and brain concentrations fall precipitously because of rapid redistribution. The drug is rapidly cleared by hepatic biotransformation, mainly to the 3-glucuronide. The clearance is high which suggests that extrahepatic elimination may be occurring. The terminal half-life is 1–2 h. The onset of antagonist effect is extremely rapid, but the duration of action is quite brief. The duration of naloxone is nearly always shorter than that of the opioids whose effects it is intended to antagonize. It has to be taken into account that opioid reversal can sometimes have important hemodynamic consequences. Increases in systemic pressure, heart rate, and plasma levels of catecholamines can occur. Oral or sublingual administration of naloxone has very low systemic bioavailability due to marked hepatic first-pass metabolism. Enteral naloxone can block opioid action at the intestinal receptor level but has no general effects [20]. Naloxone is available in different formulations: as a solution for intravenous, intramuscular, and orotracheal injection and as a spray for nasal administration [25].

18.2.10 Naltrexone

Naltrexone is an opioid antagonist, chemically related to naloxone. Compared to naloxone, it has higher oral bioavailability and a longer duration of action that allows its administration by oral route. Naltrexone has been used for relapse prevention in opioid dependence because of its ability to antagonize all the actions of opioids. Also, there is evidence that naltrexone blocks activation by alcohol of dopaminergic pathways in the brain that are thought to be critical to reward, so it is used also in the treatment of alcohol dependence, as relapse prevention substance. The most common side effect of naltrexone is nausea. An increase of transaminases could be observed, so it is contraindicated in hepatitis or hepatic failure [30].

Naltrexone is rapidly absorbed and undergoes an extensive first-pass metabolism to 6-b-naltrexol. This is an active metabolite that probably accounts for most of the naltrexone activity. The metabolite accumulates during chronic treatment and has a terminal half-life of 13 h, so significant antagonist effects may persist for 1–3 days after naltrexone is stopped [30].

A depot formulation of naltrexone that provides 30 days of medication after a single injection has been approved for the treatment of alcoholism and heroin dependence in detoxified patients. This formulation eliminates the necessity of daily pill-taking and prevents relapse when the recently detoxified patient leaves a protected environment [31].

18.2.11 Nalmefene

Nalmefene is another long-lasting, opioid antagonist. It is the 6-methylene derivative of naltrexone. It is an antagonist at the mu- and delta-opioid receptors and a partial agonist at the kappa receptors; there is no evidence of activity in any other receptor (Tables 18.1 and 18.2). There have been described some advantages over naltrexone, including greater oral bioavailability; rapidly absorbed, longer duration of action; and lack of dose-dependent liver toxicity [32]. In Europe, nalmefene has been approved as an anticraving treatment for alcohol use disorder [33].

18.3 Opioid-Related Disorders

According to the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [34], the main opioid-related disorders are opioid intoxication, opioid withdrawal, opioid use disorder, and opioid-induced disorders (psychosis, bipolar, depression, anxiety, sleep, sexual dysfunctions, delirium, and neurocognitive).

Opioid use disorder (OUD) includes physiological, behavioral, and cognitive symptoms, ending in a repeated use of opioid drugs, despite significant problems related to such use, and is characterized by compulsion to seek and take the drug; as in other drug dependence, there is a loss of control in limiting the intake and emergence of a negative emotional state (i.e., dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented [2]. OUD can be mild, moderate, or severe depending on the number of criteria fulfilled.

In the next section we present the main disorders related to opioid use with main pharmacological and psychosocial strategies used.

18.4 Treatment of Opioid-Related Disorders

Pharmacological strategies used in the treatment of opiate overdose, withdrawal, and addiction are described in Table 18.4.

18.4.1 Opioid Acute Intoxication

Acute opioid intoxication could result from clinical overdosage, accidental overdosage, or attempts of suicide. Opioid intoxication is a life-threatening emergency. Typical triad signs are depressed consciousness or coma, depressed respiration, and miotic or pinpoint pupils. The treatment goal is to sustain or restore vital functions and to immediately reverse the overdose with an opioid antagonist (naloxone).

First, it is essential to maintain the air pathway, and then, to avoid aspiration, put the

Table 18.4 Main pharmacological strategies in opioid-related disorder treatment

	Type	Objective	Process	Pharmacological treatment
Opioid acute intoxication	Opioid intoxication	Decrease mortality	Revert opioid intoxication	Naloxone
Opioid withdrawal	Opioid detoxification	Avoid withdrawal syndrome	Detoxification	Methadone Buprenorphine Clonidine/lofexidine
Opioid use disorder	Total abstinence oriented	Remove the opioid	Detoxification + Continued total abstinence	Methadone Buprenorphine Clonidine/lofexidine +/− Naltrexone
	Opioid substitution treatment	Stabilization	To stabilize brain neurochemistry	Agonist maintenance treatment
		Harm reduction	Functional improvement	Needle exchange and other risk reduction strategies

patient in lateral decubitus position; if necessary, in case of cardiopulmonary arrest, mechanical ventilation should be applied [29]. The administration of naloxone 0.2–0.4 mg intravenously will begin to reverse the effects of an opiate overdose within 1 min. If there is no response to the initial dose, repeat doses may be administered every 2–3 min (0.5 mg, 2 mg, 4 mg, and 10 mg). If the patient has no response to 10 mg, then an opioid likely is not responsible for the respiratory depression [29]. Finally, once the consciousness level is reverted, it is important to investigate a possible suicide intention risk of the patient and to perform a psychiatric assessment.

Increasing access to naloxone is a major component to reverse the overdose epidemic, and with the increase in overdoses from fentanyl and other synthetic opioids, multiple naloxone doses are necessary for reversal. There have been developed various strategies like community educational overdose prevention programs, injectable and nasal self-administered kit formulations with higher dose, and also the use of new technologies with apps that monitor a person's respiratory rate and trigger an alert when diminished breathing is detected, and a device is being developed that automatically administers naloxone in response to a reduction in respiratory rate or oxygen saturation [35].

18.4.2 Opioid Withdrawal

The withdrawal syndrome for short-acting opioids (heroin or morphine) begins 6–12 h after last use. Early symptoms include opiate craving, anorexia, anxiety, and irritability. These are coupled with clinical signs of increased respirations and blood pressure, sweating and yawning, rhinorrhea, lacrimation, piloerection (gooseflesh), tremor, and dilated pupils. After 48–72 h, the symptoms progress to include nausea, vomiting, diarrhea, insomnia, tachycardia, abdominal cramps, and involuntary muscle spasms and limb movements. Signs subside over 5–7 days. Signs and symptoms associated with withdrawal from long-acting opioids such as methadone are similar to those described above, but they may not begin until 24–48 h after the last dose and may last for 2–3 weeks or more. Withdrawal syndrome of buprenorphine is usually less intense and of shorter duration. Withdrawal can also appear when an opioid antagonist, such as naloxone or naltrexone, is provided to a subject under any opioid agonist drug use; this is called precipitated withdrawal.

18.4.3 Opioid Use Disorder

Opioid use disorder includes physiological, behavioral, and cognitive symptoms, ending in a repeated use of opioid drugs, despite significant problems related to such use, and is characterized by compulsion to seek and take the drug; as in other drug dependence, there is a loss of control in limiting the intake and emergence of a negative emotional state (i.e., dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented [2]. Opioid addiction can be mild, moderate, or severe depending on the number of criteria fulfilled. OUD presents high rates of comorbidity (psychiatric disorders, infections such as HIV and hepatitis C), mortality (overdose), and legal and social problems [1]. There are two main therapeutic strategies in opioid addiction: abstinence-oriented treatment and medication assisted treatment (MAT).

18.4.3.1 Abstinence-Oriented Treatments

In the abstinence-oriented, the goal is to remove the abused opioid in a controlled fashion, with a complete eradication of the opioid agonist treatment. Abstinence is usually achieved in two stages: detoxification and continued total abstinence.

18.4.3.2 Detoxification

Detoxification involves the substitution of the abused opioid by other long half-life opioid agonist or partial agonist (methadone or buprenorphine, usually) or an alpha2-adrenergic agonist (clonidine or lofexidine) and a progressive reduc-

tion in order to reduce the intensity of the withdrawal syndrome [36–38].

In general, the use of long-acting opioids (such as methadone) is recommended in opioid detoxification, with a long and slow tapering, medical supervision, ancillary medications, and psychosocial treatment to improve the outcomes and reduce the risk of relapse. Offering withdrawal management as a stand-alone option to patients is neither sufficient nor appropriate. Rapid and ultra-rapid protocols for detoxification are also not recommended. Methadone detoxification guidelines recommend starting with an initial dose of 10–45 mg/day, orally, depending on the severity of opioid withdrawal symptoms. Every 2 h it is necessary to assess the intensity of withdrawal and ensure that the dose will not exceed 60 mg/day. The same dose of the first day should be administered for 2–3 days and then reduced to 5–10 mg/day until total suppression. The detoxification usually lasts 10–20 days.

When buprenorphine (or buprenorphine–naloxone) is used in the detoxification treatment, initial doses of 4–6 mg of buprenorphine are recommended, and then increase the dose until 8–10 mg/day. After 2–3 days, the recommendation is to reduce the dose to 2 mg every 1–2 days until complete suppression. It is important to administer the first dose 24 h after the last heroin use, when the first withdrawal symptoms appear, in order to avoid a precipitated withdrawal.

Alpha2-adrenergic agonists (clonidine or lofexidine) are also effective for reducing the severity of opioid withdrawal symptoms and increasing the probability of completing withdrawal management, but compared to methadone, alpha2-adrenergic agonists are somewhat less effective in mitigating withdrawal symptoms and are more likely to present adverse effects such as hypotension, specially clonidine (not US FDA approved for withdrawal); they could be used as adjunctive therapy [39].

18.4.3.3 Continued Total Abstinence

After complete opioid detoxification, naltrexone is a pharmacologic alternative to maintain the abstinence. The main advantages of naltrexone include the following: decrease in opioid craving, can be administered in a standard outpatient office setting, and the absence of abuse potential. Also, it is well tolerated with few adverse effects, except for the risk of increase of liver enzymes. Despite all these advantages, naltrexone has shown low rates of efficacy, with poor retention and high relapse rates. To improve the described problems with retention and relapse with naltrexone, an injectable sustained-release formulation has been developed with a recent trial that shows a similar safety and efficacy compared to buprenorphine, but naltrexone had a substantial induction hurdle with a lower rate of participants that succeed in the induction [40]. Only one study has compared the efficacy of depot naltrexone versus methadone maintenance treatment [41] in 46 volunteers in a prison setting. The study was randomized, and the results showed similar reductions in the use of heroin and benzodiazepines and criminality 6 months after prison release. In conclusion, depot formulations of naltrexone seem to be promising in order to improve outcomes in opioid dependence disorder in less well-integrated subjects with a strong motivation to become totally abstinent. Oral naltrexone is a treatment option for patients also with a strong motivation to become totally abstinent of all opioid agonists and very well integrated.

18.4.3.4 Medication Assisted Treatment: Opioid Substitution Treatments (OST)

The objective is to stabilize brain neurochemistry by replacing a short-acting opioid with a long-term acting opioid that has relatively steady-state pharmacokinetics, such as methadone or buprenorphine. Opioid agonist maintenance treatment has a minimal euphoric effect, blocks the euphoria associated with the administration of exogenous opioids, and eliminates the phenomenon of opioid withdrawal [2]. The most frequently studied medications for maintenance treatment are methadone and buprenorphine and, to a lesser extent, sustained-release morphine, diacetylmorphine (heroin), and (R)-methadone.

Methadone Maintenance Treatment (MMT)

In general, methadone maintenance treatment (MMT) has been considered the first-line treatment for opioid dependence. MMT has demonstrated its efficacy in retaining patients in treatment and decreasing illicit opioid use, decreasing risk behaviors related to the HIV/sexually transmitted diseases, decreasing criminal behavior related with drug use, reducing the risk of fatal overdose, and improving health-related quality of life. Methadone dosing should be based on clinically guided dose titration. The main problem with methadone has been described in the first part of this chapter and is related with an increased risk of QTc prolongation, so the electrocardiogram monitoring previously to initiate is mandatory in these patients. Methadone dosing should be based on clinically guided dose titration. Usual maintenance dosage of methadone is 60–100 mg/day; some patients achieve abstinence or are free of withdrawal symptoms when treated with less than 40 mg/day of methadone. Some studies suggest that methadone doses of 60–100 mg/day or higher are more effective than lower doses for reducing or stopping illegal opioid self-administration in opioid-dependent patients. Regarding the duration of maintenance treatment, there are no clear recommendations; however, the literature shows better improvements with longer treatments, so the advice is to favor indefinite treatments and start the suppression when significant changes in lifestyle have been made [42].

(R)-Methadone Maintenance Treatment

(R)-Methadone (or L-methadone or Polamidon®) is the active component of the racemic methadone, and it is used in Germany as the maintenance treatment of opioid use disorder. As described previously, (R)-methadone shows more affinity of the mu receptors and has more analgesic potency than racemic (R,S)-methadone. Efficacy studies show no differences between the (R)-enantiomer and the racemate [43]. As the cardiac side effects of methadone reside in the (S)-enantiomer, the substitution of the racemate by the (R)-methadone has demonstrated a reduction in the QTc interval [44], reducing the risk of sudden death in methadone-maintained patients. Unfortunately, the direct costs of the treatment with (R)-methadone are much higher than the use of the racemate.

Buprenorphine Maintenance Treatment

Buprenorphine is, after methadone, the most widely used opioid for maintenance. Buprenorphine is a partial opioid agonist, with a ceiling effect for respiratory depression and with reduced abuse potential [42]. Buprenorphine is commercialized alone or in combination with naloxone, to decrease abuse risk. The commercialization of buprenorphine in combination with naloxone is as sublingual tablets (4:1 ratio, sublingual tablets containing buprenorphine 2 and 8 mg and naloxone 0.5 and 2 mg) or as soluble film (sublingual film containing buprenorphine 2, 4, 8, or 12 mg and naloxone 0.5, 1, 2, or 3 mg).

To initiate buprenorphine or buprenorphine–naloxone treatment successfully and to avoid a precipitated withdrawal, it is essential to determine that the patient is opioid-free for at least 24 h (in case of short-acting opiates) and observe the presence of opioid withdrawal symptoms. The recommended initial dose is 4 mg sublingually and should be administered at the clinic, and the patient should remain under observation for 2 h. Supplemental doses can be given if withdrawal symptoms persist, with a maximum recommended first-day dose of 8 mg. The dose can be raised in 2–4 mg increments over the next 2–3 days. Doses of 8–16 mg buprenorphine are superior to lower doses, and doses of 12–24 mg are preferable for maintenance treatment. Doses should not exceed a maximum single daily dose of 24 mg. Because of the ceiling effect, there is no pharmacological justification for daily doses over 32 mg.

The main advantages of buprenorphine compared to methadone maintenance treatment are the lower risk of fatal respiratory depression during intoxication, the quick induction to full doses, its cardiac safety because it has no effect on the QTc interval, the lower risk of interactions, and the destigmatization of patients compared to methadone [42].

Slow-Release Oral Morphine (SROM)

In the last years, maintenance treatment with SROM for opioid dependence disorder had captured more interest as an alternative to methadone, with a better safety profile (non-QTc prolongation and lower risk of drug–drug interactions), good tolerability, treatment satisfaction, and retention [6], being included in the Canadian treatment guidelines [36]. However, in terms of efficacy, there are contradictory results in the studies performed [45]. The major concerns with SROM treatment are the risk of misuse; the severe adverse event, such as overdose; and the risk of diversion. Another problem associated with SRMO treatment is the difficulty to monitor illicit opioid abstinence as SRMO and heroin will give a positive test in the screening tests.

Diacetylmorphine (Diamorphine, Heroin) Maintenance

Diacetylmorphine maintenance has also been studied in patients with a history of unsuccessful agonist treatment in specific programs in a few countries with good acceptance by patients and public opinion [10]. The treatment has been usually prescribed alongside methadone and has demonstrated an increase in treatment retention and reduced engagement in illegal activities in patients who previously failed in other maintenance programs. The main problem is related with the rate of serious adverse events, mainly the risk of overdose; for that reason, the treatment is only recommended in patients refractory to other substitution treatments and should be provided in settings with proper medical assistance [46].

18.4.3.5 Psychosocial Interventions in Opioid Use Disorder

Psychosocial treatments are those that use any psychological or social strategy to achieve an improvement or a behavioral change. Opioid treatment guidelines (as the WHO guidelines 2009) [47] recommend the use of psychosocial treatments.

Interventions at a psychological level range from unstructured supportive psychotherapy and motivational interviewing techniques to highly structured psychological techniques. The main psychological strategies in OUD are cognitive behavioral therapy (CBT) and contingency management. Cognitive approaches primarily aim to change addictive behaviors by changing faulty cognitions that serve to maintain behavior or by promoting positive cognitions or motivation to change behavior. Behavioral approaches aim primarily to modify behaviors underpinned by conditioned learning, that is, by classical and operant conditioning. Contingency management rewards or punishes specific types of behaviors using a structured, transparent approach that increases learning of desired behaviors. Also, there is scarce knowledge about the effectiveness of psychosocial interventions alone or in combination with pharmacological strategies and which intervention is the most effective. A Cochrane review performed by Amato and cols in 2011 [48] showed no evidence that any intervention improves outcomes with opioid agonist therapy. But in a recent study [49], John Marsden and colleagues report the results of randomized controlled study where 273 patients in methadone or buprenorphine were randomly assigned to a group with a weekly psychosocial interventions (as a flexible approach performed by assistant psychologists) and medical management or to a group of treatment as usual, setting as objective the absence of unprescribed drug use. Fewer than 20% of participants met that goal, but differences where significative (being better for psychosocial intervention group), and authors conclude that overall, the intervention was cost-effective.

In terms of social interventions, the main interventions used in substance use disorders are as follows: vocational training, which includes a range of programs designed to help patients find and retain employment; housing services that can vary from group accommodation for the homeless to more stable, affordable, long-term accommodation; the referral to participate in activities, such as enjoying leisure activities of their choice; and self-help groups, which, in the context of opioid use disorder, are voluntary, small-group structures formed by peers to assist each other in their struggle with opioid dependence. Usually abstinence ori-

ented, they often provide both material assistance and emotional support and promulgate an ideology or values through which members may attain a greater sense of personal identity. Social skills training refers to methods that use the principles of learning theory to promote the acquisition, generalization, and durability of skills needed in social and interpersonal situations. Training should take place in the context of real everyday life experiences, not in closed, unrealistic settings.

In opioid use disorder, the efficacy of psychosocial interventions has little evidence due to the difficulty in the design of controlled trials.

18.4.3.6 Harm Reduction Strategies

Broadly defined, harm reduction refers to policies, programs, and practices that aim to reduce the adverse health, social, and economic consequences of licit and illicit substance use. It includes programs of needle/syringe exchange, overdose prevention with take-home naloxone, and supervised injection or consumption services. Harm reduction strategies could be perceived by patients or wider public with concern generating possible barriers, but there is no evidence that these actions could promote the consumption; rather to the contrary, the research has shown that this approach could even promote entry into addiction treatments besides the reduction of risky behaviors, HIV and HCV infection, and overdose deaths [36].

18.5 Conclusion

This chapter has reviewed the last evidence and clinical practice recommendations in relation to opioid-related disorders. In the context of the current opioid crisis, there is a growing concern about how to mitigate the impact and avoid further losses, and in that sense, naloxone remains a fundamental tool to prevent deaths from overdoses, with development of different programs and studies to improve the accessibility of this drug. Methadone, buprenorphine, and, to a lesser degree, naltrexone are effective drugs for the treatment of long-term maintenance, with new formulations that probably will facilitate compliance by the patient avoiding relapses. It is necessary to study the inclusion of alternatives such as SROM and diacetylmorphine, already available in some countries, and also to elucidate with greater clarity the best recommendation of psychosocial interventions in patients with opioid use disorder.

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19 Addiction of Hallucinogens, Dissociatives, Designer Drugs and "Legal Highs": Update on Potential Therapeutic Use

Magi Farré, Esther Papaseit, Francina Fonseca, and Marta Torrens

Contents

M. Farré (✉) · E. Papaseit
Universitat Autònoma de Barcelona, Barcelona, Spain

Hospital Universitari Germans Trias i Pujol (IGTP), Badalona, Spain
e-mail: mfarre.germanstrias@gencat.cat

F. Fonseca · M. Torrens
Universitat Autònoma de Barcelona, Barcelona, Spain

Institut de Neuropsiquiatria i Addiccions, Hospital del Mar, Barcelona, Spain

IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain

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Abstract

Hallucinogenic drugs have as their primary effect the production of disturbances of perception. Hallucinogens can be classified according to their chemical structure as indoleamines (similar to serotonin), phenethylamines (similar to catecholamines), dissociatives (phencyclidines) and others (including salvinorin, dextromethorphan, muscarinic antagonists and cannabinoids). The hallucinogenic effects appear to be related to the agonistic action on 5-HT2A receptors in the cortex. These actions seem to cause a functional imbalance at various levels (cortical areas, limbic system, which is a group of brain structures involved in emotional regulation), contributing to distort the integrative action. Hallucinogens produce substance use disorder, induce acute tolerance to its effects and do not present withdrawal syndrome. The novel psychoactive substances (NPS) can induce substance use disorder, intoxication and in some cases withdrawal syndrome (for those with psychostimulant properties). Depending on the substance and pharmacological effects, the DSM-5 diagnostic criteria for hallucinogens or stimulants can be applied. The therapeutic aim in these cases is to reduce consumption and achieve the abstinence. There are no specific drugs for treating the addiction caused by these substances. Some hallucinogens are under evaluation for its therapeutic use in different mental disorders.

Keywords

Hallucinogens · LSD · Psilocybin · Mescaline MDMA · Esketamine · Therapeutic use Substance use disorder · New psychoactive substances

19.1 Introduction

This chapter is a review of the different families of hallucinogenic, dissociative and novel psychoactive substances. It provides a brief historical introduction, origin, chemistry and mechanism of action, its pharmacological and adverse effects and the relevant psychiatric clinical aspects. In addition, an update on its potential therapeutic use is included.

Hallucinogenic drugs have as their primary effect the production of disturbances of perception, thought or mood at low doses with minimal effects on memory and orientation. A hallucination is defined as a sensory perception without objective reality. An illusion is a perceptual distortion of an actual stimulus in the environment; it is a distortion of the perceived. Hallucinations can develop in any sensory modality but most commonly are visual or auditory in nature.

Subjects with hallucinations induced by acute consumption of a hallucinogenic are aware that the experience is caused by the substance and are able to maintain a sense of reality. There are a variety of widely accepted synonyms for halluci-

nogens, including the terms psychedelics and psychotomimetics.

Hallucinogens include a diverse group of substances with different chemical structures, including natural products and synthetic drugs. Hallucinogens can be classified (Table 19.1) according to their chemical structure as indoleamines (similar to serotonin), phenethylamines (similar to catecholamines), dissociative (phencyclidines) and others (including salvinorin, dextromethorphan, muscarinic antagonists and cannabinoids). Hallucinogens can be found natu-

Table 19.1 Classification of hallucinogens

Indoleamides	LSD derivatives	Lysergic acid amides: ergine, isoergine Lysergic acid diethylamide (LSD-25 or Lysergide)
	Substituted tryptamines	Psilocybin Psilocin O-Acetylpsilocin (4-acetoxy-DMT) Dimethyltryptamine (DMT) Bufotenine (cebilcin, 5-OH-DMT) Diethyltryptamine (DET) 5-Bromo-N,N-dimethyltryptamine (5-Bromo-DMT) 5-Methoxy-N,N-dimethyltryptamine (5-methoxy-DMT) 5-Methoxy-dimethyltryptamine (5-MeO-DMT) Ibogaine Ayahuasca (contains DMT)
Phenethylamines	Methoxyamphetamines "hallucinogenic amphetamines"	Mescaline (3,4,5-trimethoxyphenethylamine) 4-Bromo-2,5-dimethoxyamphetamine (DOB) 4-Methyl-2,5-dimethoxyamphetamine (DOM, serenity, tranquility and peace or STP) 2,4,5-Trimethoxyamphetamine (TMA-2) paramethoxyamphetamine (PMA) 4-Bromo-2,5-dimethoxyphenylamphetamine (2CB-MFT) 2,5-Dimethoxy-4-bromo-phenethylamine (2-CB, nexus) 2,5-Dimethoxy-4-iodophenethylamine (2C-I) 2,5-Dimethoxy-4-ethylthiophenethylamine (2C-T-2) 2,5-Dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7) 8-Bromo-2,3,6,7-benzo-dihydrodifuran-ethylamine (2CB-Fly) Bromo-benzodifuranyl-isopropylamine (bromo-dragonfly)
	Methylenedioxyamphetamines "entactogen amphetamines"	3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy", "Adam") 3,4-Methylenedioxyamphetamine (MDA, "love pill") 3,4-Methylenedioxyethylamphetamine (MDEA or MDE, "Eve") N-Methyl-1-(3,4-methylenedioxyphenyl)-2 butanamine (MBDB) 3,4-Methylenedioxymethcathinone (methylone, "explosion") 4-Methyl methcathinone (mephedrone) β-keto-N-methylbenzodioxolylpropylamine (bk-MBDB, butylone)

(continued)

Table 19.1 (continued)

Dissociatives (phencyclidines)	Phencyclidine (PCP) Ketamine Methoxetamine 3-Methoxyphencyclidine (3-MeO-PCP)	
Others	Opioid derivatives Anticholinergics Salvinorin A Thujones Muscimol and ibotenic acid Cannabinoids	Dextromethorphan Atropine, scopolamine, trihexyphenidyl *Salvia divinorum* (contains salvinorin A)

rally in some plants and animals and can be synthesized in the laboratory. Some hallucinogen drugs are included in the category of designer drugs, legal highs and new psychoactive substances [1, 2].

19.2 Classical Hallucinogens

19.2.1 Origin and Synthesis

Hallucinogenic substances are among the oldest substances used by human kind. Many cultures recorded using certain plants specifically to induce visions or alter the perception of reality. Often these hallucinations were part of a religious or initiation experience. In this context they are referred to as entheogens. Shamans in Siberia were known to eat the hallucinogenic mushroom *Amanita muscaria*. Peyote, a cactus found in the southwestern United States and Mexico, was used by native peoples, including the Aztecs, to produce visions.

The modern synthetic drug era began in the late 1930s with the synthesis of lysergic acid diethylamide (LSD) by the Swiss chemist, Albert Hoffman. Some years later in 1943, after accidentally absorbing a small amount, he experienced its psychoactive effects. After World War II, there was an explosion of interest in hallucinogenic drugs in psychiatry, on either it's potential for psychotherapeutic applications or on its use to produce a "controlled psychosis", in order to understand psychotic disorders. LSD was marketed by Sandoz laboratories under the trade name Delysid ® as a potential tool for psychotherapy in the 1950s. The growing popularity of LSD in the 1960s associated with the hippie movement resulted in its ban in the United States in 1967. In recent years, there is a new interest in the investigation of therapeutic use of hallucinogens [3, 4].

19.2.2 Epidemiology and Pattern of Consumption

For a number of years, the overall prevalence levels of LSD and hallucinogenic mushroom use in Europe have been generally low and stable. Among young adults (15–34 years), national surveys report last-year prevalence estimates of less than 1% for both substances in 2017 or most recent survey year, with the exception of Finland (1.9%) and the Netherlands (1.6%) for hallucinogenic mushrooms and Norway (1.1%) and Finland (1.3%) for LSD [5].

The lifetime prevalence of LSD use in the United States in students on the 12th grades is among 4.9–5.1 in the past 3 years and similar for hallucinogens other than LSD. The trend in annual prevalence in young adults (30 years) is lower, among 0.2–0.9% in the last 3 years [6].

In the United States, of all substance use disorders, other hallucinogen use disorder (exclude dissociative) is one of the rarest. The 12-month prevalence is estimated to be 0.2% among 12- to 17-year-olds and 0.4% among adults age 18 and older in the United States [7].

19.2.3 Mechanism of Action

LSD activity is predominantly on serotonin receptors (5-HT), but also on dopamine receptors. LSD as other classical hallucinogens are partial agonist on serotonin 5-HT2 receptors and also on the 5-HT1A/1C receptors, both presynaptic and postsynaptic. There is a good correlation between the relative affinity of these compounds for 5-HT2 receptors and their potency as hallucinogens in humans.

The hallucinogenic effects appear to be related to the agonistic action on 5-HT2A receptors in the cortex. Ketanserin, a 5-HT2 antagonist, blocks some of the specific effects of LSD and other hallucinogens. It also activates the dopaminergic receptors and causes glutamatergic activation. All these actions seem to cause a functional imbalance at various levels (cortical areas, limbic system, which is a group of brain structures involved in emotional regulation), contributing to distort the integrative action. At a peripheral level, it acts as a serotonergic antagonist and also has an action in dopaminergic system (D1 and D2 at least) and is alpha adrenergic. Most classical hallucinogens share actions of LSD, but dissociative anaesthetics and dextromethorphan are NMDA receptor antagonists (N-methyl-D-aspartate or NMDA), and salvinorin A is a potent kappa-opioid receptor agonist. Some anticholinergic derivatives (*Amanita muscaria* mushroom, plants containing atropine derivatives) at high doses can induce an intoxication with hallucinations due to its action as antagonists of the muscarinic receptor in the CNS [1, 8, 9].

19.2.4 LSD

LSD is an extremely potent substance; active doses are between 0.5 and 2 microgram/kg (50–150 micrograms per dose). LSD is well absorbed by the gastrointestinal tract. It is rapidly metabolized, and only 1% of the dose is excreted in urine without being biotransformed. It undergoes hydroxylation (addition of a group-OH) and conjugation with glucuronic acid in the liver. Its half-life is about 3 hours (2–5 hours), but its effects last longer [2, 10].

Psychoactive effects peak at 2–4 hours and can last for up to 12 hours depending on dose, tolerance, body weight and age. Users of LSD typically experience autonomic symptoms within several minutes and psychoactive effects approximately 10 minutes later. The autonomic symptoms are mainly sympathomimetic, such as elevated blood pressure and pulse, diaphoresis, piloerection, nausea, hyperreflexia and tremor. Anisocoria (unequal pupils) and hippus (rhythmically dilating pupils) are not uncommon [10].

Sensory effects generally appear 1 hour after administration. Initially there are fluctuations or changes in brightness or illumination, shapes are distorted and the colours are more intense and bright and constantly vary in pitch and intensity. Auditory distortions are less common. At higher doses, synesthesia may occur (perceiving a sensation in a different modality such as hearing colours). Distortions regarding the perception of time include time halting, stretching, repeating and ceasing to exist. The sense of self can change dramatically, even to depersonalization. It feels as if the mind left the body and there was a union of the self with the universe. There are frequent religious, philosophical or mystical experiences. Psychological symptoms include multiple mood alterations, ranging from happy to sad. When the overall experience is perceived as enlightening or emotionally stimulating, it is referred to as a "good trip". Other times the experience might be nightmarish, with fears of insanity or losing control and anxiety. Such negative experiences are referred to as "bad trips". The cause of good trips versus bad trips is not known. The psychic experience generally lasts 8–12 hours and is often followed by a pleasant "psychic numbness" [1, 2, 10].

19.2.5 Hallucinogen Use Disorder

Long-term hallucinogen use is not common. Tolerance to the psychological effects of LSD and other hallucinogens, but not the physiological effects, develops quickly. In contrast to highly addictive drugs such as cocaine and heroin, they do not produce physical dependence or withdrawal syndrome upon cessation of consumption.

Usually, there is a clear and accurate memory of what happened during the hallucinogenic experience [1, 2, 8].

19.2.6 Intoxication of Hallucinogens

Patients have symptoms of sympathetic activation, perceptual changes, and psychiatric symptoms (agitation, anxiety, panic, psychosis). There are also frequent "bad trips" that present with psychiatric symptoms (anxiety or important panic reaction). Intoxications are occasionally accompanied by delirium (is a separate diagnostic category). The elimination of the substance gradually improves symptoms. There are no documented fatalities from LSD use, but fatal accidents and suicides have occurred during intoxication.

19.2.7 Hallucinogen Persisting Perception Disorder

It is defined as "the transient recurrence of disturbances in perception that are reminiscent of those experienced during one or more earlier Hallucinogen Intoxications". Flashbacks are referred to as hallucinogen persisting perception disorder by the DSM-5 when they cause significant distress [11].

The most common phenomena are visual distortions such as colour confusion, geometric hallucinations and trailing, but the content of the flashback may involve any of the senses. It is not known what causes flashbacks. Theories include persisting damage to visual processing systems, dysfunction of inhibitory cortical interneurons, reverse tolerance and that they are an atypical dissociative state. Flashbacks may occur several days to several years after the antecedent use of LSD and have been reported with mescaline, phencyclidine and marijuana. Some users find these episodes pleasant and even refer to them as "free trips". For others they are terrified about it and they recur frequently. An antecedent good trip does not predict a good flashback. It is unclear what determines who will experience flashbacks and whether or not the experience will be pleasant.

Flashbacks have reportedly been induced by many situations including stress, exercise, pregnancy, sexual intercourse, dark environments, flashing lights, monotony and use of other psychoactive drugs. It is estimated that anywhere from 15% to 60% of LSD users experience flashbacks. The flashback experience is often precipitated by psychiatric illness as well as another drug use. Regardless of treatment, the frequency of flashbacks tends to decrease with time. Suicidal behaviour, major depressive disorder and panic disorders are potential complications [2, 12].

19.2.8 Persistent Psychosis Related to Mental Illness

Occasionally, LSD appears to precipitate a "persistent psychosis" characterized by visual hallucinations, mania, grandiosity and religiosity. It is estimated to occur in 0.08–4.6% of people who have used lysergic acid diethylamide.

Chronic effects include descriptions of permanent schizoid disorders and subsequent or prior ingestion associated with LSD. Although the association between the occurrence of permanent psychosis and LSD is well established in various publications, it is not known precisely what the actual risk is. It seems that LSD would not be the direct cause of the development of permanent disorders, but LSD intake would act as a trigger of a preexisting disease state [2, 8].

19.2.9 Hallucinogen-Induced Affective Disorders

While feeling overwhelmed, scared and afraid of losing control occurs in panic attacks, LSD intoxication is further characterized by dramatic and persistent perceptual distortions. As with any altered mental state, the clinician should have a low threshold for suspecting delirium. Unlike delirium, there is no fluctuation level consciousness with LSD intoxication. There is no specific

pharmacological treatment for this disorder. When the patients stop the consumption, anxious-depressive syndrome may appear requiring symptomatic treatment [2, 8].

19.2.10 Somatic Complications of Hallucinogens

Although LSD and other hallucinogens are considered relatively safe when compared with other drugs of abuse, there are case reports of respiratory failure, hyperthermia and coagulopathies associated with massive doses. Early on a relationship between lysergic acid diethylamide and chromosomal damage was suspected, but this has been consistently refuted and lysergic acid diethylamide does not appear to be teratogenic. LSD, however, does induce uterine contractions which could disrupt pregnancy.

19.2.11 Treatment of Hallucinogen Use Disorder

The aim is to reduce consumption and achieve the abstinence. It is easy to stop consuming initially, because there is no physical dependence, but abstinence is more difficult at long term. Often bad trips facilitate abstinence or not to repeat the experience. As in the other drug addiction programmes, psychiatric and psychological support components are used.

There are no specific drugs for treating disorders caused by these substances. Psychotropic drugs will be used according to the patient's symptoms (benzodiazepines, antipsychotics, antidepressants). The "bad trip" generally does not require inpatient hospitalization because of its limited time course and quick recovery. The patient should be placed in a quiet, non-stimulating environment and provided continuous reassurance that his or her state of mind is drug induced and will not result in permanent brain damage. When medications are needed, benzodiazepines are probably the best choice, as long as delirium has been ruled out. The use of neuroleptics should be reserved for instances where none of the aforementioned efforts have succeeded. High-potency (less anticholinergic) neuroleptics should be used because anticholinergics have been associated with paradoxical reactions such as hypotension and anticholinergic crises. The use of haloperidol and chlorpromazine has a high potential risk of favouring the occurrence of seizures [1, 2, 8].

19.2.12 Mescaline

Mescaline is the 3,4,5-trimethoxyphenethylamine. It is a phenethylamine hallucinogen found in several species of North and South American cacti, including peyote (*Lophophora williamsii)* and San Pedro. Mescaline was first isolated from peyote cacti in 1896 and was synthesized approximately 20 years later.

Natural peyote has a bitter taste. It is dried and chewed, soaked in water and drank or injected. The hallucinogenic dose is approximately 5 mg/kg (0.3–0.5 g). Each button contains about 50–100 mg of mescaline, and users typically ingest 3–8 buttons. Within the first 30 minutes, before the onset of psychological symptoms, users can experience nausea, vomiting, restlessness and headaches. By 1–2 hours, however, these unpleasant physiologic symptoms dissipate, and the psychic phase characterized by euphoria, sensory distortions, and feelings of confidence begins. The entire experience lasts up to 12–14 hours. As in the case with LSD and the other serotonergic hallucinogens, tolerance develops rapidly, and physical dependence does not occur. Treatment of acute intoxication and adverse consequences as with LSD and psilocybin involves reassurance and use of benzodiazepines if necessary [1, 2, 4].

19.2.13 Tryptamines

There are a number of noncontrolled tryptamines that are used for their psychedelic properties. They have effects similar to the tryptamines already controlled such as psilocybin (found in *Psylocybe* mushrooms or "magic mushrooms")

or dimethyltryptamine (DMT). Tryptamines can be synthesized, although they also exist in plants, fungi and animals [1].

Albert Hoffman isolated and then synthesized psilocybin. It was marketed by Sandoz laboratories under the trade name Indocybin ® as a potential tool for psychotherapy in the 1960s. The mushrooms can be eaten fresh, dried or brewed. They are usually ingested orally. Psilocybin is a prodrug that is converted in the body into the pharmacologically active compound psilocin by a dephosphorylation reaction. Typical doses of psilocybin range from 4 to 20 mg (40 μg/kg) corresponding to 1–2 g of dried mushrooms. Sympathomimetic symptoms occur at lower doses (3–5 mg), and psychological effects are elicited by doses above 8 mg. Psychological effects begin within 30 minutes of ingestion, peak at 2–3 hours and dissipate by 12 hours. Psilocybin occasioned mystical-type experiences. Only one third of "magic mushrooms" bought on the street actually contain psilocybin (many are simply store-bought mushrooms laced with phencyclidine), and there are many wild poisonous mushrooms. Adulteration and misidentification are the most common causes of serious adverse outcomes. As with the other serotonergic hallucinogens, tolerance develops quickly but physical dependence does not occur [1, 13, 14].

19.2.14 Dextromethorphan

Dextromethorphan is the dextro isomer of levorphanol, a codeine derivative, used as a cough suppressant at doses between 15 and 30 mg orally every 6–8 hours. It is marketed in single or in multicomponent medicines for the treatment of symptoms associated with the common cold or flu. It is a hallucinogen when administered at high doses of 240–480 mg.

Dextromethorphan hallucinogenic effects are due to its antagonistic action on NMDA glutamate receptors. It has no opioid activity.

Readily absorbed orally, it is metabolized to dextrorphan, which is the active ingredient in cough by cytochrome P450 CYP2D6. Up to 5–10% of Caucasians have a deficiency of this isoenzyme and therefore cannot metabolize dextromethorphan to dextrorphan (poor metabolizers). The elimination half-life is 1.5–4 hours for dextromethorphan in extensive metabolizers. It is a minority used substance, commonly used as ketamine to provoke feelings of mind-body separation and the so-called near-death experiences. Poisoning presents with light-headedness, fatigue, nausea and vomiting and ataxia. Also described are nystagmus, mydriasis or even coma and death, plus cases of psychosis, dystonia and serotonin syndrome. In case of poisoning, supportive measures and symptomatic treatment are recommended [1, 15].

19.2.15 *Salvia divinorum*

Salvinorin A is the psychoactive substance in the plant *Salvia divinorum*. It can induce dissociative effects and is a potent producer of visual and other hallucinatory experience. Salvinorin A appears to be the most potent naturally occurring hallucinogen. Salvinorin A is present in the dried plant at about 0.18%. It is a potent and selective κappa-opioid receptor agonist; in addition, it is a potent D2 receptor partial agonist, and it is likely this action plays a significant role in its effects as well. *Salvia divinorum* is usually smoked and produces rapid and intense effects with a short action (15–30 minutes). Its effects include various psychedelic experiences, including past memories (such as revisiting places from childhood memory), merging with objects and overlapping realities (such as the perception of being in several locations at the same time). In contrast to other drugs, its use often prompts dysphoria, i.e. feelings of sadness and depression, as well as fear. In addition, it may prompt a decreased heart rate, slurred speech, lack of coordination and possibly loss of consciousness.

Differing studies suggest no overall consensus so far with regard to the long-term effects of *Salvia* on mood [1, 2].

19.2.16 Ayahuasca

Ayahuasca, also commonly called *yagé*, is a hallucinogenic brew of various psychoactive infusions or decoctions prepared with the *Banisteriopsis caapi* vine (that contains the beta-carboline alkaloids harmaline and harmine). It is either mixed with the leaves from the genus *Psychotria* (*Psychotria viridis*), which contains dimethyltryptamine (DMT). DMT is not absorbed by oral route because it is metabolized by deamination enzymes in the gut, but when the two plants are ingested together, the beta-carboline alkaloids inhibit the deamination enzymes that ordinarily degrade DMT (monoamine oxidase, MAO). Ayahuasca is used largely in religious rituals. The psychedelic effects of ayahuasca include visual and auditory stimulation, the mixing of sensory modalities and psychological introspection that may lead to great elation, fear or illumination. It produces intense vomiting and occasional diarrhoea. In native or religious communities using ayahuasca, there is no evidence of psychological maladjustment, mental health deterioration or cognitive impairment [4, 16, 17].

19.2.17 Ibogaine

Ibogaine is an indole alkaloid found in plants as *Tabernanthe iboga*. The plant originates in Africa and traditionally is used in sacramental initiation ceremonies. Ibogaine is a hallucinogen at the 400-mg dose range. Ibogaine is a tryptamine that acts as an agonist for the 5-HT2A receptor. In addition it also acts as an antagonist of the NMDA receptor set and an agonist for the kappa-opioid receptor. Ibogaine is metabolized in the human body by cytochrome P450 CYP2D6, and the major metabolite is noribogaine (12-hydroxyibogamine). Noribogaine is most potent as a serotonin reuptake inhibitor and acts as a moderate kappa-opioid receptor antagonist and weak mu-opioid receptor full agonist. In recent years ibogaine has been studied and even patented as a pharmacotherapy for opiate and other addictions involving doses that range as high as 1500 mg orally. There are not well-controlled studies in humans assessing its efficacy in opiate detoxification. The ingested material is taken from the plant or pure powder. Ibogaine can produce a QT-interval prolongation and induce ventricular tachycardia after initial use. Fatalities following ibogaine ingestion are documented in the medical literature [18–20].

19.3 Dissociatives

Dissociatives include phencyclidine (PCP, angel dust), ketamine (Special K), esketamine and other recent derivatives that sometimes are classified in the novel psychoactive substances category (as methoxetamine, methoxydine or 4-MeO-PCP, among others). Chemically, dissociatives are arylcyclohexylamine derivatives. These substances were developed as anaesthetics. Phencyclidine quickly was discarded because of a high frequency of postoperative delirium with hallucinations. It was classified as a dissociative anaesthetic because, in the anaesthetized state, the patient remains conscious with analgesia, with staring gaze, flat facies and rigid muscles. The use of ketamine persists, especially in animals and humans, as analgesic and anaesthetic.

19.3.1 Phencyclidine

Phencyclidine is just consumed in Europe but is very common in the United States. In the United States, 2.5% of those ages 12 and older acknowledged ever using PCP. The highest lifetime prevalence was in those aged 26–34 years (4%), whereas the highest proportion using PCP in the last year was in those aged 12–17 years (0.7%) [6, 7].

PCP is injected intravenously, smoked, snorted or ingested orally. It is a substance that causes medical complications resulting in often more toxic than LSD. It is estimated that up to 3% of deaths in drug users in the United States are due to phencyclidine.

Phencyclidine is an antagonist of NMDA glutamate receptors. It also activates dopaminergic ventral tegmental area, the area starting in the reward pathway. There is tolerance to the effects, but not physical dependence. Only a small percentage of daily users tend to use it infrequently. The elimination half-life is 21 hours. At low doses (less than 5 mg), ataxia, dysarthria, blurred vision, nystagmus and weakness are produced. At higher doses (5–10 mg), hypertonia, hyperreflexia, hypertension, tachycardia, sweating, fever, vomiting, stereotyped movements and muscle stiffness appear. Often there is emergence of aggressive and transient confusional episodes (with psychomotor agitation, belligerence and impulsivity). Also it induces changes in perception, disorganized thinking and feeling of unreality. And at even higher doses, it produces analgesia, amnesia and coma.

The intoxication is a medical emergency because it can be severe and life-threatening. Hyperpyrexia, muscle stiffness, seizures, severe hypertension, intracerebral bleeding and respiratory depression can be observed. Patients go to the emergency room with high hostility, aggressiveness, agitation, anxiety and self-injurious behaviour. It is the substance that produces more pictures of psychosis. It is symptomatically with the administration of anxiolytics (diazepam) and antipsychotics (haloperidol) [2, 8].

19.3.2 Ketamine

Ketamine has two optical isomers: S and R; the S-(+) isomer is more potent than the R(−) isomer. Ketamine is used by intramuscular or intravenous route as analgesic and anaesthetic. Ketamine has been evaluated for the therapy of treatment-resistant depression. Recently, the S-isomer or esketamine has been recently marketed in some countries for the treatment of treatment-resistant depression in conjunction with an oral antidepressant [21].

The recreational use of ketamine has been reported among subgroups of drug users in Europe for the last two decades. National estimates, where they exist, of the prevalence of ketamine use in adult and school populations remain low. In 2017, last-year prevalence of ketamine use among young adults [16–34] was estimated at 0.6% in Denmark and 1.7% in the United Kingdom [5]. In the United States the past-year use of ketamine appears to decline among 12th graders (1.2–0.7% over the past 3 years) [6].

Although the pharmaceutical presentation is injectable solution, it is transformed and crystallized in powder to consume. The illegal use of ketamine (Special K, Super K, kit kat, K) has been increasing in recent years and is part of the so-called club drugs, drugs used in electronic music parties. Another type of consumption is related to the search for new sensations. Consumers also use ecstasy and gamma hydroxybutyrate (GHB). Like PCP, ketamine is an antagonist of the NMDA glutamate receptors. It is administered by injection (intramuscular or intravenous), orally, smoked and inhaled. The elimination half-life of ketamine is 2–3 hours. The effects are fast, short-lasting and dose-dependent and can cause perceptual changes (from dissociation body sensation to near-death experiences) and psychopathological reactions similar to those of phencyclidine [21].

Appealing effects described by users include visual hallucinations and out-of-body experiences; undesirable effects include memory loss and decreased sociability. General central nervous system depressant effects include poor concentration and poor recollection similar to alcohol intoxication, which is not unexpected for an anaesthetic drug. Ketamine effects include profound changes in consciousness and psychotomimetic effects such as changes in body image (feeling that the body is made of wood, plastic or rubber) and possible feelings of spiritual separation from the body, including out-of-body experiences. At low doses, users describe mild dissociative effects, distortion of time and space and hallucinations. At large doses, users experience severe dissociation with intense detachment such that their perceptions seem to be located deep within their consciousness and reality is far off in the distance; this is called the “K-hole”. The analgesic and dissociative effects may result in injury or even death in users.

Tolerance develops rapidly to the desired effects, resulting in reduced length of the subjective experience and requiring an increase in dose to maintain the expected effects. Users escalate the amount used to achieve the full hallucinogenic experience, up to seven times the original amount. Use of higher recreational doses can result in more adverse effects, especially physiological side effects. Use of very high doses can result in onset of full anaesthetic effects, which may result in an overdose situation for a recreational user. Continued use of ketamine or phencyclidine despite experiencing these consequences constitutes addiction (using the phencyclidine use disorder criteria). Some people develop compulsive consumption, recalling more the type of use of cocaine or psychostimulants [2].

The clinical symptoms of intoxication from ketamine are tachycardia, altered consciousness, disorganized speech and nystagmus. Treatment consists of supportive measures. Some ketamine users suffer urinary symptoms such as urinary frequency, urgency, dysuria and haematuria, which improve or disappear after cessation of use [8, 22].

19.4 Designer Drugs and "Legal Highs": MDMA and New Psychoactive Substances

19.4.1 Definitions

The emergence of new psychoactive substances that are not controlled under existing drug laws is not a new phenomenon. Over the last 20 years, a variety of terms and definitions have been used for new psychoactive substances that emerge on the market and are not under international control. Actually, the preferred term is new/novel psychoactive substances (NPS).

The emergence started in the 1970s with the denominated "designer drugs". They were defined as a psychoactive substance produced from chemical precursors in a clandestine laboratory, which, by slight modification of the chemical structure, has been intentionally designed to mimic the properties of known psychoactive substances and which is not under international control (Buchanan and Brown 1988). Over the past few years, the globalization and the massive use of the Internet allowed the unprecedented growth in both the number and availability of these substances. In the European Union (EU), 24 novel psychoactive substances were identified for the first time in 2009, 71 in 2013, 98 in 2015 and 51 in 2017 [23].

More recently, "legal highs" has been used as an umbrella term for unregulated novel psychoactive substances, or products claiming to contain them, which are intended to mimic the effects of controlled drugs. The term includes a wide range of synthetic and/or plant-derived substances and products. These may be marketed as "legal highs" (emphasizing "legality"), "herbal highs" (stressing the natural/plant origin), as well as "research chemicals" and "party pills". "Legal highs" are usually sold via the Internet or in bricks and "head shops" or "smart shops". In most cases they are intentionally mislabelled with regard to their intended use (e.g. labelled as "not for human consumption", "plant food", "bath salts", "room odourizers", "incenses") and the active substances that they contain. This "legal highs" market can be distinguished from other drug markets by the speed at which suppliers circumvent drug controls by offering new alternatives to restricted products.

The NPS is defined by the United Nations Office on Drugs and Crime as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat". The term "new" does not necessarily refer to new inventions—several NPS were first synthesized 40 years ago—but to substances that have recently become available on the market [24].

19.4.2 Origin and Synthesis

As mentioned above, the term "designer drug" was coined in the 1980s. It originally referred to

various synthetic opioids, mostly based on modifications of fentanyl (alfa-methyl-fentanyl) and pethidine [25]. The term entered widespread use when 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") experienced a boom in the mid-1980s, first in the United States, followed by Europe in the 1990s, and then in other parts of the world. Another term that emerged in the late 1990s and early 2000s is "research chemicals" (RC). The term was coined by some marketers of designer drugs, specifically, psychedelic drugs of the tryptamine and phenethylamine families. The idea was that by selling the chemicals for so-called scientific research rather than for human consumption (they included an advice of "not for human use or consumption"), drug laws could be circumvented. The same strategy was behind the marketing of some of the cathinone-related substances as "bath salts" not intended for human consumption.

Substances sold as "legal highs" are mainly manufactured in chemical laboratories in Asia, according to the International Narcotics Control Board and the Europol, although some manufacture also takes place in Europe, the Americas and other regions. They are legally imported, either as chemicals or as packaged products [5].

New psychoactive substances can be classified as shown in Table 19.2.

Phenethylamine, including MDMA, and tryptamine derivatives are shown in Table 19.1 (see Sect. 19.1. Introduction).

19.4.3 Epidemiology and Pattern of Consumption

The use of NPS has grown rapidly over the past decade, in contrast to the prevalence rates for the use of internationally controlled drugs, which seem generally to have stabilized in the same time period [26].

According to United Nations, the number of stimulant NPS identified over the period 2009–2017 increased more than fourfold, from 48 substances in 2009 to a peak of 206 in 2015, a number that has remained stable since then [24].

Table 19.2 Classification of substances categorized as NPS based on the systems used by UNODC and EMCDDA. Some substances of each class are included as examples

Group	Substances
Synthetic cannabinoids	JWH-018 JWH-073 JWH-200 JWH-250 AM-694 CP 47,497 Cannabicyclohexanol CP 55,940 HU-210 THC-O-acetate AB-PINACA AB-FUBINACA UR-144 XLR-11
New synthetic opioids	Fentanyl and derivatives, carfentanil, isotonitazene
Synthetic cathinones	Cathinone Methcathinone (ephedrone) 4-Methylmethcathinone (mephedrone) Methylenedioxypyrovalerone (MDPV) Pyrovalerone Naphyrone (naphthylpyrovalerone, NRG-1) Ethylone (see Table 19.1 entactogens) Methylone (see Table 19.1 entactogens) Butylone (see Table 19.1 entactogens)
Phenethylamines	See Table 19.1 Paramethoxymethamphetamine (PMMA) 2,5-Dimethoxy-4-iodophenethylamine (2C-I) 2,5-Dimethoxy-4-methyl-phenethylamine (2C-D) 2,5-Dimethoxy-4-iodoamphetamine (DOI) 2,5-Dimethoxy-4-bromophenethylamine (2C-B) 4-Methylthioamphetamine (4-MTA) 25B-NBOMe
Piperazines	1-Benzylpiperazine (BZP) 1-(3,4-Methylenedioxybenzyl) piperazine (MDBP) 1-(3-Chlorophenyl)piperazine (mCPP) 1-(3-Trifluoromethylphenyl) piperazine (TFMPP) 1-(4-Methoxyphenyl)piperazine (MeOPP)

Table 19.2 (continued)

Group	Substances
Ketamine and phencyclidine-type substances	See Table 19.1 Ketamine N-Ethylnorketamine 3-Methoxyphencyclidine (3-MeO-PCP) 4-Methoxyphencyclidine (4-MeO-PCP) Eticyclidine (PCE, CI-400, N-ethyl-1-phenylcyclohexylamine) 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) Rolicyclidine (PCPy; 1-(1-phenylcyclohexyl) pyrrolidine) Tenocyclidine (TCP; 1-(1-(2-thienyl)cyclohexyl) piperidine) 2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexane (3-MeO-PCE)
Tryptamines	See Table 19.1
Plant-based psychoactive substances	Kratom (*Mitragyna speciosa*) *Salvia divinorum* Khat (*Catha edulis*)
Other:	
Aminoindanes	2-Aminoindane (2-AI) 5,6-Methylenedioxy-N-methyl-2--aminoindane (MDMAI) 5,6-Methylenedioxy-2-aminoindane (MDAI) 5-Methoxy-6-methyl-2--aminoindane (MMAI)
Benzofuranes	5-(2-Aminopropyl)-2,3-dihydrobenzofuran (5-APDB, 3-Desoxy-MDA, EMA-4) 6-(2-Aminopropyl)-2,3-dihydrobenzofuran (6-APDB, 4-Desoxy-MDA, EMA-3)
Piperidines	Pipradrol Desoxypipradrol (2-diphenylmethylpiperidine, 2-DPMP)
Synthetic cocaines	Dimethocaine 4-Fluorotropacocaine
Medicines	Phenazepam Etizolam Ethylphenidate Phenibut 4-Methylphenmetrazine

Well-known examples of NPS include substances such as synthetic cannabinoids contained in various herbal mixtures, new synthetic opioids, piperazines, products sold as "bath salts" (i.e. cathinone-type substances such as mephedrone and methylenedioxypyrovalerone (MDPV)) and various phenethylamines. From 2004 onwards, synthetic cannabinoids such as Spice appeared in the market, followed by synthetic cathinones and other emerging groups of NPS.

Among young adults (aged 15–34), last-year prevalence of use of these substances ranged from 0.1% in Norway to 3.2% in the most recent findings from the Netherlands, in 2016, with 4-fluoroamphetamine (4-FA) being the most commonly used. Survey data on the use of mephedrone are available for the United Kingdom (England and Wales). In the most recent survey (2017), last-year use of this drug among 16- to 34-year-olds was estimated at 0.2%, down from 1.1% in 2014/2015. In their most recent surveys, last-year estimates of the use of synthetic cannabinoids among 15- to 34-year-olds ranged from 0.1% in the Netherlands to 1.5% in Latvia [5]. The annual prevalence of use of bath salts among 12th-grade students fell by half between 2012 and 2018 [6].

The consumption of ecstasy is associated with attending electronic-dance music events or raves. It is estimated that 13.7 million adults in the European Union (aged 15–64), or 4.1% of this age group, have tried MDMA/ecstasy during their lives. Recent data about use among young adults suggest that 2.1 million young adults [15–34] used MDMA in the last year (1.7% of this age group), with national estimates ranging from 0.2% in Portugal and Romania to 7.1% in the Netherlands [5].

In North America, it is estimated that 0.9% of the population aged 15–64 were past-year "ecstasy" users in 2017. The annual prevalence of "ecstasy" use was reportedly highest among young adults aged 18–25, who accounted for 400,000 past-year users [24].

19.4.4 Pharmacological Properties and Consequences of the Use of MDMA (Ecstasy)

3,4-Methylenedioxymethamphetamine (MDMA) is a ring-substituted amphetamine structurally similar to methamphetamine and mescaline. MDMA has become widely known as "ecstasy" (shortened to "E", "X" or "XTC").

MDMA acts as a potent releaser and/or reuptake inhibitor of presynaptic serotonin (5-HT), dopamine (DA) and norepinephrine. MDMA is more potent and active on serotonergic neurons. MDMA is also a mild inhibitor of monoamine oxidase (MAO) and also has some direct actions in several types of receptors including the 5-HT2 receptor, the M1 muscarinic receptor, the 2-adrenergic receptor and the histamine H1 receptor [27].

Ecstasy is presented for use as tablets-pills, capsules or powder (crystal). Some wrap the powder in a cigarette paper and swallow it (bomb, bombing). It is usually taken orally, but some user snorted the contents. The MDMA content of pills or tablets varies widely between regions and different brands of pills and fluctuates. Pills may contain other active substances meant to stimulate in a way similar to MDMA, such as amphetamine, mephedrone, methamphetamine, ephedrine or caffeine. In some cases, tablets sold as ecstasy do not even contain any MDMA [28].

In general, users begin reporting subjective effects within 30–60 minutes of consumption, a peak appear at about 75–120 minutes, reaching a plateau that lasts about 3.5 hour. This is followed by a comedown feeling of a few hours. The usual dose is 50–125 mg with additional doses along the recreative session. The most frequent effects after MDMA administration are euphoria, well-being, happiness, stimulation, increased energy, extroversion, feeling close to others, increased empathy, increased sociability, enhanced mood, mild perceptual disturbances, somatic symptoms related to its cardiovascular (increase in blood pressure and heart rate) and autonomic effects (dry mouth, sweating, tremor, mydriasis tremor, jaw clenching and restlessness) and moderate derealization but not hallucinations. Some of the effects differential from those elicited by classical amphetamines (e.g. feeling close to others, increased empathy, increased sociability) are collectively termed as empathetic or entactogenic, and MDMA is considered the prototypical drug producing such effects [29–31].

MDMA-induced acute toxic effects are in relation to its pharmacologic actions. Mild toxicity signs include nausea, vomiting, restlessness, tremor, hyperreflexia, irritability, pallor, bruxism, trismus and palpitations. Moderate intoxication signs include hyperactivity, aggressive behaviour, panic attack, psychosis, confusion, muscle tension, tachycardia, arterial hypertension and increase in body temperature. Severe intoxication can include delirium, coma, seizures hypotension, tachydysrhythmias, hyperthermia (>40 °C) and renal failure associated with rhabdomyolysis. A serotonin syndrome (increased muscle rigidity, hyperreflexia and hyperthermia). Intracranial haemorrhage has been described. Heat stroke is a severe complication that can cause death; it includes hyperthermia, rhabdomyolysis, myoglobinuria, disseminated intravascular coagulation and renal failure. Fulminant hepatitis and hepatic necrosis have been described. Hyponatremia is an uncommon complication associated with inappropriate antidiuretic hormone (SIADH) secretion and excessive water intake. Its chronic use is linked to a progressive neurodegeneration of the serotonergic neurotransmission system [3, 32].

Two main pathways are involved in MDMA metabolic clearance: (1) O-demethylation partially regulated by CYP2D6 followed by catechol-O-methyltransferase (COMT)-catalyzed methylation (HMMA) and/or glucuronide/sulfate conjugation and (2) N-dealkylation leading to 3,4-methylenedioxyamphetamine (MDA), further subject to similar metabolic reactions than MDMA (O-demethylation and O-methylation). MDMA metabolic clearance accounts for about 75% of plasma clearance, and 30% of its metabolism is regulated by CYP2D6. In addition MDMA is a competitive inhibitor of CYP2D6; after a single dose, most hepatic

CYP2D6 is inactivated within 2 hours and returning to a basal level of CYP2D6 activity after at least 10 days. Other isoenzymes of cytochrome P450 and a relevant contribution of renal excretion play part in their clearance. Globally, the clinical relevance of CYP2D6 polymorphism is lower than that predicted by in vitro studies [32–34].

In addition, there is some evidence that MDMA produces in the mid-long-term selective long-lasting serotonergic neurotoxicity in animal models when administered at highly relative doses and/or after repeated administrations. The direct extrapolation of these results from animal to human is difficult [27, 33, 35, 36].

MDMA therapeutic use is under investigation. Few recent randomized, controlled trials of MDMA-assisted psychotherapy for post-traumatic stress disorder have been published showing some therapeutic efficacy [37–39].

MDMA can induce use-abuse, but it is not clear and, in some cases, it produces drug dependence but not drug withdrawal. Users reported tolerance to its desired effects and tend to cease spontaneously the consumption. MDMA can cause intoxication, and in this case the DSM-5 diagnostic criteria for stimulants can be applied [11]. There are no specific drugs for treating disorders caused by MDMA. Psychotropic drugs will be used according to the patient's symptoms (benzodiazepines, hypnotics, antipsychotics, antidepressants). As in the other drug addiction programmes, psychiatric and psychological support are used.

19.4.5 Consequences of the Use of "Legal Highs" and New Psychoactive Substances

NPS can induce substance use disorder, intoxication and in some cases withdrawal syndrome (for those with psychostimulant properties). Depending on the substance and pharmacological effects, the DSM-5 diagnostic criteria for hallucinogens or stimulants can be applied [11].

The clinical picture of the intoxication by NPS depends on the class of substances; in the case of cathinones and phenethylamines, the symptoms and signs are similar to an intoxication by a stimulant (amphetamine, MDMA). Synthetic cannabinoids can induce severe toxic effects including psychosis, respiratory depression, cardiac events including cardiac arrest, nephrotoxicity, gastrointestinal problems including hyperemesis, severe rhabdomyolysis, hyperthermia, acute cerebral ischaemia and seizures. In the case of tryptamines, the intoxication is similar to other hallucinogens [3, 40].

The use of ephedrone (methylcathinone) has recently been associated with symptoms like those seen in patients with Parkinson's disease (manganism) due to the compound manganese dioxide which is a by-product of synthesis with permanganate [41].

The use of MDPV was, in a number of cases, associated with highly bizarre behaviour, including a number of suicides, deaths associated with MDPV delirium and highly violent homicides [42].

Mephedrone is consumed intravenously in some countries as a substitute of heroin. Mephedrone is a common substance used in "chem-sex" to facilitate sexual sessions lasting several hours or days with multiple sexual partners. Mephedrone is usually taken by oral route but in some cases intravenous ("slamming"). Other substances used in "chem-sex" sessions are γ-hydroxybutyrate (GHB), γ-butyrolactone (GBL) and crystallized methamphetamine or cocaine [43].

The therapeutic objective is to reduce consumption and reach the abstinence. In some cases of NPS stop consuming can be easy because there is no physical dependence, in other cases (more psychostimulant profile) some symptoms of withdrawal syndrome can be observed. There are no specific drugs for treating disorders caused by these substances. Required of psychotropic drugs will be used according to the patient's symptoms (benzodiazepines, hypnotics, antipsychotics, antidepressants). As in the other drug addiction programs are used psychiatric and psychological support components [2].

It is very important to perform a psychiatric evaluation by a specialist to detect, if present, the

comorbidity with other psychiatric diseases and evaluate the need for an early pharmacological treatment. It is important to be aware that cases of poisoning can be by NPS, not yet known pharmacodynamics and their effect. Also, they cannot be detected by usual urinary tests. It is recommended storing samples for study.

19.5 Update on Therapeutic Use of Hallucinogens

In the 1950s and 1960s, there was a scientific interest in psychedelic compounds, and they were studied as tools to understand the neurobiology of mental functions and as therapeutic agents for mental disorders, including substance abuse, depression, personality disorders (e.g. antisocial) and palliative care, and as adjuncts to psychotherapy. The scientific investigation of these substances was overshadowed by their widespread recreational use, criminalization and its inclusion in the schedule I class by the United Nations Convention on Psychotropics Substances of 1971. Schedule I substances are considered to have high abuse potential, poor safety and no therapeutic indication. Over the past decade, there has been a resurgence of scientific interest in psychedelic drugs [1, 4].

19.5.1 LSD

Early studies from the 1950s to 1970s indicated that LSD may have antidepressant and anxiolytic properties [4, 17]. LSD-assisted psychotherapy was often performed in patients with anxiety and cancer and in patients with depression or related disorders [4]. Due to methodological issues, these studies need a replication in the future. One recent study assessed the effects of LSD-assisted psychotherapy on anxiety in 11 patients with life-threatening diseases (eight with cancer). The study found nonsignificant decreases in depression and increases in quality of life [44]. A follow-up study at 12 months in nine patients reported sustained decreases in anxiety, an increase in quality of life and no lasting adverse reactions after LSD, but there was no report of long-lasting effects and no control group [4]. Single or few doses of LSD reduced cluster headache intensity and induced remission more effectively than conventional medications; however, no controlled studies have been conducted. LSD was also well studied as treatment for alcohol use disorder [45]. The study identified 6 controlled eligible trials, including 536 participants. There was evidence for a beneficial effect of LSD on alcohol misuse (OR, 1.96; 95% CI, 1.36–2.84), although the results should be read with precaution because of risk of different biases.

19.5.2 Psilocybin

Psilocybin has been recently evaluated for obsessive-compulsive disorder in a trial including nine subjects; a reduction of symptoms was reported. A double-blind, randomized, placebo-controlled study assessed the safety and potential therapeutic effects of psilocybin in the treatment of psychological distress associated with the existential crisis of terminal disease. The trial included 11 subjects, and significant decreases were observed in anxiety scores at the 1- and 3-month follow-up [4, 17]. Psilocybin obtained from the FDA the Breakthrough Therapy Designation in 2018. This is a process designed to expedite the development and review of drugs that are intended to treat a serious condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

Two recent studies recently reported the efficacy of psilocybin in the treatment of anxiety and depression associated with life-threatening cancer. In a double-blind, placebo-controlled, crossover trial, 29 patients with cancer-related anxiety and depression were randomly assigned and received treatment with single-dose psilocybin (0.3 mg/kg) or niacin, both in conjunction with psychotherapy. In conjunction with psychotherapy, single moderate-dose psilocybin produced rapid, robust and enduring anxiolytic and antidepressant effects in patients with cancer-related

psychological distress [4]. The effects of psilocybin were studied in 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. This randomized, double-blind, crossover trial investigated the effects of a very low (placebo-like) dose (1 or 3 mg/70 kg) vs. a high dose (22 or 30 mg/70 kg) of psilocybin administered in counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up. High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning and optimism and decreases in death anxiety. At 6-month follow-up, these changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety [46].

In an open-label feasibility trial, 12 patients (six men, six women) with moderate-to-severe, unipolar, treatment-resistant major depression received two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in a supportive setting. Psychological support was provided before, during and after each session. Relative to baseline, depressive symptoms were markedly reduced 1 week and 3 months after high-dose treatment. Marked and sustained improvements in anxiety and anhedonia were also noted. Symptom improvements remained significant 6 months posttreatment in a treatment-resistant cohort [47, 48].

19.5.3 MDMA

In the late 1970s and early 1980s, psychiatrists/psychologists who employed MDMA in combination with psychotherapy described that it exerted therapeutic effects, especially by promoting subjects to talk openly and honestly about themselves and their early relationships without defensive conditioning intervening, even in individuals who were chronically constricted and apprehensive. Psychiatric attention with respect to therapeutic MDMA has especially focused on post-traumatic stress disorder (PTSD) and, more recently, on social anxiety in autistic adults and anxiety associated with life-threatening illness [32, 37, 39].

Six double-blind, randomized, placebo-controlled phase II clinical trials have demonstrated initial safety and efficacy for MDMA-assisted psychotherapy in the treatment of resistant PTSD [38, 39] and were conducted from April 2004 to February 2017. Active doses of MDMA (75–125 mg, $n = 72$) or placebo/control doses (0–40 mg, $n = 31$) were administered to individuals with PTSD during manualized psychotherapy sessions in two or three 8-hours sessions spaced a month apart. Three non-drug 90-minutes therapy sessions preceded the first MDMA exposure, and three to four followed each experimental session.

Results showed that after two blinded experimental sessions, the active group had significantly greater reductions in symptoms in the Clinician-Administered PTSD Scale (CAPS-IV) in comparison to placebo. After two experimental sessions, more participants in the active group (54.2%) did not meet CAPS-IV PTSD diagnostic criteria than the control group (22.6%). All doses of MDMA were well tolerated. Although the results are promising, it is relevant to take into account the small sample size. These studies supported expansion into phase III trials and led to FDA granting Breakthrough Therapy Designation for this promising treatment in 2017 [38, 39].

19.5.4 Esketamine

Ketamine has been assessed for the therapy of depression [49]. Similar to ketamine, esketamine appears to be a rapid-acting antidepressant. It received a Breakthrough Therapy Designation from the FDA for treatment-resistant depression (TRD) in 2013 and major depressive disorder (MDD) with accompanying suicidal ideation in 2016. The drug was studied for its use in combination with an oral antidepressant in people with TRD who had been unresponsive to treatment. Six phase III clinical trials for this indication were conducted in 2017. It is available as a nasal spray [50, 51].

Esketamine's efficacy and safety in treatment-resistant depression were evaluated in three 4-week, placebo-controlled, parallel-group studies and one longer-term randomized withdrawal study. Long-term safety was also evaluated in a 12-month open-label safety study. For esketamine, the positive short-term trial and the positive randomized withdrawal trial provided substantial evidence of effectiveness, although two short-term studies failed to demonstrate a statistically significant treatment effect. A major safety concern is esketamine's abuse potential [50]. In February 2019, FDA approved the nasal spray version of esketamine provided that it be administered in a clinical setting, with patients remaining on-site for at least 2 hours after administration (because some patients temporarily experienced sedation, visual disturbances, trouble speaking, confusion, numbness and feelings of dizziness/faintness during the period immediately after administration) [50].

19.5.5 Ayahuasca

The number of adequate therapeutic studies with ayahuasca is very limited; scientists from Brazil, the United States and Spain have performed observational studies to evaluate its therapeutic potential. In a parallel, double-blind, randomized, placebo-controlled trial with 35 patients with treatment-resistant MDD [52], a single ayahuasca dose induced significant reduction in depressive symptoms from 1 to 7 days after its intake. Tolerability of ayahuasca was good; the common adverse reactions were nausea (71%), vomiting (57%), anxiety (50%), restlessness (50%) and headache (42%). Although results are promising, the sample size and only one controlled trial are important limitations. Future studies should explore the use of ayahuasca in anxiety and mood disorders using different multiple doses, to assess efficacy and safety [17].

19.6 Conclusion

Hallucinogens are a heterogeneous group of substances that have as their primary effect the production of disturbances of perception. The hallucinogenic effects appear to be related to the agonistic action on 5-HT2A receptors and antagonism at NMDA receptors and agonist at opioid-kappa receptors. Hallucinogens produce substance use disorder, with acute tolerance but not withdrawal syndrome. Novel psychoactive substances (NPS) can induce substance use disorder, intoxication and in some cases withdrawal syndrome (for those with psychostimulant properties). The therapeutic objective for hallucinogen use disorder is to reduce consumption and achieve the abstinence. There are no specific drugs for treating the addiction caused by these substances. Some hallucinogens are under evaluation for its therapeutic use in different mental disorders (LSD, psilocybin, ayahuasca and the designer drug MDMA).

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Inhalant Addiction

20

Tania Real, Silvia L. Cruz,
María Elena Medina-Mora, Rebeca Robles,
and Hugo González

Contents

T. Real · R. Robles · H. González
National Institute of Psychiatry Ramón de la Fuente Muiz, Mexico City, Mexico

S. L. Cruz
Department of Pharmacobiology, CINVESTAV, Mexico City, Mexico

M. E. Medina-Mora (✉)
Mental Health Global Research Center, National Institute of Psychiatry Ramón de la Fuente Muiz/ UNAM, Mexico City, Mexico

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Abstract

This chapter is divided into seven sections, beginning with a general overview of this group of substances, their definitions, and the current classification of the disorders associated with their use. This is followed by a description of prevalence, the groups of the population affected, and the patterns of use in different regions of the world. Particular attention is paid to use among vulnerable groups, to inhalant effects and consequences, the social determinants that underlie the problem, and opportunities for solution. These sections are followed by a brief overview of the evidence for prevention and treatment strategies currently in use. This chapter ends with a discussion on policies to address the problem.

Keywords

Inhalant · Effects · Special population
Recovery potential · Policy

Inhalants are a special class of drugs that require attention from health and social welfare experts and policy makers. Many products that are misused are easily available. Although there are legal restrictions to sell and distribute certain products to minors [35], inhalants are not included in Drug International Regulations. These substances also less frequently targets for health and social interventions, as well as for research and funding.

Inhalants are the only drugs of abuse defined by the route of administration rather than by its attributes, specifically similar mechanism of actions or common pharmacological effects. They include a wide group of substances with different uses, short- and long-term negative effects, and consequences. These products have legal uses in industry and households and are therefore easily available. Inhalants are used by the general population saliently among persons in vulnerable conditions, mainly children and adolescents from poor sectors of society, young students (specially but not exclusively, those under 17 years of age), some indigenous groups, workers that use solvents for their everyday work (e.g., varnishers, house painters, anesthesiologists, etc.), and heavy drug users, especially when they do not have access to other substances, among other groups.

20.1 Definition and Classification

A working definition proposed by Balster and colleagues states:

> Abused inhalants contain volatile substances that are self-administered as gases or vapors to induce a psychoactive or mind-altering effect. These volatile substances are available in legal, relatively inexpensive and common household products which can be gases, liquids, aerosols or, in some cases, solids [7].

NIDA [73] includes in its definition the main issues that characterize this varied group of substances and their effects: the intentionality of their use, due to the chemicals' mind-altering effects; the nature of the short-term effects most of them producing a rapid high that resembles alcohol intoxication; the effects when sufficient amounts are inhaled, as nearly all solvents and gases produce a loss of sensation and even unconsciousness; the long-term irreversible effects that can include hearing loss, limb spasms, bone marrow, and brain damage; and, finally, the risk of mortality when sniffing high concentrations of inhalants that may result in death from heart failure or suffocation.

A wide variety of substances are grouped together into this class, which by its own nature challenges definitions and classifications. Inhalants include (1) solvents (liquids or semisolid substances that evaporate and include glue, shoe polish, toluene, and gasoline), (2) aerosol sprays (volatile substances or gases such as spray paints, hair sprays, cleaners for computers, etc.), (3) gases (anesthetics for medical use such as ether, chloroform, butane, and refrigeration products), and (4) nitrites that include products containing butyl nitrite and amyl nitrite, known as "poppers," locker room deodorizers, or "rush," and nitrous oxide known as "whippets."

From the physicochemical point of view, members of this group (a) are gases or can easily become vapors at room temperature (without heating), (b) are nonpolar molecules with high affinity for lipids and can therefore cross all biological membranes, (c) are flammable, and (d) mostly are lighter than water in their liquid form, but as vapors are heavier than air, which means that they are not easily dispersed from rooms where they have been inhaled [25].

Because many substances can meet these criteria, they can be classified on the basis of their chemical structure (hydrocarbons, ethers, ketones, etc.), commercial use (solvents, anesthetics, propellants, etc.), physical state (gases, liquids, aerosols), or effects (central nervous system) (depressants, vasodilators, etc.). Each classification has its own limitations and some substances may fit into several categories. For example, butane is a hydrocarbon gas used both as fuel and as propellant; nitrous oxide is a propellant and also an aesthetic gas used in dentistry.

Moreover, a single substance can have different names such as toluene, methylbenzene, phenylmethane, or toluol. This contributes to the difficulties associated with inhalant research. Table 20.1 shows some commonly misused compounds, their synonyms, and chemical structure, examples of commercial products, threshold limit values (TLV: maximum average concentration to which workers can be exposed 8 h/day, 5 days/week, without experiencing significant adverse health effects), and vapor concentrations in air that are dangerous to life and health (IDHL). This table also includes the CAS number, a unique chemical abstract service number that can be used to obtain the most important information on individual compounds. A detailed table of the physicochemical properties of main inhalants can be found elsewhere [20].

Although there is not enough evidence to establish a scientific-based pharmacological classification of inhalants, it is possible to distinguish at least three different categories with various mechanisms of actions: (a) solvents, fuels, and anesthetics; (b) nitrous oxide; and (c) volatile alkyl nitrites. The first one is the most extensive group and includes inhalants that are misused throughout the world in the form of gasoline, industrial solvents, adhesives, paints, sprays, inks, pen markers, and many other commercial products. Among solvents, toluene is the most frequently misused and the best-studied inhalant compound. It is the main component of paint thinners (mixed with xylene, ethylbenzene, and other solvents in different proportions), inks, adhesives, and degreasing agents. Commercial xylene (a mixture of the three isomers: ortho-, metha-, and para-xylene) is used in the leather

Table 20.1 Inhalants: synonyms, products, and safety limits

Class	Compound	Structure	Synonyms	CAS#	Products	TLV (ppm)	IDLH (ppm)
Hydrocarbon, acyclic	n-Hexane		Hexyl hydride, dipropyl	110-54-3	Gasoline, solvents, glues, varnishes	50	1100
Hydrocarbon, alicyclic	Cyclohexane		Hexamethylene, hexanaphtene	110-82-7	Lacquers, resins, varnish removers, solvents, cigarette smoke	300	1300
Hydrocarbons, aromatic	Benzene		Benzol, phenyl hydride, cyclohexatriene	71-43-2	Gasoline	0.5	500
	Toluene		Toluol, methyl-benzene, phenylmethane	108-88-3	Solvents, paints, thinners, glues, lacquers, gasoline, inks, cigarette smoke	50	500
	Xylene		Xylol, dimethyl-benzene, methyl toluene	1330-20-7	Cleaning agents, thinner. Used in printing, rubber, and leather industries	100	900
	Ethylbenzene		Phenyl ethane, ethyl benzol	100-41-4	Gasoline, paints, inks. Used as styrene precursor	100	800
	Propylbenzene		Phenyl propane, isocumeme	103-65-1	Gasoline. Used in textile dyeing and printing	N.E.	N.E.
Hydrocarbons, halogenated	1,1,1-TCE		Trichloroethane. TCE, perchloroethylene, tetrachloroethane, methyl chloroform	71-55-6	Cleaning products, paints, correction fluids, degreasers	350	700
	1,1,2-Trichloroethylene		TCE	79-01-6	Solvents, dry cleaning products, degreasers (car parts) Plastic spray fixative	50	1000
	Diethylether		Ethyl ether, octapentane, ethoxy ethane	60-29-7	Anesthetic, solvents, fuels	400	1900
	Chloroform		Trichloromethane, methyl trichloride	67-66-3	Anesthetic, spot removers, precursor for refrigerants	10	500
	Halothane		Fluothane	151-67-7	Anesthetic	50	N.E

Inorganic	Nitrous oxide		Dinitrogen monoxide	10024-97-2	Anesthetic, laughing gas, propellant (hair sprays, whipped cream, cooking spray), engine combustion enhancer	50	N.E
Hydrocarbon, acyclic	Propane		Dimethyl methane, LP gas	74-98-6	Industrial fuel, refrigerant, aerosol propellant	1000	2100
	Butane		Methylethyl ethane, Freon 600 LP gas	106-97-8	Lighter fuel, gas tanks for cooking, refrigerant, aerosol propellant (deodorant sprays)	800	N.E.
Hydrocarbons, halogenated	1.1-difluoroeihane		Ethylene fluoride, Freon 152a, R152a, HCF152a, Dymel	75-37-6	Propellant (PC duster), refrigerant (air conditioning)	1000	N.E.
	1,1,1.2-Tetrafluoroethane		Freon 134 R134	811-97-2	Propellant (PC duster), refrigerant (car air-conditioning systems)	N.E.	N.E.

Sources: PubChem, NIOSH ICSC (International Chemical Safety Cards), ATSDR (Agency for Toxic Substances and Disease Registry), Household Products Database, and Haz Map

CAS# Chemical Abstract Service number, *TLV* threshold limit value, *IDLH* immediately dangerous to life and health

and rubber industries and in histology laboratories. 1,1,1-TCE or trichloroethylene is another solvent present in correction fluids, but it is no longer produced in most developed countries because it is harmful to the ozone layer. Gasoline is a mixture of several solvents, which can or cannot contain lead. Several anesthetic gases such as halothane, ether, and chloroform are included in the same group with solvents because they share some of the effects and mechanism of actions of misused solvents.

Nitrous oxide constitutes a class of its own due to its unique pharmacological profile and affinity for specific receptors. It is used as a propellant in whipped cream products and as an anesthetic gas for dental procedures. As for nitrites, they are smooth muscle relaxant and vasodilator drugs rather than depressant substances and are inhaled from small bottles, some of which "pop" when opened (hence the name "poppers") [24].

20.2 Disorders Due to Use of Volatile Inhalants in ICD-11

In an important effort to aligning the World Health Organization's classification of disorders due to substance use with global service needs, the *International Classification of Diseases* 11th Revision (ICD-11) includes several changes based on a public health approach. This involved a greater specification of different harmful patterns of substance use, as well as a new category to denote single episodes of harmful use of all substances, including inhalants [80]. These changes allow for the early detection and intervention of people in risk to develop a problem related with the use of a substance.

Thus, according to the ICD-11 beta platform (https://icd.who.int/browse11/l-m/en), disorders due to use of volatile inhalants are classified, given the pattern and consequences of their use, in (i) volatile inhalant intoxication, (ii) volatile inhalant dependence, (iii) volatile inhalant withdrawal when inhalant use is reduced or discontinued, (iv) single episode of harmful use of volatile inhalants or unintentional exposure (e.g., occupational exposure), and (v) harmful pattern of use of volatile inhalants, which is evident over a period of at least 12 months if substance use is episodic or at least 1 month if use is continuous (i.e., daily or almost daily).

Definitions of "harmful use" and "harmful pattern" clarify that, in both conditions, a damage to physical or mental health of the substance user and/or other person has been caused by the substance itself or by the consequent behavior of the substance user. Harm to health of the individual occurs due to one or more of the following: (1) behavior related to intoxication, (2) direct or secondary toxic effects on body organs and systems, or (3) a harmful route of administration; and that harm to health of others includes any form of physical harm, including trauma, or mental disorder that is directly attributable to behavior due to volatile inhalant intoxication on the part of the person to whom the diagnosis applies.

Additionally, several volatile inhalant-induced mental disorders are recognized, including (i) volatile inhalant-induced delirium; (ii) volatile inhalant-induced psychotic disorder; (iii) volatile inhalant-induced mood disorder, which could be with depressive symptoms, with maniac symptoms, or mixed; and (iv) volatile inhalant-induced anxiety disorder.

Moreover, in the block for neurocognitive disorders (characterized by primary clinical deficits in cognitive functioning that are acquired rather than developmental), categories for amnestic disorder and dementia due to use of volatile inhalants have been included. Amnestic disorder due to volatile inhalant misuse is defined as a syndrome of memory impairment with specific features of amnestic disorder that is judged to be the direct consequence of the use of this type of substance.

Dementia due to use of volatile inhalants is characterized by the development of persistent cognitive impairments (e.g., memory problems, language impairment, and an inability to perform complex motor tasks) that are judged to be a direct consequence of inhalant use or exposure and that persist beyond the usual duration of

action or withdrawal syndrome associated with the substance.

It should be added that all ICD-11 definitions of mental and neurocognitive disorders due to use of volatile inhalants (and all substances) specified that produced symptoms persist beyond the usual duration of volatile inhalant intoxication or withdrawal; that the amount and duration of volatile inhalant use must be enough to be capable of producing them; and that they are not better accounted for by a disorder that is not due to use of volatile inhalants [81].

20.3 Epidemiology: How Widespread Is Its Use?

Inhalant misuse worldwide has mainly spread among young people. In some countries, the phenomenon appears among some adults and seniors, working in the formal and informal economies, as well as among some members of rural and indigenous groups [97].

In the Americas in general population, since 12–65 years, past-year prevalence rates vary around the world, around 0.1% or lower in half of the region countries. Some places stand out for higher use: as the United States (0.6%), Belize (1%), Bolivia (0.3%), and Barbados (0.8%); and use is higher in males than females, except for Guyana and Jamaica; also, there are variations in use according to age groups. In Guyana and Jamaica, inhalant misuse has been reported in young adults from 18 to 34 years, but in El Salvador, Bolivia, and Costa Rica, use is prevalent among those between 12 and 17 years of age [75].

According to a study on secondary students from 8th to 12th grade in the United States [53], inhalant misuse increased from the late 1970s to the mid-1990s, especially in the 8th, 10th, and 12th grades. Trends have changed since 2001, when use began to decrease. The last measurement in 2018 shows that annual prevalence is 8.7% in 8th grade, 6.5% in 10th grade, and 4.4% in 12th grade. Despite variations, the trend is for use to decline, and it is believed that this decrease may have been associated with information campaigns.

In Canada, the Ontario Student Drug Use and Mental Health Survey [14] indicates that among students in 7th and 12th grade, inhalants occupy the 11th place of use in the last year, with 3.4% prevalence (3.0% for females and 3.7% for males). Between 1999 and 2017, inhalant misuse in this population decreased from 8.9% to 3.4%. It is worth mentioning that inhalant treatment centers are spread among Canada, specifically addressing native indigenous groups among which volatile solvent use was prevalent [32].

According to OAS/CICAD Report [75], in most Latin American and Caribbean countries excluding tobacco and alcohol, inhalants are the most commonly used substance after cannabis, especially among high school students, although there are countries where it is the number one drug of choice. In general population, the lowest prevalence of the last year of use of inhalants among general population was reported in the Dominican Republic (0.03%), versus the highest in Belize (1%), Barbados (0.8%), the United States (0.6%), and Bolivia (0.3%). In other countries for which information is available, the prevalence rate is around 0.1%. Inhalant use is higher among males than females in every country except Guyana and Jamaica. Higher prevalence of inhalant use is among young people aged 12–17 in Chile, Mexico, Colombia, Ecuador, Panama, the United States, and Uruguay. In Guyana and Jamaica, inhalant use has been reported only among young adults (18–34).

Among secondary school students, the highest rates of past-year inhalant are found in Caribbean countries: Saint Lucia, Saint Vincent and the Grenadines, Barbados, Grenada, Saint Kitts and Nevis, Trinidad and Tobago, Jamaica, Antigua, and Barbuda, with rates between 7.5% and 11%. The lowest prevalence is in the Dominican Republic (0.5%) which is also in this subregion, followed by Costa Rica and Honduras (below 1%), Peru (1%), and Canada (1.4%). Largest differences by sex are in Panama and the Dominican Republic, where for every female who used inhalants in the past year, three males did so. Among eighth-grade students is greater than or equal to that of the tenth and twelfth graders.

Consumption in university students comes from eight countries: Andean Community and Brazil, El Salvador, Panama, and Uruguay. Brazil reports the highest rates, 6.5%, and the other countries' rates are below 0.5%. In Ecuador and Peru, inhalant use is higher among females.

In Mexico, inhalant misuse has shown fluctuations among students in various regions, for instance, annual prevalence increased from 4.4% in 2006 to 7.5% in 2009 and decreased to 5.8% in 2016 among high school students [99, 101]. According to the National Household Survey 2017 conducted among population 12–65 years of age, annual prevalence of use in the last year was still low, 0.2%, but higher than the 0.1% in 2008 [51]; this same trend is reported by the System of Epidemiological Surveillance that gathers information from cases attending treatment in nongovernmental organizations: Inhalants occupy the fourth place as a starting drug, followed by alcohol, tobacco, and marijuana. In 6.9% of the population, inhalants can be considered the impact drug that leads to treatment.

Data from university students show that Brazil's past-year prevalence was 6.5%. Panama, El Salvador, Peru, Colombia, Ecuador, Bolivia, and Uruguay throw data with prevalences below 0.5%.

In Russia, Koposov et al. [55] reported that the prevalence of inhalant use was 6.1% among boys and 3.5% among girls of sixth- to tenth-grade students in public schools in Arkhangelsk city. Of these, 3.6% ($n = 41$) of boys and 2.4% ($n = 39$) of girls used inhalants irregularly, while 2.5% ($n = 28$) of boys and 1.0% ($n = 16$) of girls reported using inhalants several times a week.

The European School Survey Project on Alcohol and Other Drugs [38] reported that the average prevalence of lifetime inhalant use was 7%, and the country with the highest rate was Croatia (25%), followed by Slovenia (14%). The lowest prevalence rates (1–2%) were found in the Faroes, the former Yugoslav Republic of Macedonia, and Moldova. The use of inhalants shows generally stable lifetime prevalence rates over the observed period. The gender-specific trends reveal a narrowing of the gender gap, with rates among boys slightly decreasing but rather unchanged rates among girls.

For Arabian countries, Bassiony [8] reports in eight studies found that the prevalence of inhalant use among Saudi patients ranged from 0.9% to 17.9%. It has also been reported in Asia; in a survey in Thailand, Verma et al. [98] report that 20% of adolescents in middle and high schools have experimented with inhalants. In Japan in general population (15–64) survey, the lifetime prevalence of drug use was 1.5% for organic solvents [91]. Also in a systematic review of substance use among young people in China during their lifetime, ever having used solvents was 4.8% [103, 104]. A study in the Republic of Uzbekistan to assess drug use among young people (students in the 9th grade) found low levels of drug use, about 0.5% of the students indicated that they had consumed cannabis and inhalants, once or twice in their life [39].

20.4 Use Among Special Populations

Studies conducted in different parts of the world show that drug use among adolescents differs from place to place. The highest rates of inhalant misuse are associated with low-income, chaotic, fractured, or abusive households and living on the streets [108]. According to SAMSHSA [85], in the United States, past-year inhalant use among adolescents was 2.7% for Blacks, 2.6% for Whites and adolescents of two or more races, and 4.6% among American Indians or Alaska Natives.

Villatoro et al. [100] analyzing data from the National Household Survey in Mexico found that those drug users that reported having ever inhaled a substance, as compared to cannabis users that had not experimented with these substances, came more often from more disorganized and violent communities; users also report having been involved in fights, selling drugs, and other problem behaviors more often. Ortiz and colleagues [76], also in Mexico, reported the misuse of solvents in the context of a religious festivity among street children. The respondents reported consum-

ing between 10 and 30 "monas" (a piece of cloth soaked with a thinner-type solvent) a day. Ortiz and colleagues studied groups of children, adolescents, and young people living on the street and described certain dynamics around consumption such as presence of a dealer a privileged role and is able to wield power over the group, sellers who worked for the dealer. Drug distribution is part of a complex system of theft and transportation. Sometimes migrants are received by streetchildren groups and become part of the groups, street children from newborn to 50 and older, and people with a variety of professions such as windshield washers, construction workers, PET collectors, and sex workers coexist, which implies a complex social interaction.

In India, Gigengack [44] reported that children from street families, children of the street, ragpickers, and part-time street children use a diluter and whitener. Interviews suggest that children are seeking intoxication in pursuit of pleasure despite the harm that comes with it.

This practice has also been reported across indigenous communities in Australia; a survey of school students showed that around 23% of indigenous students (12–15) had use illicit substances in their lifetime, compared with 11% of all students. Twenty-four percent of the indigenous students had use inhalants [47].

Swaim and Stanley [93] reported time prevalence of inhalant use between 8th-, 10th-, and 12-grade American Indian students was 13.2%, 10.7%, and 10.8% compared with 7.7%, 6.6%, and 5.0% from a national sample of US adolescents.

Other studies have focused on the association of inhalant misuse with risky behaviors and HIV infection, as in the case of nitrite use among males that have sex with males [103, 104].

20.5 Patterns of Use

As is the case with other drugs, inhalers can be classified as experimenters, regular users, heavy users, and persons with dependence. Among students, especially among those in early adolescence, the most common pattern is of experimentation with a low proportion of regular users and even smaller proportion of students that have developed dependence. For instance, among American and Australian students, experimental inhalant use rates during early adolescence are high (26% of 12-year-old students), whereas the proportion that report inhaling on a regular basis is more than six times smaller (4%) [52, 105]. In Mexico City, and Jalisco, rates of experimentation (use one to five times) among young students (7–9 years of school) are also considerably higher (66% and 76%, respectively) than those that report having used on over five occasions (44% and 24%) of all persons that have ever used [21, 99]. This pattern differs from the one observed among adolescents living on the streets who are heavily involved in inhalation, with daily heavy use being the most common pattern combined with periods of complete abstinence [63].

Few studies report rates of dependence; Perron et al. [78], using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) household sample of persons 18 years of age and older in the United States, documented that 19.5% of the lifetime inhalant users met the criteria for DSM-IV inhalant use disorder (abuse 17.2% or dependence, 2.3%).

Inhalants are usually "sniffed" directly from container to nose, but inhaling fumes through mouth ("huffing" or "chroming") is also common. The open tube of glue, nail polish, etc. is usually placed close to the nose and the fumes are inhaled. Sometimes users heat substances to accelerate the vaporization process which increases the risks of gas explosions; other forms of use include inhaling from damp rags or shirt sleeves or from plastic bags or paper bags ("bagging"). Fatal accidents may occur when the inhaler places the complete bag over his head; balloons filled with substances such as nitrous oxide have also been reported [71]. Some authors have reported that the route of administration is related to environmental factors such as the presence of police and the need to disguise use [64]. A case study in India reports petrol inhalation by a 10-year-old boy who started to inhale it acci-

dentally by applying his face against the keyhole of the petrol tank of his father's motorbike [9].

Preference for specific substances varies according to the characteristics of the groups that use them and their effects. Takagi et al. [94], for example, when assessing preferences for type of paint among inhalers in Australia, found that the chrome-using group compared to non-chrome users was more likely to report deliberately inhaling to experience altered perceptions (such as visual and auditory hallucinations). A greater proportion of chrome users reported that the perceptual alterations they experienced after sniffing paint differed between paint colors, with more vivid hallucinations being produced with chrome colors. Similarly, Leal [57] reported that children living in the streets in downtown Mexico City preferred pure toluene for its psychotropic effects and lower level of toxicity. Cruz and Dominguez [26] have also reported hallucinations among heavy inhalers in Mexico that use toluene or a mixture of solvents.

Common choices for solvents among American Indian youth and Alaskan natives are gasoline (28%), glue (23%), paint removers and nail polish remover (18%), and paint sprays (17%). In this group as is often also the case of street children [64], most of the substances inhaled contain mixtures of chemicals, making it almost impossible to determine which compounds are responsible for the effects experienced by the abuser and observed by therapists [10].

Trotter [95] reported that inhalant abuse was sometimes combined with drinking the liquid residue left in aerosol cans after sniffing the propellant [95]. Hillabrant [49] reports interviews with Navajo adolescents who report the fad of drinking hair spray, users of which faint after five bottles in an hour.

Some groups in Mexico use "compressed air" at special gatherings known as "perreos" or "grinding, booty dancing, bumping, or housing" in the Caribbean. Inhalants and alcohol are the substances used; attendees might buy a piece of rag soaked with toluene that has been flavored. Risky sexual behavior and fights are common [45]. In Brazil, lança perfume (chloroform/ether) is used [68], mainly by higher social class students [86]. Also in Mexico a study to determine factors that differentiate inhalant users from other drug users and those who do not consume any drugs reported that inhalant users are primarily secondary students, have a low perception of risk of illegal drug use and have easy access to them, compared with non-users or consumers of other substances. In addition, users of inhalants have greater impulsiveness, have more friends with antisocial problems, have a family member who is a consumer of drugs, and are in a social context in which peers tolerate the use of substances [67].

Medina-Mora et al. [66] reported inhalation is more prevalent among youth coming from low socioeconomic; it is almost four times higher among males of 12–17 years of age and 20 times higher among females that do not work or study (2.3% and 4%) as compared to those enrolled in school or working (1% and 0.2%). It is also more frequent among students that do not attend school.

20.6 Health Effects

Inhalants Short-term effects are similar to alcohol and other central nervous system inhibitors, initial stimulation, and persistence. They act as anxiolytics, antidepressants, and anticonvulsants and are associated with impaired motor coordination, emotional lability and difficulty speaking. Chronic effects include neurotoxicity, cognitive impairment, headaches, diminished sensorial abilities (loss of vision, audition, and coordination), and an increase in mental disorders and sleep disturbances.

There is evidence that the more widely used inhalants share cellular mechanisms and have similar effects to other drugs, particularly depressors of the central nervous system [25], but the use of these substances has also been associated with illusions and hallucinations [26]. When used by pregnant rats, they affect development and irregular heartbeat during intoxication has also been described [23]. Unfortunately, a significant shortage of information remains, despite the

increase in research projects addressing the neurobiology of inhalants; the majority are still conducted on toluene. Little is known of abstinence, and researchers do not know the extent to which cognitive and other effects can be reversible, though some laboratory experiments with enriched environments have provided some evidence of reversibility [59].

20.6.1 Acute Effects

Inhalants vary in their chemical composition and consequently in how and where they act. In fact, it is rather surprising that such a dissimilar group of substances should have common effects, although this is partly due to their common administration route. Misusing inhalants implies introducing gases other than air into the body causing poor brain oxygenation (hypoxia) and the deleterious consequences associated with it. This happens with all inhalants regardless of their pharmacological profile and is a significant health hazard in itself.

Once in the body, inhaled vapors rapidly reach various specific molecular targets to induce a state of intoxication similar to that produced by other central nervous system depressant drugs such as alcohol and barbiturates. The pulmonary route is highly efficient as an administration route because the lungs are profusely irrigated and have extensive absorption surface. This results in a rapid intoxication, which is, however, short-lived due to inhalants' high volatility. In order to maintain the effects, users repeat the experience every few minutes to maintain the desired level of active substance in the brain.

Several solvents and fuels produce a transient state of excitation followed by a more persistent sedation, lack of motor coordination (ataxia), slurred speech, cognitive impairment, and slow reactivity toward stimuli [89]. At high concentrations illusions and hallucinations are common and are known to play an important role in the motivation to inhale and socialize [26, 61]. When anesthetic gases are intentionally used, sedative effects on top of psychoactive actions can be extreme.

Other effects depend on the type of compound inhaled. Let us consider the case of solvents. The respiratory system is the first to come into contact with the irritant vapors of these substances, producing coughing, frequent nose bleeding, rashes, and dry skin around the nose and mouth. Irritation is frequent in all the parts (usually hands and arms) that come into contact with rags or tissue papers soaked with solvents because—as degreasing agents—solvents damage the dermal lipid layer. Among this type of inhalants, apparently only toluene produces notorious detrimental effects in acoustic perception, initially described as a strong buzz and chronically associated with inner ear damage. On the other hand, if the gas inhaled is nitrous oxide (also known as laughing gas), hilarity, mood swings, altered perception, and anesthesia may occur. Inhalation of 1,1-difluoroethane, a gas used as propellant in computer dusters, can cause frostbite in the tongue, mouth, larynx, and other soft tissues in addition to its psychoactive actions.

Volatile alkyl nitrites differ from all other inhalants because they produce vasodilation and smooth muscle relaxation rather than cognitive effects. Amyl nitrite was introduced as medication for the treatment of angina pectoris until it was subsequently replaced by nitroglycerine. Amyl, butyl, and isobutyl nitrites are sought as sexual enhancers due to their ability to increase genital irrigation. These compounds decrease blood pressure, increase heart rate, and, under some circumstances, can cause syncope. These harmful cardiovascular effects may be enhanced if alkyl nitrites are combined with phosphodiesterase-5 inhibitors, the active ingredients of medications used to treat erectile dysfunction.

20.6.2 Chronic Effects

Repeated inhalant use produces chronic irritation of respiratory airways with breathing difficulties and increased frequency of respiratory illnesses, anosmia (decreased capacity to detect odors), and general cognitive impairment. Chronic inhalant users have higher incidence of neurobiological abnormalities including diffuse

cerebral and cerebellar atrophy, enlarged brain ventricles, and general white matter damage. These abnormalities have been correlated with attention dysfunction, impaired motor control, and memory loss along with reduced speed of information processing, among other detrimental effects [110]. Inhalation of toluene-based products can cause hearing loss, visual impairment, and severe ataxia [40].

Benzene, a component of gasoline, produces anemia and leukemia because it impairs blood cell formation in the bone marrow. The toxicity associated with gasoline inhalation can be related not only to benzene but also to the presence of lead in countries that do not use unleaded gasoline. Hexane, another organic solvent used in inks and other products, causes peripheral neuropathy because it is metabolized to 2,5-hexanedione, a highly toxic compound.

Halogenated compounds, that is, those containing chloride, fluoride, or bromide in their structure such as 1,1,1-trichloroethane, trichloroethylene (a degreasing agent and spot remover), halothane (a liquid anesthetic), or 1,1-difluoroethane (PC duster) can produce liver and kidney failure as well as cardiac arrest.

Repeated exposure to nitrous oxide produces a vitamin B_{12} deficiency, which can lead to damage to the neuron's myelin sheath manifested as ascending lower extremity weakness and numbness [58]. As to nitrites, chronic users of this compound can experience bilateral vision loss due to retinal damage [4].

20.6.3 Prenatal Effects

The fact that the gender gap is getting smaller poses specific challenges for service providers and researchers owing to the harmful effects of inhalants in women of reproductive age. A fetal solvent syndrome, similar to that caused by alcohol, has been described in babies born from mothers that used inhalants during pregnancy, and this syndrome includes facial anomalies, delays in growth, and impaired neurobehavioral development [19]. Low weight at birth and craniofacial abnormalities have also been documented both in clinical and preclinical studies [46]. Follow-up studies of children exposed to inhalants during gestation have shown growth retardation, learning impairment, cerebellar dysfunction (affecting balance) language deficiencies and hyperactivity. It is worth mentioning that some of these studies cannot rule out the use of other drugs and, in fact, it is fairly common for inhalants to be used in combination with other psychoactive substances. However, animal studies in which environmental conditions are controlled and only solvents are used to support these findings.

20.6.4 Molecular Effects

The available evidence indicates that toluene, the best-studied misused solvent, has a complex mechanism of action, which includes effects on diverse molecular targets. A detailed description of toluene's mechanism of action is beyond the scope of this chapter and has been reviewed elsewhere [18], but a few relevant data might be worth noting. Toluene inhibits the function of certain channels activated by excitatory neurotransmitters such as the glutamatergic NMDA receptors [22] and nicotinic receptors [5]. At similar concentrations, toluene enhances the function of inhibitory neurotransmitter receptors such as GABA [6] and glycine [13]. Calcium channels, potassium channels, and sodium channels are also affected by toluene [23, 30, 88]. Like other drugs of abuse, toluene increases dopamine release in key areas of the dopaminergic mesolimbic system Less data are available on other solvents, but the evidence indicates that at least the effects on GABAergic and glutamatergic systems are common to many substances including the majority of inhaled gases.

20.6.5 Morbidity and Mortality

Mortality is associated with this practice. Sudden sniffing death is a rare but serious complication that can occur at any moment, even after single use, that is, it is not necessarily associated with

repeated or prolonged exposure. Death can be due to a combination of factors including poor oxygen supply, a direct cardiac effect (arrhythmias) and sensitization to catecholamine stimulatory effects. Sudden death can occur when an intoxicated user is startled because catecholamines are released, the heart function is increased, and cardiac arrest becomes more probable [19]. It has also been reported as a result of an adrenaline surge. It can occur during abuse or in the subsequent few hours because solvents, dissolved in lipid-rich cell membranes, dissipate slowly.

Other causes are derived from the interaction between the substances abused, the user, the route of administration, and the environment. Suffocation and trauma may occur when the user puts a plastic bag sprayed with a solvent over the head to enhance the amount inhaled; the plastic bag may occlude the airway if the user loses consciousness. Death by aspiration usually of vomit is similar to that observed for alcohol and other depressants and results from a combination of a decreased level of consciousness and the loss of protective airway reflexes. Risk of accidents is high as users become less inhibited and less alert and oriented, which facilitates engagement in risky behaviors [106].

Lifestyles of some subgroups as street children raise the burden related to violence and increased risk of HIV from sexual abuse and prostitution [64]. In a survey conducted in 100 cities in Mexico among working children and adolescents from 6 to 17 years of age, Medina-Mora found that less than 1% declared prostitution as their source of income. Increased risk of seroconversion among street population has been reported [83].

The toxic exposure surveillance system database of the American Association of Poison Control Centers showed 63 deaths in 11,670 cases of intentional inhalant abuse reported from 1996 to 2001 to poison control centers in that country, linked to gasoline inhalation (45%), air fresheners (26%), and propane/butane (11%) [92]. In two particular states, Virginia and Texas, a higher rate was found, 39 and 144, respectively, the majority linked to fuel inhalation.

There is a wide range of diseases linked to this practice that includes ichthyosis-like dermatitis on the extremities, decreased visual acuity, toxic hepatitis, distal renal tubular acidosis, metabolic acidosis, leukemia, and aplastic anemia.

There is also evidence of tolerance, dependence, and withdrawal, among many others: despite this evidence, there is insufficient data to allow the assessment of the proportion of the global burden of disease related to this behavior [29].

20.7 Correlates

In a review published in 2008, Medina-Mora and Real found evidence of high rates of psychiatric comorbidity, mood, anxiety, and personality disorders being common among lifetime inhalant users; they also reported a higher prevalence of lifetime dysthymia and anxiety disorders among female inhalant users, but a lower prevalence of antisocial personality disorder. Among inhalant users with comorbid disorders, those who developed social or specific phobia had experienced the onset of these disorders prior to the initiation of inhalant use; all other mood and anxiety disorders usually developed following the onset of inhalant use. Odds of psychiatric disorders were higher for inhalant users who were women, poor, and less educated, with an early onset of inhalant use, family histories of psychopathology, and personal histories of substance abuse treatment.

These same authors also concluded from their review of literature that among incarcerated youth, inhalant users as compared to users of other substances showed significantly higher levels of criminal behavior, antisocial attitudes, current psychiatric symptoms, earlier onset of offending and substance use, and more extensive histories of head injury, kidney disease, hormonal problems, mental illness, suicidality, trauma, and substance-related problems [65]. Mustonen et al. [70] reported recurrent inhalant use (five times or more) in adolescence and subsequent onset of psychosis.

The complex nature of this problem requires (a) holistic, cultural sensitive interventions at the

individual, family, and community level to public policies aimed at reducing the risk associated with the substances themselves; (b) control of inhalant availability, with special focus on children and adolescents; (c) changes of social determinants that underlie this disorder; and (d) reduction of health disparities.

20.8 Prevention

Prevention incorporates different strategies, including education, skill building, environmental changes, and policy development. In the school setting prevention, some programs suggest that everyone should be involved: students, teachers, administrators, school nurses, guidance counselors, school social workers, school psychologists, librarians, parent volunteers, school police or safety officers, coaches, clerical staff, cafeteria workers, custodians, and bus drivers [102].

Other authors suggest efforts to prevent volatile substance abuse focused on interventions with community. Specially disseminate information to health workers, educators, media representatives, and parents.

Many strategies focus on educating very young children informing about dangers of inhalants and disseminating messages that show inhalants like poison. In Texas, some of these programs have tried to redefine the problem as a public health rather than a substance abuse issue; these visions facilitate the involvement of community partners, nurses, emergency room personnel, medical associations, and poison centers.

Other prevention interventions developed and provided educational materials and resources to families, school, and media. Products include staff training and curricula for schools and resources to teach parents skills [72].

Some populations require special attention like Indian population in different countries. Alaska Natives have developed school programs aimed at making students aware of the dangers of inhalants [49].

A program for young migrants from Morocco aimed at covering basic needs and detecting early those persons recently involved with inhalants. A change of demand is expected by means of workshops on health promotion and promotion of sport activities and art activities [42].

As in treatment, prevention includes teaching and helping children and teenagers to build strengths, increase cultural self-identity, and develop social and emotional skills and also helping families [31].

20.9 Treatment

Considering the wide variety of compounds included in the inhalants' category, several approaches are required to provide effective treatment to chronic users.

20.9.1 Recovery Potential and Treatment

Despite the impact of the negative effects of inhalant misuse reviewed in this chapter, there is some evidence on the recovery potential of cognitive and neurological deleterious effects that occur following abstinence from solvent misuse, pending on the extension and duration of inhalant misuse [33]. Bowen and Cruz [20] described evidence indicating that the myeloneuropathy associated with chronic use of nitrous oxide improves with inhalant discontinuation and vitamin B_{12} supplementation [2] and that retinal damage produced by chronic nitrite inhalation can recover after cessation [4]. Unfortunately, some negative sequelae, such as benzene-induced leukemia or liver toxicity produced by halogenated compounds, seem to be more devastating. Support with behavioral cognitive therapy, attention to organic damage (e.g., hearing or sight loss), and treatment of psychiatric comorbid disorders when needed are important components to successful treatment programs.

In this same review, Cruz concludes that to date, there is no available pharmacological therapy for treating this substance use disorder, but found some evidence of limited success, such as using risperidone to control the paranoid psychosis in a male who had been inhaling gasoline and

carburetor cleaner daily for 5 years [69]. Other authors have reported that inhalant-induced psychotic disorder was reduced in the severity of symptoms when treated with either carbamazepine or haloperidol [48]. Also, daily administration of lamotrigine decreased craving in a 21-year-old male with a 4-year history of inhalant misuse [90]. More investment in research is needed to develop better pharmacological treatment for this population.

Psychosocial interventions have proven to be effective; these include housing, programs aimed at promoting school attendance and retention, activity-based programs (to engage drug users in therapeutic relationships, develop skills and provide alternatives to substance misuse, e.g., art activities), counseling, outreach of children in risk of becoming street children [37], family therapy (focused either on addressing family dynamics or dysfunctional family behaviors), and indigenous-led residential approaches [62].

As can be seen, effective psychological interventions are directed to increment personal, educational/vocational, and social functioning and to reduce risk behaviors, which are valid and desirable results of the treatment of disorders related to drug use. Treatment and rehabilitation services should not focus exclusively on the ultimate goal of abandonment of the use of drugs; instead, they should consider the intermediate objectives of reducing drug use and its harmful consequences as an integral part of the whole rehabilitation and social reinsertion process [96]. For such purpose, the support and participation of the community and patient orientation is a crucial principle for effective treatment of disorders due to the use of drugs [96], especially in the case of inhalant users, which are generally vulnerable individuals who are socioeconomically disadvantaged and marginalized.

Good treatment models are an important factor for improving quality of life of those affected and reducing the costs for society, and availability of services and service utilization complete the equation. We know from the World Mental Health Survey that the treatment gap for mental disorders including substance use disorders is important, between 35.5% and 50.3% in developed countries and 76.3% and 85.4% in developing countries [34], and that the treatment gap in some countries as in Mexico is similar for substance use disorders [16], but few studies report rates of service utilization by type of substance, among those with dependence to inhalants.

Perron and colleagues [78] within the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) documented that among those with dependence (2.3%), 66% used some sort of service, mainly 12 step programs (68.5%) followed by drug rehabilitation programs (61.2%) and private practitioners (55.6%); 15% reported at least one barrier to receiving services, with the low-income group reporting more barriers (22.8%). The most common treatment barriers reported were related to a lack of understanding of what dependence means; between 41% and 43% gave argument thoughts that *the individual should be strong enough to handle it alone* or *that the problem would get better by itself.* The same proportion (42%) reported that they didn't want to go; and in around one third (28.8%) barriers were related to stigma: *feeling too embarrassed to discuss it with anyone*. Lack of resources was reported by one-fifth of those with dependence (23.2%). This information highlights the need to introduce policies to increase both, coverage of treatment and service utilization.

20.10 Evaluation of Biomedical Conditions and Their Complications

20.10.1 Physical Exam

In the physical examination of a patient who was recently exposed to solvents, clinical signs and behavioral changes can be found that may suggest this diagnosis. The characteristic odor is an important fact because it can persist in the breath or in the clothes for several hours after its last use. In users who have been chronically exposed, it is common to find very dry skin and mucous membranes, which facilitates bacterial infection, resulting in perinasal or perioral pyoderma. Irritation of mucous membranes causes users to

cough, sneeze, pant, or salivate frequently. Conjunctival epistaxis and irritation can also be observed. More severe cases may present with dyspnea and tachycardia, nausea, vomiting, diarrhea, and abdominal pain [56]. These symptoms usually resolve in about 2 or 3 h. The neurological symptoms of intoxication go from an initial stage of euphoria and disinhibition to a state of confusion, sputtering language, and weakness. In severe poisonings, the user could present ataxia, decreased reflexes, and nystagmus [36, 56].

Hypokalemia is the main risk among inhalant users exposed to toluene-based products. When potassium levels are low, numbness, fatigue, muscle weakness, and cramps occur. This condition can lead to cardiac infarction and kidney failure and is one of the main causes of death. Treatment consists of parenteral potassium replenishment [28].

20.10.2 Evaluation of the Presence of Cognitive Impairment: Mini-Mental State Examination

A relevant aspect when evaluating a patient with problems due to the use of solvents and other substances is to evaluate the cognitive state. In the case of chronic consumers, it is possible that there are various types of deficits, including dementia, so the use of a rapid test can help to suspect the presence of these states from the first evaluation. The "Mini-Mental State Examination" test is a fast application instrument developed by Folstein et al. [41] that has been validated in the Mexican population [11]. Its use is suggested for the assessment of dementia in several clinical guidelines [12] although it is widely used in other populations to assess mental status. This test qualifies several areas, with a maximum score of 30, and is easy to apply per clinician in a short period of time. A score higher than 27 indicates a normal cognition, while a lower score represents a mild cognitive impairment (19–26 points), moderate (10–18 points), or severe (<10 points). Based on the experience of the First Nations Youth Residential Treatment Centers in Canada, the Mini-Mental or any other diagnostic test should be applied to inhalant users only after a short (1- or 2-week) recovery period, with appropriate sleep and nourishment (Debra Dell, Youth Solvent Addiction Committee; personal communication). Otherwise, neurocognitive impairment is usually overestimated.

20.10.3 History and Current Status of Substance Use

Information on the history and current use of substances should include information on the substance or substances of preferential use as well as the use of secondary substances. Explore about consumption of susbtance for medical use (tranquilizers, stimulants, etc.). For each of the substances used, describe the age of initiation, frequency and amount of use, patterns of low and high consumption, reasons for its use, context including the way in which it obtains or purchases the substance, periods of abstinence and how it achieved them, and history of previous relapses [79].

20.10.4 Evaluation Instruments

Addiction Severity Index (ASI). The Severity Index of Addiction (ASI) is a semi-structured instrument of 200 items, widely used in various scenarios, designed to evaluate 7 areas of potential problems in patients with substance use disorders: medical status, employment, drug use, alcohol use, legal status, family and social status, and psychiatric status. Each area receives a rating which is useful for clinical and research purposes. ASI investigates current status and various problems throughout life. It has been used in diverse populations and its application requires specific training [60]. There is a Spanish translation of the sixth version in English [15]. It is an instrument with adequate validity and reliability.

According to the Clinical Practice Guideline (GPC) prevention and detection of the use of inhalable substances in adolescents in the first level of care, the Inhalant Substance Use Evaluation Card can be applied.

Laboratory tests Laboratory tests that should be done to users with acute solvent poisoning include a blood count, oxygen saturation, serum electrolytes, liver function tests, creatinine, urea nitrogen, glucose, and urine [56]. The detection analysis of drug metabolites in urine is useful to rule out exposure to other drugs, since solvent tests are not routinely found in hospitals.

Cabinet auxiliary studies Chest X-ray plates and an electrocardiogram may be useful especially in patients with cardiological or pulmonary manifestations of solvent exposure [56]. Magnetic resonance imaging of the skull is a very suitable way to assess the damage caused by the abuse of toluene and other compounds. However, it is not as sensitive to detect incipient data, so when they are apparent in studies, the changes are usually very advanced and irreversible after 5–7 years or more of chronic abuse [17].

In brain images, the most characteristic feature is atrophy, which may include cerebellar atrophy, ventricular dilatation, widening of the sulcus and grooves and enlargement of the basal cistern, brain stem atrophy in particular in the pontine area, generalized cerebral atrophy, atrophy of the hippocampus, and atrophy of the optic nerve. Also in 20% of the patients a thinning of the corpus callosum can be observed [17]. Diffuse alterations in the white matter and loss of the boundaries between the white and gray matter are also frequently found. Twenty percent of chronic abusers can present T2 hyperintensities in the thalamus. Unlike other processes that cause atrophy, injuries due to the use of solvents are bilateral, as in alterations due to opioid abuse or metabolic processes [17].

The most prominent finding in chronic toluene abusers is diffuse hyperintensities in white substance in T2 being found in about 46% of patients. The most affected areas are the periventricular white matter, the centrum semiovale, and the cerebellar white matter. Other areas affected to a lesser extent are the internal capsule and the bridge. There is a concordance between the extension of T2 hyperintensities and neurological deficits [17].

20.11 Psychiatric Medical Evaluation

20.11.1 Subtypes of Consumers of Inhalable Solvents

In a study of incarcerated adolescents, it was sought to identify subgroups among users of solvents based on their reasons for using them. Through an analysis of latent classes, three subtypes of solvent consumers were identified: the experimenters, with occasional and limited use, active consumers, and consumers for "self-medication" who use solvents primarily to cope with feelings of sadness, loneliness, anger, etc. [43]. The subgroups did not differ in terms of demographic characteristics but did so in clinical measures such as the presence of anxiety, problems associated with the use of substances, overall severity of the symptoms, and number of different types of solvents used. The results showed heterogeneity for the reasons of use and distress associated with consumption [77].

20.11.2 Comorbid Mental Disorders

The active use of inhalants, in particular solvents, can induce acute secondary or induced psychiatric symptoms. According to the DSM-V psychiatric classification, solvent poisoning can be associated with acute psychotic disorders, mood disorders, and anxiety disorders [3]. On the other hand, in epidemiological studies, it has been found that there is a high comorbidity of the abuse and dependence of inhalants with various psychiatric disorders throughout life. A study in the United States with epidemiological data of 43, 093 adults from 18 to 98 years of age of which 664 (1.7% of the sample) reported use at some time in the life of inhalants (88% abuse criteria, 12% dependency criteria), 60% began consumption before 18 years. In this studied sample, there was a high comorbidity with other psychiatric disorders at some point in life: 48% mood disorders, 36% anxiety disorders, and 45% personality disorders. In addition, there was also a high frequency of major depression (41%), dys-

thymia (18%), manic episodes (15%), specific phobias (18%), obsessive-compulsive personality disorder (17%), and antisocial disorder (32%). A high percentage presented several psychiatric disorders throughout their lives [109]. These data reflect the importance of assessing the current or past presence of psychiatric disorders.

In adolescents who misuse solvents, a high presence of comorbid disorders has also been found. In a study of 847 adolescents admitted to treatment, it was found that those with abuse or dependence on solvents were more likely to present abuse or dependence on alcohol, hallucinogens, nicotine, cocaine, and amphetamines. In addition, 40% had suffered from major depression and one third had ever attempted suicide [84].

20.11.3 Anxiety Disorders

In this epidemiological study, a higher lifetime prevalence of some psychiatric disorders in women was found, for example, anxiety disorder in 53% (30% in men), panic disorder without agoraphobia in 25% (11% in men), and specific phobias in 28% (14% in men). When assessing the presence of disorders in the last year, the prevalence of anxiety disorders remained high with 25% of the sample [109].

Clinically, anxiety disorders are very frequent and are usually a reason for requesting attention. The individual experiences these states as unpleasant, and in many cases, they are accompanied by physical symptoms such as tachycardia and sweating. The Hamilton Anxiety Scale, which is an instrument applied by the clinician, can be used to determine the severity of anxious symptoms

20.11.4 Affective Disorders

In the case of affective disorders, women had a higher percentage of dysthymia throughout their lives (24% vs. 16% in men). Regarding the age of onset of consumption, those who started before the age of 18 had greater percentage of manic episodes (10%) than those with late onset (4%), and subjects with early onset and 54% of early initiators had a major depressive episode at some point in their lives. Twenty-six percent of the sample reported having had an affective disorder in the last year, and subjects with previous treatments for substance abuse had a higher percentage of affective disorders (47% vs. 24% in those who did not attend previous treatments) [109].

Depressive disorders are very frequent in the general population and even more frequent in patients with substance use disorders, so it is necessary to evaluate the presence of them from the general diagnostic interview. Depressive disorders are characterized by a low mood, decay, irritability, subjective feeling of discomfort, and impotence. In addition, to a greater or lesser degree, symptoms of cognitive, volitional, and somatic type are present. Sometimes it can be associated with suicidal ideas, which must always be assessed and managed.

The Hamilton Depression Scale is useful to assess the severity of depressive symptoms and allows to determine in a very short time the current severity of depression.

20.11.5 Psychotic Disorders

The psychotic disorders in consumers of solvents are usually of acute type, with an important hallucinatory component. This has been reported since the 1960s, with a high proportion of visual hallucinations and, to a lesser extent, auditory hallucinations. In a qualitative study with adolescents using solvent based on toluene, Cruz and Dominguez [26] found that the use of solvents was clearly associated with hallucinatory experiences, these being visual, auditory, tactile, and olfactory. They also expressed a continuum between dreams, illusions, and complex hallucinations [25].

20.11.6 Personality Disorders

Among abusers of volatile substances, there is a higher prevalence of antisocial behaviors, inter-

personal violence, mood disorders, anxiety, personality disorders, use of other substances, and treatment in mental health services in the last year compared to non-users of volatile substances [43].

20.12 Exploration of Medical Complications

20.12.1 Kidney

At the renal level, the use of solvents, especially toluene, is associated with renal tubular acidosis, urinary stones, glomerulonephritis, and renal failure [59].

20.12.2 Kidney Tubular Acidosis

Compounds with toluene are especially nephrotoxic since it is assumed that toluene inhibits the secretion of protons in the distal tubules. The subsequent renal tubular acidosis (TKA) is characterized by a hyperchloremic metabolic acidosis with a strong loss of potassium and phosphates, which can cause weakness, muscle spasticity, and cardiac arrhythmias. Renal tubular acidosis is also associated with recurrent urinary stone formation [56].

Liver. It has been documented that the use of solvents can produce toxic hepatitis and liver failure [59]. The vapors of chlorinated hydrocarbons and chloroform are known to be hepatotoxic that can cause toxic hepatitis. Sometimes some metabolites released by the kidney and liver are free radicals that cause damage to the membranes of the hepatocytes, and in some individuals complete liver and kidney failure have been observed after exposure to inhaled solvents [56].

20.12.3 Other Organs and Tissues

Benzene has been associated with suppression of the bone marrow and with the subsequent development of leukemia, lymphomas, and aplastic anemia [56, 59].

Lungs The most direct pulmonary effects are related to direct damage to the lung tissue or are related to asphyxia, since volatile solvents can displace oxygen and produce hypoxia and loss of consciousness. There are some solvents that can produce chemical pneumonitis [56, 59].

In an epidemiological study in the United States among adults between 35 and 45 years of age, it was found that the duration of inhalant abuse was positively and significantly associated with a higher probability of suffering from tuberculosis, bronchitis, asthma, and sinusitis. These diseases are necessary [50]. On the other hand, it has been reported that the inhalation of gases from hydrocarbons such as butane can cause laryngeal edema and laryngospasm [19].

20.12.4 Heart

Adverse cardiac effects have been reported in acute intoxication by toluene and other solvents, whose cardiotoxicity can cause severe arrhythmias and death [40]. The syndrome of sudden death by solvents was described by Bass in 1970 and is caused by cardiac arrhythmias, apparently due to a sensitization of the myocardium to catecholamines (adrenaline, noradrenaline), so that when feeling scared or agitated a user has a rapid increase of these substances and can cause ventricular fibrillation [56, 59].

At low doses, hydrocarbons can produce hypotension due to peripheral vasodilatation and reflex tachycardia, while increasing the dose produces an increase in cardiac output and bradycardia. In the case of nitrates, they cause vasodilatation with stagnation of blood in the lower extremities, which can cause orthostatic hypotension and syncope [56].

20.12.5 Pregnancy

In animal models, prenatal exposure to toluene is associated with malformations, growth retardation, slow reflexes, and decreased attention. There is evidence that these negative effects are

increased if the experimental animals are exposed to stress [27].

In humans, the use of inhalants in pregnancy has been associated with multiple risks such as miscarriage and premature birth, reaching frequencies of up to 9% of the products of mothers who had exposure to toluene during pregnancy [19]. There have also been reports of withdrawal symptoms in the neonate characterized by very acute crying, insomnia, overactive Moro reflex, tremor and hypotonia, and difficulty feeding [19].

20.12.6 Fetal Solvent Syndrome

Since the use of inhalants is prevalent in young women of childbearing age, it is important to highlight the possibility of pregnancy, which is accompanied by a series of characteristic complications. The use of toluene during pregnancy in humans has been linked to congenital malformations including craniofacial deformations similar to those found in fetal alcohol syndrome such as cleft palate, micrognathia, microcephaly) as well as developmental delay [56, 59]. In addition, on many occasions, the effects of the consumption of other substances are added [19].

The monitoring of these infants up to 3 years has documented alterations in development such as growth retardation, hyperactivity, language disorders, and cerebellar dysfunction characterized by lack of coordination [19].

20.13 Psychiatric Medical Intervention

20.13.1 Pharmacological Management of Disorders Due to the Use of Solvents

The psychiatric medical treatment of the addiction to solvents follows the general lines of the treatment of other addictions. In a Cochrane systematic review, no adequate studies were identified, observational or experimental controlled and prospective studies, limited to reports of isolated cases, so they conclude that there is insufficient evidence to recommend any pharmacological treatment for this type of abuse [54].

20.13.2 Management of Damage to Organs and Systems

Acute poisoning Solvent users are usually brought to medical attention only when they are in a life-threatening situation or when there have been injuries. The intervention can save the user's life and must include assessment of the airway, breathing, and circulation. Cardiorespiratory monitoring is recommended because of the risk of sudden death or profound depression of the central nervous system. Life support includes oximetry and hydration with saline and close observation [56].

20.13.3 Policy Options

As reviewed in this chapter, inhalant misuse is a phenomenon characterized by significant inequalities, regarding the social context of the most affected users who tend to come from more poor, disorganized, or isolated communities, who are differentially exposed to low-quality substances, violence, and other adverse experiences; who have lower opportunities of education and work; who are differential; and who have worst health outcomes and socioeconomic consequences such as school dropout, unemployment, informal labor, stigma, and barriers to accessing health care. This scenario calls for the inclusion of intervention efforts to reduce these social determinants within a framework of community interventions.

Some recommended measures include attending needs of education and employment; ensuring access to health systems for different needs such as vaccination, nutrition, and acute and chronic disorders including mental health disorders; and providing alternatives to inhalation such as sports and other recreational, artistic activities along with active search of persons in risk or using substances and counseling [66, 82]. Community interventions aimed at reducing dis-

organization and violence include environmental design, urbanization, participation of organizations that provide support to families, prevention programs that promote group cohesion and conflict resolution without violence, and in general empowering communities to make accurate diagnosis, develop action plans, formalize process, and monitor progress [107, 111].

Good example of policies aimed at reducing the risk associated with the toxicity of substance*s* was the development, in Australia, of Opal fuel which contains very low levels of the aromatic compound that causes intoxication, benzene, toluene, and xylene, making it less attractive for inhalation. Other examples of this type of interventions are the modifications to the formula aerosol spray paints replacing aromatic chemicals toluene and xylene to less intoxicating ones [1] and the development of glues based on water for use at schools.

Control of availability with special focus on children and adolescents in supermarkets, hardware stores, or service stations and integrating commerce organizations in avoiding selling inhalants to these groups of the population are other examples.

Harm reduction interventions aimed at educating about the special dangers associated with certain substances and ways of administration, reducing risk of accidents and mortality, are controversial but can be considered when approaching heavy using populations as a first step.

Legislation can provide governments, retailers, and community and health workers means to address misuse such as to remove products from users or stores, move users to safe places, mandate treatment, restrict packaging and sale of inhalants, etc. The existing laws generally do not make illegal the possession of inhalants [1].

Training of frontline health workers, teachers, police, and community counselors requires appropriate training in identifying those at risk, interventions based on evidence, and referral to services.

Provide information to parentes, teachers, police, and community organizations on the substances with an abuse liability, identification of persons that are abusing, adequate handling, and referral of cases.

More invesment on basic and applied reseach on susbtance misuse is required, ensuring translational research from the molecular to the clinical level and to the community.

1. The term inhalants refers to:
   (a) Industrial products of easy access, which are inhaled to produce a psychoactive effect
   (b) Solvent products
   (c) Gases, nitrites, aerosols, and solvents
2. People seeking treatment due to inhalant use:
   (a) They have no chance of recovery; it is preferable to focus on prevention.
   (b) They could go to treatment centers that include CBT, care for organic damage, and comorbidity.
   (c) Treatment in organic damage reduction is the only one that has proven to be effective.
3. The modifications made to the ICD-11, which include the consumption of inhalants, are due to:
   (a) Need to describe more precisely consumption and damage patterns, for a better intervention
   (b) The increasing number of substances of abuse
   (c) Increasing global prevalence of inhalant use
4. Sudden Sniffing Death can be a consequence when:
   (a) The person consumes inhalants daily
   (b) It can occur in a first attempt
   (c) It is a consequence of the consumption of other substances but not of inhalants
5. Examples of successful public policies are those that include:
   (a) Those policies that guarantee that the industry withdraws the most toxic products from market
   (b) Policies aimed at harm reduction, teaching children resistance substance use skills
   (c) Those policies that include combined strategies of industry support, modification of legislation, harm reduction, availability control, and psychoeducation

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Anabolic Steroid Use Disorders: Diagnosis and Treatment

21

Gen Kanayama and Harrison G. Pope Jr

Contents

Abstract

The anabolic-androgenic steroids (AAS) are a family of hormones that comprise the natural male hormone testosterone and its many synthetic relatives. Once used almost exclusively by elite athletes, AAS have now spread to the general population, with some tens of millions of users worldwide. Contrary to popular belief, most AAS users are not competitive athletes, but take these drugs simply to gain muscle. Because widespread AAS use did not arise until the 1980s in the United States and about a decade or more later in other countries, even the oldest AAS users – individuals who started AAS as youths in the 1980s or 1990s – are only now reaching middle age. Thus, the long-term adverse effects of AAS are only beginning to be recognized, as more individuals enter the age of risk for these effects.

AAS users rarely disclose their drug use to clinicians and often come to clinical attention only because of adverse effects such as cardiovascular complications, AAS-withdrawal hypogonadism, and various effects on other organ systems. Because AAS users rarely seek treatment, little is known about optimal treatment strategies for this form of substance use disorder. The limited available data suggest that treatment should focus on underlying body image disorders, correction of AAS-withdrawal hypogonadism, and possible

G. Kanayama · H. G. Pope Jr (✉)
Biological Psychiatry Laboratory, McLean Hospital, Belmont, MA, USA

Harvard Medical School, Boston, MA, USA
e-mail: hpope@mclean.harvard.edu

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therapeutic attempts to address the hedonic properties of AAS. Data on treatment of AAS-induced mood syndromes are also limited, although general principles for treatment of both hypomanic and depressive episodes are probably appropriate when these syndromes arise from AAS use.

Keywords

Anabolic-androgenic steroids · Testosterone · Body image · Hypogonadism · Men

21.1 Introduction

The anabolic-androgenic steroids (AAS) are the family of drugs that include the natural male hormone testosterone, together with numerous synthetic derivatives of testosterone that have been created over the last 80 years (Table 21.1). AAS could also correctly be called simply "androgens" [37], but the term "anabolic-androgenic steroids" has become the more common term and will be used here. When taken in supraphysiologic doses, AAS can allow individuals to gain large amounts of muscle mass and lose body fat, often well beyond the limits of what can be attained naturally [58, 61]. Because of these properties, the use of AAS has grown into a major worldwide substance use disorder. Since AAS use is arguably the newest of the world's major substance use disorders, many aspects of AAS still remain poorly understood, both by clinicians and by investigators. However, the last two decades have seen substantial advances in our understanding of this form of substance use, as summarized in this chapter.

The history of AAS, illustrated in Fig. 21.1, begins at about the time of the Second World War [37]. Testosterone was first identified in Germany in the 1930s, and hundreds of synthetic AAS were quickly created thereafter. By the early 1950s, elite athletes began to discover that these drugs could greatly improve performance, especially in sports requiring muscle strength. As early as 1954, the Russian team was found to be using AAS at the weightlifting championships in Vienna, and over the course of the next decade, AAS spread rapidly through the elite athletic world. By the late 1960s, drug testing for AAS had been instituted at the Olympics and similar elite events. Also in the 1960s and 1970s, in the so-called golden age of bodybuilding, AAS were widely used by competition bodybuilders, who performed for a general public largely unaware that the muscular prowess that they were seeing was attributable to use of drugs. Even most clinicians also remained unaware of the powerful muscle-building effects of AAS. For example, in 1977, the American College of Sports Medicine issued a position paper stating that there was no conclusive evidence that AAS were actually

Table 21.1 Examples of frequently used anabolic-androgenic steroids (AAS)

Compounds administered orally	**Compounds injected intramuscularly**
Stanozolol (Winstrol)	Stanozolol (Winstrol-V[a])
Mesterolone (Mesteranum, Proviron)	Testosterone esters blends (Sustanon, Sten)
Oxymetholone (Anadrol, Hemogenin)	Testosterone cypionate (Depo-testosterone)
Oxandrolone (Anavar)	Testosterone enanthate (Delatestryl)
Fluoxymesterone (Halotestin, android-F, Ultandren)	Testosterone propionate (Testoviron, Androlan)
Methyldrostanolone (Superdrol)	Drostanolone propionate (Masteron)
Mibolerone (Cheque drops[a])	Trenbolone acetate (Finajet, Finaplix[a])
Methandienone (formerly called methandrostenolone) (Dianabol)	Trenbolone hexahydrobenzylcarbonate (Parabolan)
Methyltestosterone (android, Testred, Virilon)	Nandrolone decanoate (Deca-Durabolin)
Compounds administered transdermally	Methenolone enanthate (Primobolan depot)
Testosterone gel (AndroGel, Testim, Axiron)	Boldenone undecylenate (Equipoise[a])

[a]Veterinary preparation

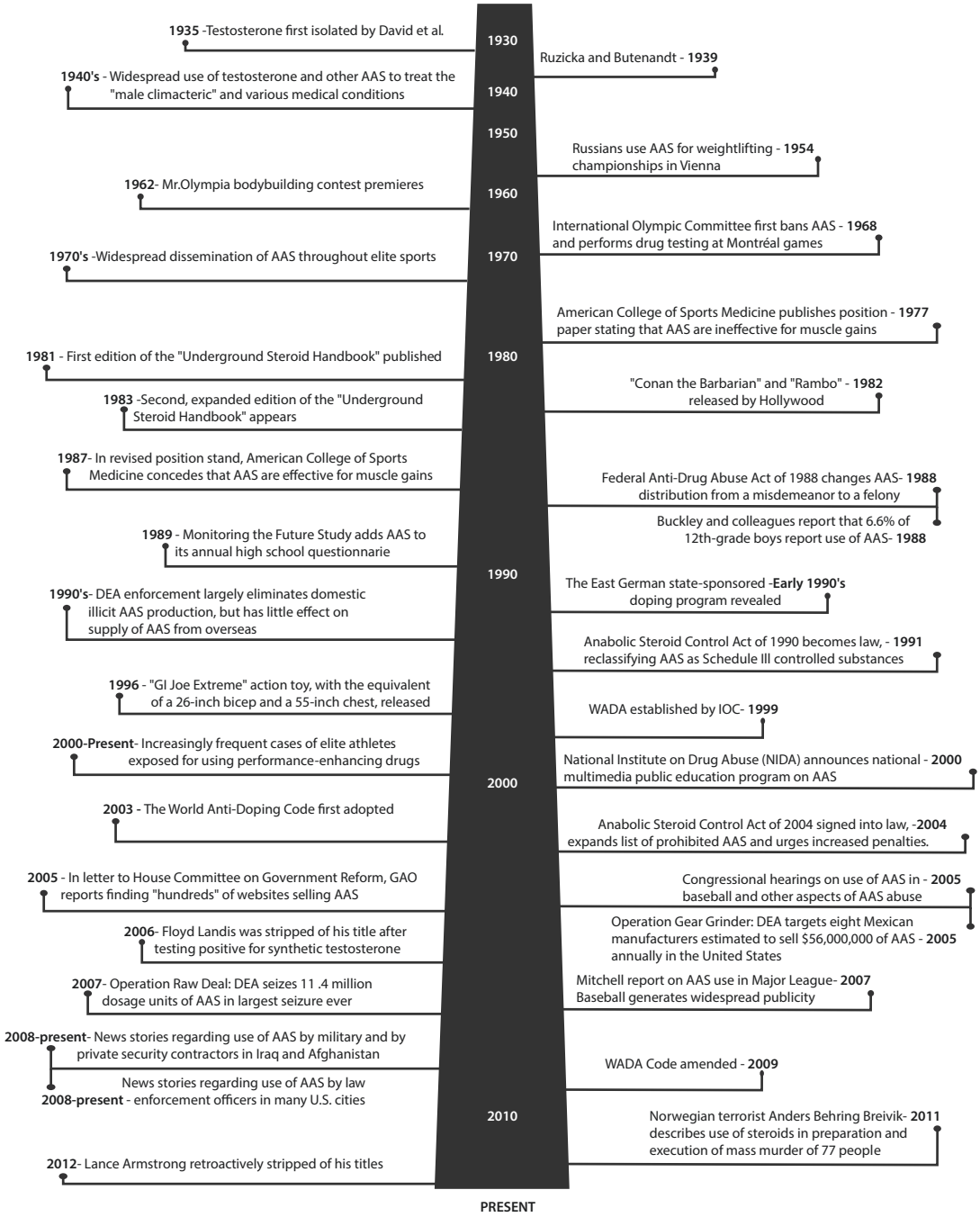

Fig. 21.1 The history of AAS

effective for gaining muscle mass – a statement that was to prove seriously erroneous [37].

Starting in about the 1980s in the United States, and about a decade thereafter in many other Western countries, AAS began to percolate out of the elite athletic world and onto the street. One catalyst for this transition was the appearance of various "underground guides" in the

United States, starting in the early 1980s, explaining how to obtain and use AAS, how to perform self-injections, and how to deal with side effects [37]. Also fueling enthusiasm for AAS use in the 1980s was a growing Western focus on male body image [56, 65]. Soon, growing numbers of ordinary rank-and-file weightlifters in local gymnasiums around the United States began to use AAS. Most of these individuals were not competitive athletes at all, but simply were using AAS to enhance personal appearance. Despite the widening use of these drugs, AAS still remained little understood by the general public, and most clinicians still had little or no experience with diagnosing or treating AAS users.

By the late 1980s and early 1990s, the US government began to recognize the problem of illicit AAS use, and in 1991, the US Congress passed the Steroid Trafficking Act, reclassifying AAS as controlled substances. However, possession and use of AAS without a doctor's prescription has remained legal in many countries around the world. Even in countries where AAS are illegal, users can readily purchase these drugs through Internet websites and receive shipments of AAS with little risk of interception [9]. Consequently, AAS use has become a relatively common substance use disorder in many countries, especially in Scandinavia, the United Kingdom, other British Commonwealth countries, and Brazil. Other countries on the European continent are now also showing growing rates of AAS use, whereas AAS use in Eastern Asian countries, such as China, Korea, and Japan, remains extremely rare. The uneven distribution of AAS use around the world appears likely attributable to cultural factors, as we have detailed in previous reports [33, 77].

21.2 Epidemiology of AAS Use

It has been difficult to estimate accurately the number of persons who have used AAS in various countries. Although there are numerous published surveys of AAS use among various student populations, especially high school students in the United States, these surveys have been vulnerable to the problem of false-positive responses to questions about "steroid" use. Specifically, if respondents on a questionnaire are asked whether they have used, say, heroin or cocaine, they will know almost certainly that they either have or have not used these drugs (although they may of course elect not to disclose this use). But when asked on an anonymous survey whether they have used "steroids," many respondents, especially those of high school age, may misinterpret the question and answer that they have used "steroids" when in fact they have been administered corticosteroids by a physician or have purchased an over-the-counter preparation in a supplement store that they erroneously believed was a "steroid." In a detailed analysis of this issue [25], we have shown that most American surveys of high school students have almost certainly produced grossly inflated estimates of the prevalence of AAS use as a result of false-positive questionnaire responses.

These false-positive survey responses have led to several widespread misconceptions about the epidemiology of AAS use. First, many surveys have created the impression that AAS use was not uncommon in teenage girls, and this belief has become a subject for popular reports in the news media and even for hearings conducted by the US Congress in which one of the authors of this chapter (HGP) was called to testify [57]. In fact, however, AAS use is virtually nonexistent in teenage girls, and the survey findings to this effect represent almost entirely false-positive responses [25]. Indeed, we are unaware of any published study in the last 25 years that has reported even a single female teenage AAS user who was actually evaluated in person by the investigators. Moreover, we are aware of only one study in the last 25 years dedicated specifically to female AAS users [21]. In this study, which was conducted by our laboratory, we spent 2 years advertising in three American cities and located only 25 female AAS users. In a recent analysis of five studies published since the year 2000 that surveyed AAS users without regard to gender [58, 61], it was found that of 1157 AAS users in the studies collectively, only 25 (1.8%) were female (95% confidence interval: 0.8%, 2.7%). In summary, therefore, AAS use is

overwhelmingly concentrated in men. Upon reflection, this is hardly surprising, since women rarely aspire to look extremely muscular and women are also vulnerable to the various masculinizing side effects of AAS, such as beard growth, deepening of the voice (which may be permanent), and masculinization of secondary sexual characteristics.

A second misconception arising from high school surveys is that AAS use is a common phenomenon in teenagers. Again, however, this misconception arises largely from false-positive responses generated by anonymous surveys. In an analysis of nine studies around the world published since the year 2000 that assessed the age of onset of AAS use in 3218 individuals collectively, less than 1% began AAS use prior to their 16th birthday, and the median age of onset was approximately 23 [58, 61]. Therefore, although the problem of teenage AAS abuse should not be dismissed, the evidence suggests that the vast majority of AAS users are young adults in their 20s and 30s.

A third misconception, widely shared by both clinicians and members of the general public, is that AAS use occurs primarily among athletes. This misconception is likely fueled by the numerous reports in the popular media about various elite athletes believed to have used these drugs for performance purposes. In fact, however, the great majority of AAS users are not competitive athletes at all, and they have used these drugs purely for the purposes of increasing strength and enhancing personal appearance. For example, in a recent study at our center, in which we recruited men from gymnasiums in Massachusetts, Florida, and California, USA, only 6 (6%) of 94 AAS users who were questioned responded that they had used AAS primarily for athletic purposes. Another 13 (14%) reported that they had used AAS partially for athletic purposes, and the remaining 75 reported that they had never used AAS for any athletic purpose [55]. Similarly, in a recent Internet study of 500 AAS users, 392 (78%) were classified as non-athletes [49]. In summary, therefore, the great majority of AAS users are *male, over the age of 18, and not involved in any competitive athletics*.

How many AAS users exist in various countries? National household surveys in the United Kingdom [5, 10], Australia [6], and Brazil [19] have suggested a lifetime prevalence of 0.5% to 2.0% among men in these countries. In the United States, no household surveys of the general population have been conducted since 1994, at which time the American National Household Survey estimated that about 1,000,000 Americans had used AAS [72]. A recent review, combining American household survey data with more recent American studies involving college students and young adults, has estimated that between 2.9 and 4.0 million American men have used AAS at some time in their lives [58, 61].

Given that AAS use affects many millions of people worldwide, one might ask why there is not a larger literature of clinical and research studies on AAS use. Several factors may account for this paucity of research. First, as mentioned earlier, AAS use is a relatively new phenomenon, in contrast to use of other types of drugs such as cannabis and opiates that have existed for millennia. Furthermore, the great majority of AAS users are still relatively young; even most older users – those individuals who first started using AAS as youths in the 1980s and 1990s, when AAS first entered the general population – are only now approaching middle age. Thus, most AAS users are still too young to have exhibited long-term adverse effects from AAS exposure and hence have not come to the attention of the clinical community. AAS use has also escaped clinical attention because it rarely precipitates acute toxic reactions that bring patients to the emergency room, in the manner of opiate overdoses or severe alcohol intoxication. Thus, drug detection systems based on emergency room visits, such as the American DAWN network [73], rarely detect AAS abuse. For all these reasons, a large population of AAS users exists outside the view of most clinicians and researchers.

Further compounding this situation, AAS users rarely seek treatment and rarely disclose their AAS use to physicians in any event. In one study, 56% of AAS users reported that they had

never disclosed their AAS use to any physician that they had seen [62]. This statistic is particularly striking when it is considered that it was obtained from a group of men who had already volunteered to participate in a psychiatric interview study. Thus, these men were likely more candid than AAS users as a whole, and therefore the 56% figure probably underestimates the actual degree of nondisclosure by AAS users.

Finally, clinicians should be aware that many so-called dietary supplements, sold over the counter in supplement stores or available through the Internet, may contain surreptitious AAS, other potentially performance-enhancing drugs, and other untested substances of unknown toxicity [20, 47, 66, 75]. Not only are these surreptitious ingredients often of unknown efficacy and toxicity, but the identity and dose of these ingredients may not correspond to that specified on the label. Thus, the population of known AAS users has been augmented with substantial numbers of unwitting AAS users who have ingested these drugs through dietary supplements.

21.3 Adverse Effects of Long-Term AAS Use

Cardiovascular effects Given that AAS use is relatively recent, often undetected, and inadequately studied, our understanding of the adverse effects of these drugs remains limited. However, several important adverse effects have begun to emerge as areas of primary concern. Perhaps the most worrisome consequence of long-term AAS exposure is its effect on the cardiovascular system [1, 58, 61]. This problem has been suggested by numerous case reports, emerging over the last 20 years, describing premature death from myocardial infarction in young men who were apparently using AAS. One study followed up 62 leading Finnish powerlifters for 10–15 years after the time that they had competed; these men had all likely used AAS [50]. The investigators found that 8 (13%) of the powerlifters had died on follow-up – a rate significantly higher than in matched individuals from the general population. Three of the eight deaths in the powerlifter group were attributed to myocardial infarction. It appears likely that most of the cases of myocardial or cerebral infarction in young AAS users are attributable to premature atherosclerotic disease, likely caused by the fact that AAS – especially orally active 17-alkylated AAS – produce markedly adverse effects on lipid profiles [35]. The potential consequences of this atherogenic profile are illustrated by one pilot study of 14 competition bodybuilders that found markedly elevated levels of coronary artery calcium relative to that expected for men of comparable age [68]. More recently, in the largest study to date of the cardiovascular adverse effects of AAS exposure, our group compared 86 long-term AAS users and 54 otherwise similar weightlifters reporting no history of AAS [7]. Using computed tomography coronary angiography, we found that the AAS users exhibited significantly elevated atherosclerotic plaque in the coronary arteries as compared to the nonusers, and the degree of plaque, as well as other measures of atherosclerotic disease, was signally associated with lifetime duration of AAS exposure. Three of the 86 AAS users recruited for the study had experienced a myocardial infarction prior to the age of 45.

A growing literature has also demonstrated that AAS may commonly cause cardiomyopathy. In our recent study just cited, AAS users displayed impaired systolic function, as reflected by significantly decreased mean left ventricular ejection fraction, as well as impaired diastolic function, as shown by significantly decreased early left ventricular relaxation velocity [7]. Interestingly these impairments of systolic and diastolic function were much more prominent in individuals currently taking AAS at the time of evaluation and less serious among AAS users who were currently off-drug at the time of evaluation. Many other smaller studies have also demonstrated similar evidence of cardiomyopathy among AAS users (e.g., [4, 14, 42]).

AAS may also produce other toxic effects on the cardiovascular system, including hypertension, cardiac arrhythmias, and coagulation abnormalities [1]. These effects likely combine with the effects described above to increase rates of

cardiac morbidity and mortality in AAS users [46]. At present, the overall prevalence of cardiac disease in AAS users is unknown but is likely rising as increasing numbers of long-term AAS users are now moving into the age of increased risk for these phenomena.

Neuroendocrine effects Exogenous AAS suppress the function of the hypothalamic-pituitary-testicular (HPT) axis in men, leading to decreased gonadotropin production from the hypothalamus, decreased luteinizing hormone and follicle-stimulating hormone from the pituitary, and consequent decreases in testicular production of testosterone and spermatozoa [15]. Therefore, when a man discontinues AAS use, especially after a prolonged course of AAS, he will likely exhibit AAS-withdrawal hypogonadism [74]. Normally, this interval of hypogonadism will be self-limited, because the HPT axis will gradually return to normal function and restore natural testosterone production. However, a growing literature has suggested that some men may exhibit very prolonged hypogonadism after discontinuing AAS, sometimes lasting more than a year, and in some cases perhaps becoming irreversible [13, 30, 31, 67]. The mechanism in these cases remains poorly understood, but may reflect a direct toxic effect of AAS on the testis itself. As with most other forms of AAS-induced adverse effects, the prevalence of prolonged or irreversible hypogonadism remains unknown. This is a matter of serious concern, since hypogonadism may lead to loss of libido, impaired sexual function, infertility, and in some cases severe depression. These effects may induce AAS users to quickly resume AAS to "self-treat" these dysphoric symptoms, thus leading to repeated cycles of AAS use and ultimately to AAS dependence syndromes. We discuss this issue in greater detail below.

Psychiatric effects AAS use and withdrawal may precipitate major mood disorders in some susceptible individuals. During periods of AAS use, especially use at very high doses, some individuals will develop hypomanic or manic syndromes characterized by increased self-confidence, irritability, aggressiveness, hyperactivity, and impaired judgment [22, 58, 61]. In rare cases, these syndromes may be associated with psychotic symptoms, such as grandiose or paranoid delusions [64]. In some individuals, hypomanic syndromes may also be associated with violent behavior, often entirely uncharacteristic of the individual's premorbid personality, and sometimes leading to acts of attempted or actual murder. Over the last 25 years, a number of reports have described individuals with no prior history of a major psychiatric disorder, no history of violence, and no criminal record, who committed murder or attempted murder during an episode of AAS use [22, 52, 58, 61]. At first, it was widely speculated that aggressive or violent behavior by AAS users might simply reflect the premorbid personalities of individuals prone to use AAS or might be due to expectational factors. However, several placebo-controlled double-blind studies have now been conducted in which supraphysiologic doses of AAS were given to normal volunteers [64]. In four of these studies, doses of testosterone or testosterone-equivalent equal to 500 mg per week or greater were administered to normal volunteers under blinded conditions. In these four studies collectively, 5 (4.8%) of 105 men administered AAS exhibited manic or hypomanic syndromes, but none exhibited such syndromes on placebo. These findings indicate that psychological factors alone cannot account for these mood effects and suggest that some individuals apparently harbor a biological predisposition to AAS-induced mood symptoms – although the nature of this biological predisposition remains unknown [64]. Very likely the 4.8% prevalence of hypomanic or manic syndromes observed in these blinded studies represents an underestimate of the true rate of such symptoms in the field for several reasons. First, many AAS users ingest doses far higher than the equivalent of 500 mg of testosterone week, sometimes rising to the range of several thousand milligrams per week, and thus are likely at increased risk for mood-altering effects (see below). Second, the above-cited studies recruited participants who had been screened to be free of major psychiatric or medical problems; illicit AAS users in the field do not screen themselves with such care. Third, AAS

users may ingest additional drugs of abuse in conjunction with AAS that potentiate AAS-induced psychiatric effects. Alcohol, in particular, may act in conjunction with AAS to precipitate more severe behavioral effects that would be observed with comparable doses of either drug alone [58, 61].

AAS-induced mood symptoms appear to be idiosyncratic, with a majority of AAS users exhibiting little or no mood change and only a small minority exhibiting pronounced pathology. These effects may be more common in individuals ingesting higher doses of AAS. One study found that major mood disorders were uncommon in men ingesting less than the equivalent of 1000 mg of testosterone per week (a dose equivalent to about 15–20 times the normal male endogenous production of testosterone) but became more frequent at levels above 1000 mg of testosterone-equivalent per week [63]. Aside from this observation, however, it remains unclear why certain individuals are unusually susceptible to AAS-induced psychiatric effects; for example, these effects have not been convincingly demonstrated to be associated with prior history of psychiatric disorders or with any identified predisposing biological factor.

In the same manner that AAS exposure appears to precipitate hypomanic symptoms in some individuals, it has also been found that AAS withdrawal may precipitate depressive symptoms. AAS-withdrawal depression may occasionally be severe and has even been an apparent cause of suicide attempts or completed suicide [58, 61, 64]. Again, however, these mood effects appear highly idiosyncratic, with most men experiencing little or no depression on AAS withdrawal, while an occasional man develops profound depression. This idiosyncratic pattern has been observed even under laboratory conditions in a study where normal male volunteers were rendered deliberately hypogonadal by administration of the gonadotropin-releasing hormone agonist leuprolide [69]. Under these conditions, all men experienced loss of libido and other mild nonspecific symptoms, but only a small subgroup of about 10% of the men experienced prominent depressive symptoms. As with hypomanic symptoms, the mechanism of these idiosyncratic depressive responses remains poorly understood.

Other adverse effects AAS have also been associated with a variety of other less serious or less common adverse effects on other organ systems [53, 58, 61]. For example, some users occasionally develop severe truncal acne, and many develop gynecomastia caused by estrogenic metabolites of AAS. These are both largely cosmetic issues that rarely deter young AAS users from continued use. AAS have also been implicated in occasional cases of hepatotoxicity, including peliosis hepatis (the formation of blood-filled cysts in the liver), and rare cases of hepatic adenomas, adenocarcinomas, and other tumors. However, these hepatic effects are rare. In our experience, there appears to be a widespread misconception among clinicians that serious hepatotoxicity with AAS is relatively common. This misconception is likely attributable to the fact that AAS users frequently exhibit marked elevations of so-called liver enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT). However, these same enzymes are also present in muscle tissue and hence will be elevated in muscular individuals undergoing intense resistance training. Thus, elevations of these enzymes in AAS users are generally a consequence of muscle trauma, rather than evidence of liver disease [16, 53]. Genuine liver disease should generally be suspected only in cases where aminotransferases are elevated in the *absence* of an elevation in creatine kinase (CK; an enzyme which is rapidly elevated in the presence of muscle trauma) or in the *presence* of an elevation of gamma-glutamyl transferase (GGT; an enzyme that is present exclusively in the liver and not in the muscle). In these latter cases, the possibility of a concomitant alcohol use disorder should be considered.

Musculoskeletal complications of AAS use include tendon rupture, which may occur as a result of disproportionately strengthened muscles and possibly weakened tendons [30, 31, 40]. Recent evidence has also implicated AAS in cases of focal segmental glomerulosclerosis [23]

and possibly other cases of renal failure [40, 51]. By contrast, there is little evidence that AAS tend to precipitate or exacerbate prostate cancer, with only two cases of prostate cancer in possible AAS users reported in the entire literature, both of which were published more than 20 years ago [27, 32]. The absence of such reports in more recent years, despite much larger numbers of aging AAS users, suggests that there may be little or no association between AAS use and prostate cancer – an observation consistent with recent work questioning the belief that increased testosterone can cause prostate cancer or contribute to prostate cancer flares [45].

Finally, a new and worrisome possibility is that prolonged exposure to high levels of AAS may lead to apoptosis of brain cells. Testosterone-induced apoptosis of human neuronal cells was first demonstrated in vitro in 2006 [18], with some of these effects occurring at testosterone concentrations within the range that might be attained by humans using very large doses of AAS. This observation caused the investigators to speculate that long-term high-dose AAS users might eventually experience cerebral apoptotic effects similar to those demonstrated in the laboratory. In the first study, to our knowledge, to pursue this hypothesis in humans, our group administered a battery of neuropsychological tests to 31 AAS users and 14 non-AAS-using weightlifters in the United Kingdom [34]. Although the two groups exhibited comparable performance on reaction time, a continuous performance task, and on verbal memory, the long-term AAS users showed significant deficits compared to nonusers on two tests of visuospatial memory. Furthermore, performance on one of these visuospatial tests showed a highly significant association with total lifetime dose of AAS exposure. A subsequent study in the United States, using magnetic resonance spectroscopy, demonstrated deficits in levels of scyllo-inositol in a group of eight AAS users compared to ten non-AAS-using weightlifters [39]. Scyllo-inositol prevents clumping and deposition of β amyloid, and therefore this deficit, if demonstrated in a larger sample, might represent a risk factor for early-onset dementia. A recent study in Norway found widespread cortical thinning and smaller neuroanatomical volumes, including total gray matter, cerebral cortex, and putamen, in AAS users as compared to nonusing weightlifters [8]. These differences related significantly after adjustment for several potentially confounding variables, and the magnitude of these differences appeared to be associated with cumulative lifetime AAS exposure.

21.4 AAS Dependence Syndromes

It is now well established that AAS can cause a dependence syndrome, characterized by chronic AAS use that may persist despite adverse effects [26, 28]. In an analysis of 10 studies that used criteria adapted from the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders* [3, 26, 28] to diagnose AAS dependence in 1248 AAS users collectively, the mean prevalence of AAS dependence across all studies was approximately 33% [58, 61]. Thus, it would follow that some millions of men around the world have experienced or are currently experiencing AAS dependence, with a consequently increased risk for the adverse effects enumerated above. As mentioned earlier, AAS use in women is rare, and AAS dependence in women is consequently extremely rare, with only two female cases documented to our knowledge in the world literature [12, 44].

AAS dependence may arise as part of a larger picture of dependence upon performance- and image-enhancing drugs in general [24]. This issue has been discussed in detail by Hildebrandt and colleagues, who have noted that many individuals may exhibit not only pathological use of AAS but also use of other potentially anabolic substances (e.g., human growth hormone and insulin), thermogenic ("fat-burning") substances (e.g., clenbuterol, thyroid hormones, and sympathomimetic drugs), and drugs used to counteract the side effects of AAS (e.g., aromatase inhibitors). Individuals using these various performance- and image-enhancing drugs may also display a characteristic cluster of symptoms of body image disturbance, together with symptoms of potentially pathological dieting and exercising behavior. Hildebrandt and colleagues have pro-

posed a more detailed set of diagnostic criteria to capture these various aspects of a broader dependence syndrome [24].

AAS dependence is associated not only with use of other performance- and image-enhancing drugs but also frequently with use of classical drugs of abuse as well. Recent studies have increasingly documented that AAS use may arise as but one of many forms of drug use in the midst of a pattern of polydrug abuse and dependence [17, 35, 70]. These observations further contradict the popular notion that AAS use is primarily a phenomenon among athletes pursuing a lifestyle of health and fitness. To the contrary, AAS is often simply another form of drug use seen in polysubstance abusers.

Despite the increasing overlap between AAS use and abuse of classical drugs, it must be recognized that AAS possess certain unique features. Classical drugs are typically ingested because they produce an immediate "reward" in the form of acute intoxication (a "high") shortly after ingestion. Addiction to classical drugs often occurs because individuals come to use the drugs more frequently and in higher doses to obtain the intoxicating effect. AAS, on the other hand, deliver very little sense of acute intoxication and instead deliver a delayed reward of increased muscularity and decreased body fat. Thus, it may initially seem puzzling that AAS would be prone to producing a dependence syndrome in such a large proportion of users. However, several mechanisms may contribute to the high prevalence of AAS dependence. Specifically, we have hypothesized that there are three pathways that collectively contribute to AAS dependence: an "anabolic" pathway, an "androgenic" pathway, and a "hedonic" pathway (Fig. 21.2). These three pathways may contribute to AAS dependence in different degrees in different individuals, and each

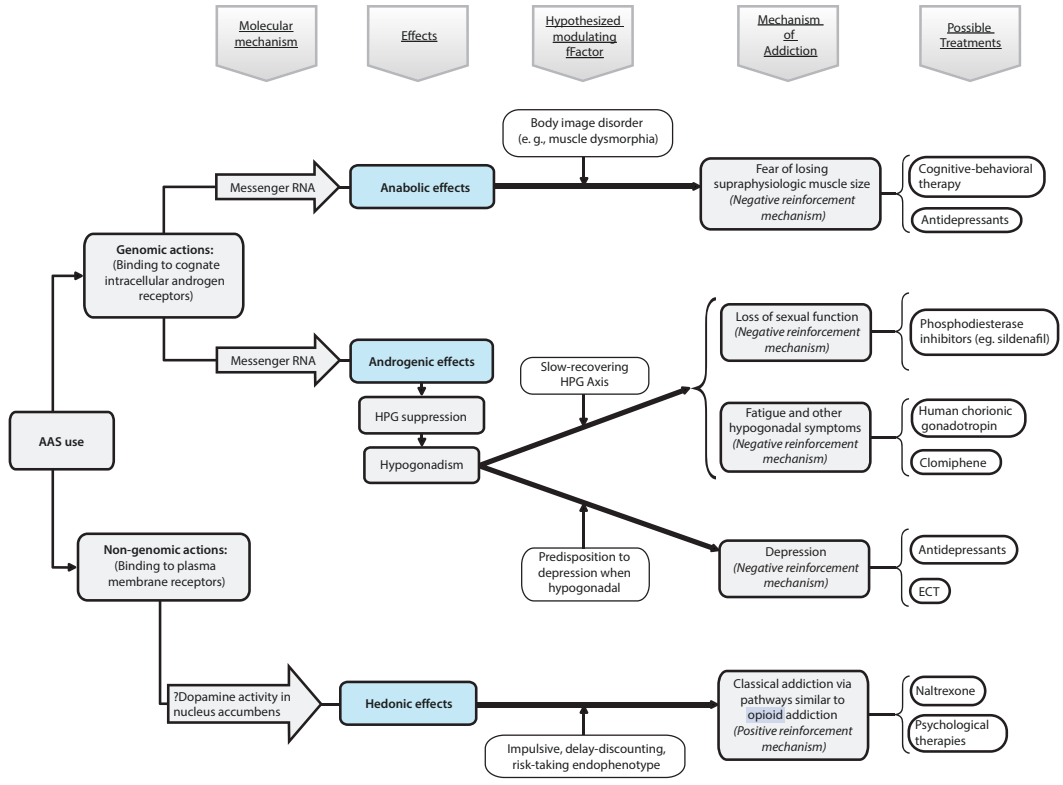

Fig. 21.2 AAS dependence: an "anabolic" pathway, an "androgenic" pathway, and a "hedonic" pathway

of these pathways may dictate particular treatment strategies as detailed in the next section.

The "anabolic" pathway refers to the ability of AAS to build muscle and decrease fat, thereby enhancing body image. Individuals with prominent body image concerns, especially those with a form of body dysmorphic disorder called "muscle dysmorphia," may be drawn to AAS use because of a pathological concern that they are not sufficiently muscular [36, 71]. Indeed, we have shown in one recent study that adolescent concerns about muscularity represented perhaps the strongest predictor of eventual AAS use among men who lift weights [55]. AAS users with body image concerns may gain large amounts of muscle mass by weightlifting and use of AAS, but paradoxically they may often grow even more concerned about their muscularity as time passes. As a result, they become anxious about discontinuing AAS, fearing that they may lose some muscle mass, and may quickly resume taking AAS after stopping a prior course because of these fears.

The "androgenic" pathway refers to the fact, discussed earlier, that exogenous AAS suppress the HPT axis. Upon stopping AAS, especially after a prolonged course of use, many men will experience profound AAS-withdrawal hypogonadism, with associated loss of libido, fatigue, and occasional pronounced depression [74]. Men experiencing these dysphoric symptoms may be prompted to rapidly resume AAS to restore themselves to normal mood and sexual functioning. This potential cause of AAS dependence was proposed some 30 years ago by Kashkin and Kleber [38] as a potential "anabolic steroid addiction hypothesis."

Finally, it has become increasingly clear that there is also a "hedonic" pathway to AAS dependence, apparently mediated by subtle hedonic effects of AAS. Unlike the anabolic and androgenic effects of AAS, which are mediated by binding to cognate intracellular androgen receptors, the hedonic effects appear to be mediated by binding to plasma membrane receptors. Thus, the hedonic effects of AAS likely arise via a mechanism similar to that induced by classical drugs, perhaps as a result of increased dopaminergic activity in the nucleus accumbens. Strong evidence for a hedonic pathway to AAS dependence arises from animal studies, which have shown that rats and mice will exhibit conditioned place preference for testosterone administration and that male hamsters will self-administer testosterone to the point of death [76]. Interestingly, self-administration of testosterone is blocked in hamsters by administration of the opioid antagonist naltrexone [76]. This is one of several lines of evidence suggesting that opioidergic mechanisms may be involved in the hedonic pathway to AAS dependence. Although a full discussion of these issues is beyond the scope of this chapter, a recent review by Nyberg and Hallberg provides an excellent summary of current knowledge in this area [48].

21.5 Treatment of AAS Abuse and Dependence

AAS users rarely seek treatment from clinicians, as mentioned above, and hence the available literature regarding treatment remains minimal. There are several reasons for this, many of which have been discussed above. First, AAS users are typically concerned with their body image, often to a pathological degree, and are reluctant to discontinue a drug that has allowed them to achieve a muscular physique. Thus, for an AAS user to approach a clinician for help in discontinuing AAS would be somewhat analogous to a patient with anorexia nervosa approaching a clinician with a request that she wants to gain body weight. In both cases, seeking treatment effectively contradicts the underlying disease. Furthermore, unlike the analogy of anorexia nervosa, where patients may develop life-threatening symptoms that bring them to clinical attention, AAS users rarely develop severe adverse effects in the early stages of AAS use and hence have little motivation to seek clinical care. As noted earlier, widespread illicit AAS use did not develop until the 1980s and 1990s, and thus most of the world's AAS users are still below the age of 50 and have not entered the age of risk for long-term medical complications of the types described above.

Finally, it should be reiterated that AAS users often have little faith in clinicians and feel that clinicians are poorly informed about AAS effects – an attitude confirmed in surveys of AAS users [62] and abundantly illustrated in AAS- and bodybuilding-related sites on the Internet [9].

For all of these reasons, clinicians should remain alert for possible AAS use when seeing younger male patients, even if these patients do not disclose AAS use on interview. Young men who seem unusually muscular, while still having low levels of body fat, may be particularly likely to represent surreptitious AAS users. As we have noted in prior publications, there is a relatively clear upper limit of muscularity that can be obtained by men while still retaining low body fat, and men above this limit are very likely lying if they claim that they have not used drugs [41, 59]. Other possible clues to surreptitious AAS use in muscular young males are prominent acne, gynecomastia, and findings of abnormal cholesterol profiles or unusually high hematocrit. We [59, 60] and others [11] have detailed these and other possible clues to AAS use in previous publications. Note that testosterone levels in surreptitious AAS users may be either grossly elevated (in cases where the individual is self-administering high doses of testosterone) or grossly depressed (in cases where an individual is self-administering other AAS, but not testosterone, thereby suppressing his own endogenous testosterone production). Thus, any testosterone level markedly below or markedly above the normal range should raise suspicion of surreptitious AAS use.

It should also be reiterated that the great majority of AAS users are not athletes. Thus, individuals reporting no competitive athletic activity may nevertheless be AAS users. Similarly, it should be remembered that AAS use is increasingly documented as a component of polysubstance abuse, and thus the possibility of AAS use should always be considered in young male patients reporting abuse of other substances. For example, in 1 study of 223 consecutive men admitted to a substance abuse treatment unit [29], it was found that 29 (13%) reported a past history of AAS use but that AAS had been documented by the admitting clinician in only 4 of these 29 cases.

Despite the above barriers to recognition and treatment of AAS users, our impression is that growing numbers of AAS users will be seen for treatment over the next decade. The prime reason for this trend, we believe, is that large numbers of AAS users are only now beginning to move into middle age and developing cardiac, neuroendocrine, and other complications that bring them to the attention of clinicians. In particular, our research group has recently seen various AAS users, generally over the age of 35, who have exhibited problems including myocardial infarction occurring prior to the age of 45, cardiomyopathy sufficient to produce symptoms of congestive heart failure, chronic hypogonadism with loss of libido and erectile function, evidence of renal failure discovered on laboratory testing, and "brittle" mood disorders with abrupt swings between episodes of hypomanic irritability and aggressiveness and episodes of depression with suicidal ideation. Often, these AAS users had never disclosed their AAS use to a physician prior to developing an adverse effect that brought them to clinical attention.

Once a clinician has identified an AAS user, and once that individual has decided that he wants help in discontinuing AAS use, what treatment options can be offered? As we have discussed in our previously referenced paper on treatment of AAS dependence [27, 32], the possible treatments will be dictated to some extent by the three different pathways that we have postulated as causes of AAS dependence. First, in men with muscle dysmorphia, who are pathologically afraid of loss of muscularity upon stopping AAS, it would seem appropriate to use treatments that have been successfully applied for other forms of body dysmorphic disorder. These include antidepressants such as selective serotonin reuptake inhibitors and clomipramine, which have been shown effective in controlled trials in patients with body dysmorphic disorder, even though these agents have not been specifically studied in muscle dysmorphia per se [54]. Body dysmorphic disorder has also been shown to respond to cognitive behavioral therapies [54],

and therefore it seems likely that cognitive behavioral approaches would be helpful for AAS users who have to develop pathological concerns with body image.

Second, it is imperative to address the neuroendocrine effects of AAS, since the dysphoric effects of AAS-withdrawal hypogonadism may often prompt AAS users to resume their drug use. Treatment of AAS-withdrawal hypogonadism should ideally be handled by an endocrinologist familiar with this population. Typically, treatment would consist of administration of human chorionic gonadotropin (HCG), which mimics the effects of pituitary-luteinizing and follicle-stimulating hormones, thus stimulating the testis to resume production of testosterone and spermatozoa. HCG may be started weeks before actually discontinuing AAS in order to "jumpstart" testicular function. In addition, clomiphene is usually added because this drug mimics the effects of hypothalamic gonadotropin-releasing hormone and thus stimulates the pituitary to begin its own natural production of luteinizing and follicle-stimulating hormones. Clomiphene exists in two isomers, the *trans* isomer (enclomiphene) and the *cis* isomer (zuclomiphene). Enclomiphene is an estradiol antagonist and is responsible for stimulating pituitary gonadotropin release; zuclomiphene is an estradiol agonist and hence does not contribute to this effect or even antagonizes this effect. Therefore, an estrogen antagonist such as tamoxifen or letrozole may be administered in conjunction with clomiphene to neutralize its estrogenic effects. More detailed discussions of these treatment strategies are available in endocrinological publications [74].

Finally, clinicians may need to address the hedonic aspects of AAS dependence. Here it seems likely that the possible treatment modalities should resemble those found effective for classical drugs of abuse, whose dependence-inducing properties are often largely based on hedonic mechanisms. There are virtually no available studies of treatment of AAS dependence using classical substance abuse treatment modalities, but we have offered speculations on possible treatment options in a recent paper [27, 32]. It is conceivable, for example, that long-acting preparations of intramuscular naltrexone might be of some value for treatment of AAS dependence, given that this modality has been shown effective for other forms of substance dependence and has also been shown to be effective at preventing testosterone dependence in animal models as mentioned above. Also, psychological therapies shown effective in treating other forms of substance dependence might well prove helpful in AAS dependence, especially in cases where AAS dependence occurs in the context of polysubstance use or dependence. Thus, motivational therapies designed to encourage commitment to treatment may be of value, and once treatment is initiated, modalities such as contingency management, supportive-expressive therapy, and behavioral couples therapy might be effective. The last approach might be particularly indicated in AAS users, since women may be abused by AAS-using men and be eager to encourage these male partners to abstain from subsequent use.

In conclusion, it should be noted that much of the above discussion remains speculative, since so few AAS users have actually sought and received a clinical treatment to date. However, our knowledge of treating AAS use will likely expand over the next decade as increasing numbers of users come to clinical attention and thus enter treatment.

21.6 Treatment of AAS-Associated Psychiatric Syndromes

As detailed above, most of the adverse effects of long-term AAS use are medical and fall outside the domain of clinicians who treat substance abuse disorders. Individuals displaying such effects will therefore likely require referral to appropriate specialists, most often cardiologists or endocrinologists. However, the psychiatric effects of AAS use and withdrawal can typically be managed by clinicians with mental health expertise. Although there is very little published literature on the treatment of AAS-induced hypomania or mania, the first priority of treatment is

clearly the removal of the offending agent. Thereafter, in our experience, standard treatment for manic symptoms (e.g., antipsychotics, valproate, and lithium) appears appropriate – although this has not been formally assessed in clinical trials. Major depressive episodes associated with AAS withdrawal will typically require endocrinological intervention to restore HPT function, as discussed above. In addition, based on our experience, standard psychiatric treatments for depression, including antidepressant medications and electroconvulsive therapy, may well be indicated. Again, we are aware of no clinical trials of psychiatric treatments for AAS-withdrawal depression, although one case series has reported success with fluoxetine [43] and one case report has described success with electroconvulsive therapy in an AAS user who failed to respond to tricyclic antidepressants and fluoxetine [2]. In AAS-withdrawal depression requiring treatment, it seems likely that treatment can be discontinued once neuroendocrine parameters have returned to normal – but we are not aware of longitudinal studies addressing this issue.

21.7 Conclusion

Most drugs of abuse have been ingested by humans for centuries or millennia, but AAS misuse represents perhaps the newest of the world's major forms of substance abuse and dependence. Although elite athletes began using AAS as far back as the 1950s, widespread AAS use by rank-and-file AAS users did not begin until the 1980s in the United States and even later in most other Western countries. Thus, even most of the world's older AAS users – those who first tried AAS as youths in the 1980s and 1990s – are only now reaching middle age and entering the age of risk for adverse cardiac, neuroendocrine, and other effects of AAS exposure. Consequently, scientific knowledge about the effects of AAS use and appropriate treatment strategies for AAS dependence remain limited. However, this situation seems poised to change over the next decade or two, as larger numbers of aging AAS users develop adverse effects that bring them to clinical attention and treatment. It is to be hoped that clinicians will become increasingly conscious of the possibility of AAS use when evaluating male patients and will be sensitized to the physical and laboratory signs of AAS use mentioned above. Similarly, it is to be hoped that increasing research will better delineate the frequency, severity, and duration of AAS-induced adverse effects.

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Prescription Drug Abuse: Risks, Diversion, and Prevention

22

Jørgen G. Bramness

Contents

Abstract

Abuse of and dependence on prescription drugs is an increasing problem and is closely related to the increasing use of prescription drugs worldwide. The problem of prescription drug abuse includes both weak and strong opioids for pain management; sedating drugs like benzodiazepines, barbiturates, and newer hypnotics; and stimulant drugs used for the treatment of narcolepsy and attention-deficit/hyperactivity disorder (ADHD). Several other prescription drugs also have the potential for abuse. This chapter focuses on the epidemiology, the diagnostics, the treatment, and the prevention of prescription drug abuse.

Keywords

Prescription drugs · Abuse · Opioids · Benzodiazepines · Central simulants · Doctor shopping

J. G. Bramness (✉)
Norwegian Competence Centre for Dual Diagnosis
Innland Hospital Trust, Hamar, Norway

Norwegian Institute of Public Health, Oslo, Norway

Institute of Clinical Medicine, UiT, The Arctic University of Norway, Tromsø, Norway
e-mail: j.g.bramness@medisin.uio.no

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22.1 Introduction

As long as we have had medicinal drugs, there has been abuse. The problem is probably increasing [67]. All health-care workers need to be aware of this, but prescribing doctors need to pay particular attention.

All prescription drugs that seek market authorization need to have their abuse potential investigated. Guidelines for such testing exist [31]. But many of today's drugs were marketed long before these modern prerequisites. Furthermore, even with careful premarket testing, the real abuse potential of many drugs may not be fully recognized. Before marketing, drugs are usually tested on smaller, selected (non-abuser) populations under strictly controlled conditions, which do not allow for inappropriate use. Thus, postmarketing surveillance is needed to reveal abuse of drugs; many drugs are not fully recognized for their abuse potential until they have been on the market for many years [4].

Even though many drugs have abuse potential, the same drugs obviously also have therapeutic benefit. If abuse potential is discovered, the drug can be scheduled with restrictions on its use. We must weigh the risks against the benefits. If the risks are perceived to be greater than the benefits, action should be taken. Ultimately, this could mean withdrawing the market authorization of a drug, but often more modest action will serve the purpose.

This backdrop is useful to keep in mind when encountering prescription drug abuse, be it as a doctor worried about prescribing drugs that could be used for reasons other than therapeutic, a therapist encountering a patient with abuse or dependence problems because of these drugs, or when contemplating using known drugs of abuse for the benefit of seriously ill patients.

22.2 Epidemiology of Prescription Drug Abuse

It is not easy to get an overview of the epidemiology of prescription drug abuse. In surveys, responders tend not to answer questions truthfully. Some are reluctant to admit breaking the law. Often, the people of most interest are not available for answers; they may be imprisoned or in treatment. Some seldom open their mailbox or do not even have an address. If you choose to do your research in a prison or a treatment institution, you will face the problem of selection bias. Not all abusers or dependants will be under treatment or imprisoned. The study of the epidemiology of abuse thus needs to draw on a variety of sources to aggregate comprehensive data. This is no less true for prescription drug abuse.

There are two main types of data that we can get from epidemiological studies. The first is signals of abuse in drugs not previously recognized as drugs of abuse. Case reports and case series often give the first signals of such abuse potential [4, 43]. These signals must be followed up by a second kind of studies with more systematic and broader data collection. This is done to substantiate the signal and to investigate the *extent* of the abuse. The different sources of data below may serve as providers of both types of information.

22.2.1 Monitoring Populations or Patients

Population Surveys Despite the mentioned drawbacks of population surveys, they can provide information on the extent of the prescription drug abuse problem. Surveys have shown us that nonprescribed use of prescription drugs is quite common. The National Comorbidity Survey showed that more than 7% of adults reported having used non-prescribed sedatives [39]. A survey, also from the United States, showed that during the previous month, around 2% of the total population (≈ 6 million people) had abused pain medication, 0.7% tranquilizers (mostly benzodiazepines), 0.4% stimulants (attention-deficit/hyperactivity disorder (ADHD) medication), and 0.1% sedatives in 2008 [85]. Several studies show that figures vary a lot [80]. Being male, being older, having a parent who has done the same, and reporting more psychiatric symptoms increased the risk [17, 22]. From other studies, we know that people with alcohol or drug-use problems have a higher risk of abusing prescription drugs [59].

Patient Surveys Such monitoring programs will provide information both on the size of a problem and will give signals of drugs to be monitored. The Drug Abuse Warning Network (DAWN) gathered information on drugs mentioned at emergency room visits across the United States from 1974 to 2011 and served as a source of information about the extent of prescription drug abuse and gave signals on new drugs of abuse [19]. The 2010 figures showed that 30% of the mentions for prescription drugs were benzodiazepines and 40% were opioids. The drugs were mentioned in 20% and 18% of all emergency room visits respectively, and prescription drugs were mentioned almost as often as narcotics. It is also valuable to get information from patients entering treatment for drug abuse [49].

Adverse Effects Databases Signals of prescription drug abuse often come from national or international adverse effects databases, such as the WHO in Uppsala Monitoring Centre Adverse Effects Database. Such databases have given us information on the abuse liability of drugs like pregabalin [35] or quetiapine [20].

Forensic Data Data from driving under the influence (DUI) cases, from autopsies, or from prisons may be useful in determining whether drugs are abused or even which drugs are popular in the catchment area [9].

22.2.2 Monitoring Sources of Drugs

Sales Statistics As described above, US doctors started treating non-malignant pain with opioids in the mid-1990s, and a sharp increase in abuse of the drug has followed. As seen in the total consumption model, the sales of the drugs can tell us something about the amount of problematic use (and other adverse events; see Fig. 22.1). The large sales of opioids in the United States are closely related to high levels of abuse. For example, among 12th graders in the United States, nonmedical use of prescription drugs (opioids) is the second most common form of abuse [60]. Sales data should include area and/or country because this gives useful hints on specific abuse trends.

Prescription Data Prescription data is another source of information. Such data could stem from claims databases in insurance institutions, national prescription databases, such as those found in many countries in northern Europe, or through pharmacy records. Basically, two types of information, both important, can stem from these sources. First, we can gain information about the abuse liability of a drug by looking at phenomena like "doctor shopping": the more doctors a drug seeker is willing to go to in order to get hold of the drug, the higher the abuse liability [74]; forged prescriptions: if many prescriptions for a drug are forged, the higher the abuse potential [33]; high use of a drug indicating some people are using it for recreational purposes [34, 72]; or skewness in use, i.e., if a large proportion of the drug is consumed by a few individuals, this is indicative of abuse liability [36, 44]. Second, these sources of information might tell us directly how many individuals show overuse of the drugs in an area [12]. These data point to the fact that drugs like carisoprodol, clonazepam, flunitrazepam, alprazolam, and all opioids are attractive abuse drugs.

Other Legal/Gray Sources Surveys in the normal population have shown that the most prevalent sources of prescription drugs for abuse are friends and family [64]. This US study showed how pain medication was most often obtained; it may be different in other countries. Having a drug problem, using a lot of alcohol, or having peers with use increased the risk. Still, we know that many individuals start to abuse through drugs prescribed to a family member [8].

Illegal Sources Prescription drugs, be it opioids, benzodiazepines, or others, are found on the black market. They are diverted illegally from people who have them prescribed, do not use them, but sell them. They are also sold after thefts from patients, pharmacies, or factories. Thus, drug abuse situations can be monitored by looking at seizures of drugs by the police or customs.

Novel Channels of Drugs The Internet is a novel source of drugs and very difficult to control. Only a small share of the drugs bought are

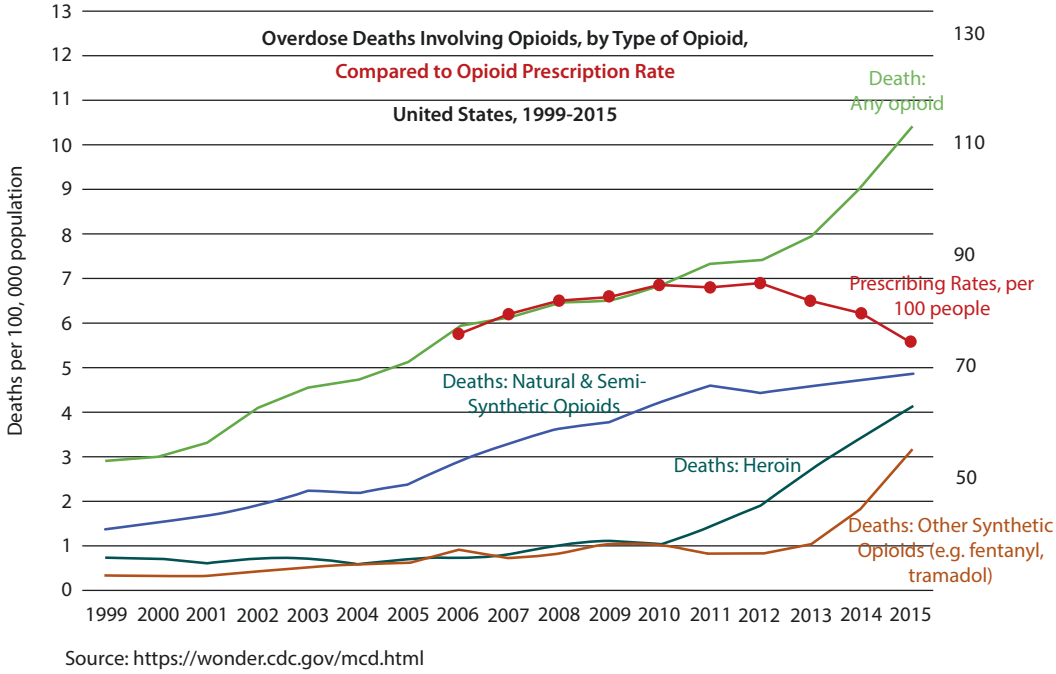

Fig. 22.1 The North American opioid epidemic. Data from Centers for Disease Control and Prevention (https://wonder.cdc.goc/med.html) showing prescription rates for opioids and deaths by medical opioids, heroin, and fentanyls

ever discovered by customs. But turning it the other way around, monitoring the Internet can be a way of picking up new trends. One such project is the European Union–funded Psychonaut Web Mapping Project that has been successful in identifying ever-increasing numbers of novel substances [27]. But data can also be collected by looking at websites for information or online reports of abuse [87].

Wastewater Analysis A novel approach that might give results in the future is to look at the presence of prescription drugs in wastewater (sewage analysis) [79]. By comparing sales statistics with findings in wastewater, one could get an idea of the black market for a drug, but also looking at weekly temporal variations in drugs, one might get a feeling how much is used for recreational use (most at weekends and less during weekdays) and how much is used on a regular basis (more evenly distributed).

In summary, we cannot today seriously say we know the extent of the problem of prescription drug abuse. No single source of data can substantiate all drugs that are abused or the extent of this abuse. Some data (surveys) will be flawed by information and selection bias; some data (databases) will not be able to identify the clinical features of abuse or dependence. We are therefore stuck with several estimates. And what do these tell us?

- These drugs are often used, but most use is clinically correct and well founded.
- Prescription drugs are, however, often abused, and the problem of abuse is increasing.
- The size of the problem is related to total sales of the drug; increased use always comes at the price of increased abuse. Countries with a high prescribing rate (such as the United States) have a substantial problem. In such countries, the problems following prescription drug abuse may equal those following the use of narcotic drugs.
- Some drugs have a higher abuse potential than others. As with other drugs of abuse, prescription drugs with high potency and a rapid effect will be more attractive to abusers.

- Patients who have legitimate use of these drugs are also at risk of abuse, but use according to the doctor's recommendations can also be problematic. Doctors should review their patient lists and act when necessary.
- Specific populations will have more risk of abuse of prescription drugs than others. These include drug abusers, psychiatric patients, but also patients with somatic problems such as pain.
- It often takes a long time from when a drug is first marketed until its true abuse potential is revealed, even with modern requirements for pre-marketing investigations. Always be open to signals of a drug's abuse potential.

22.3 Prescription Drugs of Abuse

22.3.1 Sedative Drugs

This group of drugs covers many different compounds (Table 22.1). They mainly belong to four groups: benzodiazepines, z-hypnotics, barbiturates, and barbiturate-like drugs. They are all agonist to receptor sites on the gamma-aminobutyric acid (GABA) receptor, subtype A. GABA is our main inhibitory neurotransmitter and is widespread throughout the CNS. The $GABA_A$ receptor complex is a ligand-gated ion channel. This transmembrane chloride channel is a pentamer with several different combinations of α (six subtypes), β (three subtypes), or γ (three subtypes) subunits and some other possible variants. To a large extent, the α subunit configuration determines a drug's abuse potential [5, 92]. While the barbiturates and barbiturate-like drugs can influence the receptor even in the absence of GABA, benzodiazepines and the z-hypnotics are dependent on the presence of GABA to perform their action. The consequence is that while barbiturates and barbiturate-like drugs are more dangerous and may more easily be overdosed, benzodiazepines and benzodiazepine-like drugs have a ceiling effect and thus a broad therapeutic window of use. The literature gives few, if any, examples of lethal overdoses of benzodiazepines taken alone in otherwise healthy individuals.

It is thus safe to say that when benzodiazepines were introduced at the end of the 1950s and in increasing numbers in the 1960s and 1970s, they were seen as a better and safer alternative to the barbiturates that had caused so many deaths and so much dependence [56]. The true abuse potential of these drugs was not revealed until the late 1960s and early 1970s.

Different benzodiazepines are basically the same regardless of their main indication. It is often arbitrary which indication the market authorization was filed for. It is most often a question of dosage whether a benzodiazepine is used as an anxiolytic (lower dose), a hypnotic (medium dose), or an antiepileptic drug (high dose). What differs between the compounds is their potency (mainly dependent on lipid solubility) and their pharmacokinetics. Table 22.1 shows this through the dosing and the terminal elimination half-life ($T_{½}$). It must be remembered that dosing in this table (and in much of the literature) is for the main use the drug is registered for. Taking the example of diazepam, doses would be 5–10 mg for anxiety, 10–20 mg for sleep, and up to 40 mg per day as an antiepileptic. Equipotency for benzodiazepines is thus a complex term. However, some are more potent than others (alprazolam, lorazepam, flunitrazepam, and clonazepam) and thus more attractive among abusers [6, 40, 45], partly because clinicians have a tendency to underestimate the differences in potency and subsequently dose high potency benzodiazepines relatively more highly. The $T_{½}$ is another parameter which varies between the benzodiazepines. It must however be remembered that owing to the phenomenon of acute tolerance (tolerance occurring within the same dosing), $T_{½}$ is not a good parameter for judging the time of effect for benzodiazepines. But the *relative* duration of action between the different benzodiazepines is roughly judged by this parameter. A short duration of action often also implies a short time between intake and effect, a parameter important for the reinforcing effects of a drug. Again, we see alprazolam, lorazepam, flunitrazepam, and clonazepam scoring highly on this parameter.

Z-hypnotics (zaleplon, zopiclone, eszopiclone, and zolpidem) are not benzodiazepines in

Table 22.1 Some commonly used sedatives marketed in many countries

	Compound (generic name)	Main use	Mean usual dose main use (mg)	Mean terminal half-life (hours)	Abuse potential
Benzodiazepines	Alprazolam	Anxiolytic	1	12	***
	Bromazepam	Anxiolytic	9	16	**
	Lorazepam	Anxiolytic	4	12	***
	Oxazepam	Anxiolytic	30	10	*
	Chlordiazepoxide	Anxiolytic	30	27	**
	Clobazam	Anxiolytic	30	18	**
	Diazepam	Anxiolytic	5	40	**
	Lorazepam	Hypnotic	1	12	***
	Temazepam	Hypnotic	15	14	**
	Flunitrazepam	Hypnotic	1	25	***
	Nitrazepam	Hypnotic	5	28	**
	Flurazepam	Hypnotic	15	60	***
	Clonazepam	Antiepileptic	4	36	***
Benzodiazepine-like hypnotics	Zaleplon	Hypnotic	10	1.5	*
	Zopiclone	Hypnotic	7,5	4.5	**
	Eszopiclone	Hypnotic	6	6	**
	Zolpidem	Hypnotic	5	2.5	**
Barbiturates	Barbital	Antiepileptic	750	30	***
	Phenobarbital	Antiepileptic	200	80	***
Barbiturate like drugs	Chlormethiazole	Muscle relaxant	600	6	**
	Meprobamate	Muscle relaxant	200	10	***
	Methaqualone	Muscle relaxant	150	74	***
	Chlormezanone	Muscle relaxant	200	40	**
	Orphenadrine	Muscle relaxant	100	16	**
	Chlorzoxazone	Muscle relaxant	750	1	**
	Carisoprodol	Muscle relaxant	700	2	***

Not all drugs will be marketed in all countries

their chemical structure. When introduced, their manufacturers wanted to have them introduced as "benzodiazepine-free hypnotics." However, their similarity to benzodiazepines in pharmacological effects are striking, and there is no longer doubt they can be abused. These drugs probably have a lesser capacity to relieve anxiety, and the role of anxiety in a drug's abuse potential should not be underestimated. It is thus true to state that the abuse potential of these drugs *may* be lower than for benzodiazepines, but the difference is likely to be marginal. We still see that zolpidem is a very popular drug of abuse in many countries. A distinct metal taste following the intake of zopiclone (also after i.v. intake) is probably preventive for abuse. Despite many claims to the contrary, eszopiclone has no advantages over zopiclone and probably none over benzodiazepines in terms of abuse potential. These drugs can be and are abused [43, 49].

Benzodiazepines are hugely popular among injecting drug addicts. Heroin users use them to prolong their intoxication and prevent withdrawal [82]. This may also contribute significantly to

overdose deaths [24]. Users of central stimulants will use benzodiazepines at the end of a binge or a run to "land" [52].

Barbiturates and barbiturate-like drugs are much less abused today than they were before. That does not mean that they cannot be abused. These drugs really taught us what prescription drug abuse is, with methaqualone (Quaalude®) as a prominent example. Their high lipid solubility and resulting potential to cross the blood-brain barrier quickly, and their ever-increasing effects with higher doses and no ceiling effect, even if marked tolerance triggered massive dose escalations made them very popular as drugs of abuse. When this was acknowledged, heavy restrictions were put on their prescribing, and these drugs were withdrawn in many countries, but they are still on the market in many others.

Carisoprodol is a barbiturate-like drug that has been around since the late 1950s. It is a prodrug of meprobamate, a highly abused barbiturate-like drug [70]. Carisoprodol, however, has effects itself, including being highly toxic [13]. A negative utility to risk ratio led to the market withdrawal of carisoprodol in the EU in 2008, leading to a drop in intoxications with the drug [47]. The drug is still marketed in the United States [78].

It is a point of discussion whether buspirone should be listed here. We have opted not to do so because of the low abuse potential shown for this drug in several studies. This is not to say that it cannot be abused in some situations or by some patients.

22.3.1.1 Analgesics

The mechanism of action and other pharmacological points concerning opioid analgesics, including those which are prescribed, are as described elsewhere in this book. There are at least two different groups of prescription opioid abusers. First, we have the pain patient who has aberrant use of his or her medication [93]. It is difficult to predict who the patients at risk seem to be. Second, we have the abusers without a prescription. This group includes anyone from the teenager who accesses a relative's pain medication to the marginalized heroin abuser adding prescription opioids to his or her abuse. The delineation between these two groups has become increasingly unclear in the light of the modern-day epidemic of opioids in the United States. The nonmedical use of prescription opioids in the United States is around 4% of the population [94].

Pain is a very common condition with potentially very severe consequences, such as reduced quality of life but also depression and suicide. The last three decades have seen an unprecedented emergence and culmination of a prescription opioid epidemic in the United States, and there is worry that other countries could follow. Until the mid-1980s, opioids were correctly viewed as a useful, but still problematic, tool of pain control that should be used with caution, most often only for cancer pain and acute pain conditions. From 1987 until the mid-1990s, a series of unfortunate events and statements paved the way for uncontrolled overprescribing of opioids in the United States. This included the misunderstanding that if opioids were used for pain, the patients could not become addicted [73, 76]. This huge misunderstanding paved the way for "ethics" campaigns stating that it was morally questionable to allow a patient to experience unbearable pain and that opioids needed to be used aggressively [63, 98]. Until around the year 2000, many advocated increased use of opioids in the management of nonmalignant pain [26]. Typically, the nomenclature of addiction was questioned and phrases like "pseudo-addiction" appeared [63, 76], and the American Pain Society was able to introduce pain as a "fifth vital sign" [26]. The US "direct to consumer" advertising, not found anywhere else in the world, increased the pressure on prescribing even more. It has been shown that the pharmaceutical company Purdue Pharma holding the patent for OxyContin played a major role in promoting these "alternative professional views" and the prescribing of OxyContin [96]. The company made a lot of money as the prescribing of opioids for non-cancer pain increased by a factor of 10 over a period of a few years. The increase in prescribing of opioids increased until around 2010 [25]. It must be added that foreign researchers visiting US colleagues during these years were a bit stunned by the fact that US epidemiologists were asking

themselves *why* they had so many problems with prescription opioid abuse. The obvious overprescribing was followed by increasing number of overdoses and overdose deaths [99]. There was drug diversion [21] and non-prescribed use of the same opioids. Around 2010, many people addicted to prescription opioids turned to heroin.

Prescription opioids were becoming harder to obtain, and they were expensive. In this wave, we saw a very high increase in overdose deaths due to heroin, with at least two-thirds those addicted to heroin in this wave having started with prescription opioids [53]. A third wave of opioid use with worrisome effects was the increasing use of the extremely potent fentanyl opioids [32, 50]. All this is shown in Fig. 22.1.

The North American opioid epidemic has, to a large degree, been contained to this continent, but some of the misconceptions underlying the epidemic are finding their way to other parts of the world [46]. There have been smaller increases in the use of opioids in several European countries [10], but the situation is not comparable to the United States and Canada. However, the authors urge for vigilance [95, 100]. There have been reports of fentanyl deaths in some European countries, but these reports are some years old, and it is uncertain whether or not they are related to the current opioid problem [54].

Opioid substitution treatment (OST) has been used effectively for opioid-dependent patients for more than 60 years [66] and has considerable advantages in increasing adherence to treatment programs [18], promoting rehabilitation [58], and preventing illnesses and death [23]. Worldwide methadone and buprenorphine (with or without addition of naloxone) are mostly used for the substitution treatment, but in principle, any opioid could be used. There is increasing use of long-acting morphine variants and even heroin [91]. There is always a risk that opioids given to patients will be diverted. Many different strategies have been put in place to try to avoid this with actions such as observed intake and no take-home medicines [102]. No strategy that is achievable can prevent all diversion, but reasonable measures should be taken. Some patients should be observed taking the drug. It is possible to measure serum methadone levels to make sure the drug is taken, but for other drugs, this is more difficult. Some countries have seen considerable diversion of opioids from their OST programs and overdose deaths in the wake of this [57]. For a comprehensive review of the subject, see Alho [3] (Table 22.2).

22.3.1.2 Central Stimulants

During recent years, there has been an enormous increase in the prescribing of central stimulating drugs for treating attention-deficit/hyperactivity disorder (ADHD). Using central stimulants to treat ADHD is an effective treatment in children [11] and probably also in adults [101], but not all these drugs are used as prescribed; some are also abused. This is partly true because patients with ADHD have an extra vulnerability to becoming involved in drug use [42]. The drugs can be abused by saving a whole week's worth of pills for a simultaneous intake to get a stimulant high or by selling the drugs to friends or on the black market. Epidemiological studies using wastewater indicate that methylphenidate is used as a party drug [84]. A typical therapeutic use of methylphenidate would involve using 10–30 mg, but 50–150 mg would be common in abuse. It is debatable whether bupropion should be listed here. We have opted not to do so because of the low abuse potential of this drug shown by several studies. This is not to say that it cannot be abused in some situations or by some patients.

Abuse of central stimulants includes using them as cognitive enhancers. This means otherwise healthy people take them in order to optimize cognitive abilities, using them to increase school performance or to stay awake and work for prolonged periods, be it as a student, soldiers in the field, or a truck driver with long shifts. Surveys show varying degrees of use, but quite a few students report having tried them to increase performance. Studies have found that central stimulants reduce errors and improve working memory even in those not disadvantaged [7, 77]. Some have found more mixed results and possible indications of genetic variability [90] Long-term memory may be positively influenced [62] with an increase in total recall [7]. There is more

Table 22.2 Some commonly used opioids marketed in many countries

Compound	Main use	Mean terminal half-life (hours)	Abuse potential	Comment
Morphine	Pain relief	2–3	***	
Ethyl morphine	Cough suppression	?	**	
Codeine	Pain relief	3–4	*	10% metabolized to morphine by CYP2D6
Fentanyl	Anesthesia	1–6	***	Mostly used as a transdermal patch
Hydrocodone	Pain relief	4–6	**	
Oxycodone	Pain relief	3–5	**	
Oxymorphone	Pain relief	1–2	**	
Dextropropoxyphene	Pain relief	8–24	***	
Hydromorphone	Pain relief	2–3	**	
Meperidine/pethidine	Pain relief	3–5	**	
Diphenoxylate	Constipating drug	12–14	*	
Methadone	Substitution in opioid dependence	6–8	**	High doses make once daily intake possible
Buprenorphine	Substitution in opioid dependence	20–73 hours	**	Strong binding (covalent) to receptor makes once daily intake possible

Not all drugs will be marketed in all countries

solid evidence of improved cognitive performance in periods of prolonged wakefulness, a fact that the world's many coffee drinkers can verify. Research in the combat field has, however, shown that the use of stronger central stimulants may not be optimal. In this area of research, there is interest in a wide variety of drugs stimulating the noradrenergic, serotonergic, and glutaminergic receptor systems. Such drugs could potentially be effective treatments for the cognitively impaired, such as patients with Alzheimer's disease (Table 22.3).

22.3.1.3 Other Drugs

Many prescription drugs can be abused. No complete list could ever be compiled. As prescribers, we always need to work with others to produce early warnings and to remain up to date on the possible dangers of prescribing different drugs. We must remember that abuse potential is often not revealed until a drug has been on the market for a very long time.

Several studies have shown the abuse potential of the antiepileptic GABA-ergic analogs pregabalin [88] and possibly also gabapentin [29]. This may be one reason why use of pregabalin may reduce the use of benzodiazepines [15]. Even so, a signal of abuse should not deter prescribing totally but should be included as one of many arguments to be included in the weighing of benefits and risks of prescribing.

There have been increasing reports on the abuse of the antipsychotic drug quetiapine. This is (contrary to what been believed) not only a product of marginal use on groups who have difficulties in getting hold of drugs but reflects a true abuse potential of the drug [55, 68, 75]. The extent of the abuse and the dangers associated with it are not clear, but abuse does happen.

A last group that has therapeutic potential but also an abuse potential are the $GABA_B$-receptor agonists. These include the highly abusable gamma hydroxybutyrate (GHB) [51] used for the treatment of AUD (both withdrawal and abstinence maintenance) mostly in Italy [61]. Phenibut was developed in the 1960s in the Soviet Union to enhance wakefulness in the armed forces but has a clear abuse potential [2]. The abuse potential of the most used AUC drug in France, Lioresal [1], is yet undetermined, but probably low [81] (Table 22.4).

Table 22.3 Some commonly used central stimulating drugs marketed in many countries

Compound	Main use	Mean usual dose main use (mg)	Mean terminal half-life (hours)	Abuse potential
Methylphenidate	ADHD and narcolepsy	20–30	2–3; 7–12 for extended release	**
Amphetamine	ADHD and narcolepsy	20	13	***
Dextroamphetamine	ADHD and narcolepsy	20	10	***
Ephedrine	Cough medicine	20–50	3–6	*
Diet pills	Weight loss	Varying	Varying	Varying
Caffeine	Narcolepsy and in combination for migraine	50–300 mg	Varying	Low
Melanotan	Illegal tanning product	10–30	1–2	?
Modafinil	Narcolepsy and to prolong wakefulness	200–400	15	*

Not all drugs will be marketed in all countries

Table 22.4 Miscellaneous drugs that have been reported abused

Compound	Main use	Abuse potential	Comment
Marinol and other synthetic cannabinoids	Pain and muscle spasms in MS patients	***	Being a synthetic cannabinoid with very high potency, it has a high abuse potential
Sativex (cannabis extract)	Pain and muscle spasms in MS patients	*	Abuse potential as with other cannabis products
Pregabalin	Antiepileptic	**	Case reports and reviews confirm the abuse potential of the drug [88]
Gabapentin	Antiepileptic	*	An increasing number of case reports point to the abuse potential of this GABA analog [29]
Ketamine	Anesthetic	**	This anesthetic is an antagonist to the glutamatergic NMDA receptor giving vivid hallucinations as one of its main effects [86]
Quetiapine	Antipsychotic	*	An increasing number of case reports point to the abuse potential of this antipsychotic drug [68, 75, 55]
Xyrem	GHB treatment of alcohol dependence and withdrawal	***	As for GHB [51]
Phenibut	$GABA_B$ agonist	**	Developed by the Russians in the 1960s and appears increasingly in the European market [2]
Lioresal	$GABA_B$ agonist also used for AUD treatment in France	?	This centrally acting muscle relaxant can possibly be abused in higher doses, but the euphoric and psychomotor effects are weak [1, 81]

Not all drugs will be marketed in all countries

22.4 Terminology and Diagnosis

In the face of prescription drug abuse, it is important to remember that most use of prescription drugs is legitimate and therapeutically wise. The overwhelming majority of those who receive a prescription for analgesics or for hypnotics or sedatives use these drugs for a limited period to get through a time of pain, insomnia, or life stress. However, problems can and do arise.

Some use too much. Some increase their dose. Others use the drugs for too long, after their original problem is over, in order to avoid the discomforts of discontinuation and withdrawal. The drugs can be taken for the wrong reasons. They are not meant to be used recreationally or as part of an addiction. And some people mix different drugs. This can be done for several reasons but increases the addictive potential of the drugs and increases the chances of intoxication, even lethal.

Use that is not in line with the doctor's recommendation is worrisome, but even drugs used as prescribed may become problematic. A prescription is no guarantee against harm. All prescription drug use even if used for good reasons or as prescribed may become problematic. Abuse, dependence, or addiction should be diagnosed according to the usual tools using ICD-10 or DSM-5 diagnostic criteria. A diagnosis of harmful use (abuse), dependence, or addiction is not different for prescription drugs than for other substance use disorders. However, some problematic use of prescription drugs does not fit into these categories, and other typical patterns may be visible that challenge our understanding of problematic use and the diagnostic systems. Some of these more archetypical prescription drug use patterns are listed here:

Pseudo-therapeutic Long-Term Use Sedating drugs are meant for short-term use only. The manufacturer, authority, and society guidelines say that the drugs should be used only for 3–4 weeks. Still, many patients continue to use the drugs for longer periods of time [16]. This group of patients may cause concern at the doctor's office because of discussions about the re-prescribing of the drugs. Many patients feel that their honesty is being questioned, and many doctors feel that they are being "forced" into prescribing for longer than necessary. These patients, however, are not true abusers. They certainly use the drugs for longer than intended, but seldom at high doses, most often at lower doses than prescribed, and they seldom increase their doses. These users are often termed quasi-therapeutic long-term users [41]. They are mentioned here because they are quite prevalent and clearly violate recommendations but may not represent a true problem.

Self-Medicating Pain/Anxiety/Insomnia Patients Patients with anxiety disorders and also patients with other psychiatric disorders may use different prescription drugs to self-medicate or treat their symptoms [65]. It is important to acknowledge that anxiety disorders, major depression, post-traumatic stress disorder, personality disorders, and pain conditions may lead to overuse of prescription drugs. The possibility of abuse should not stop the doctor from introducing effective and necessary treatment, but the dangers of overuse should be kept in mind. Even when drugs are used as prescribed, the patient may encounter problems such as tolerance, abstinence, abuse, and dependence (see below).

True Prescription-Drug Abuser Some patients can be labeled true prescription-drug abusers. These are patients with no or marginal reasons to use these drugs, who keep using the drugs, often in increasing dosages. They are involved in drug-seeking behaviors such as doctor shopping, prescription forging, and diversion of drugs prescribed to others. The doctor should be aware of these individuals, even though it is not a large group. These patients resemble the next group.

Polydrug Abuse Many users of heroin or central stimulants use prescription opioids as part of their addiction [37]. Benzodiazepines are used to increase the high but also to postpone withdrawal in heroin users or to end a binge in users of central stimulants. When such combination use occurs, it is often labeled as polydrug abuse, but it can be argued that it in fact represents a kind of self-medication in drug abusers who have a main drug problem, be it heroin or central stimulants. This distinction may be important for treatment choices.

22.5 Strategies for Prevention

Making drugs available only on prescription is a preventive measure. The process of prescribing came into place to increase the doctor's ability to monitor effects and adverse events, including abuse. Other measures have been introduced to send out signals about the abuse liability of

medicinal drugs. How this is done will vary between countries, but basically there are two ways. First, there can be rules and regulations on specific drugs within the prescribing system, under the laws of medicinal drugs. This could imply different rules and regulations for prescribing these drugs compared to other drugs.

- The use of special prescribing.
- Only one doctor can prescribe to one patient.
- Only one pharmacy can deliver the drug.
- Only a specialist in a certain field can prescribe the drug.
- Special forms should be used for prescribing certain drugs.
- Special authorities should be informed and can perform controls/audits.
- Only certain package sizes can be prescribed.
- No telephone or Internet prescribing allowed for certain drugs.

Second, some medicinal drugs could be placed on narcotics lists and lists of controlled or prohibited substances. This puts the drug under jurisdiction outside the health-care system and makes it police business. In many country's legislative systems, these boundaries are not so clear, and (often for historical reasons) illegal drugs and medicinal drugs are regulated by the same laws. The scheduling system in the United States is such a system (Table 22.5). The different degrees of scheduling can be followed by different rules or regulations for prescribing as mentioned in the examples above.

Prescriptions are no guarantee against aberrant use. Abuse, dependence, or overconsumption is seen despite these precautions. Research has shown us that the occurrence of overuse follows the sales of the drug in the community or group and the prevalence of abuse can be predicted by sales, following the total consumption model. This model states that there is a close relationship between the population mean of a health variable, in this case prescribing of drugs with abuse potential, and the prevalence of individuals at high risk concerning this variable [89]. The model applies for alcohol consumption and heavy drinkers and for the availability of narcotic drugs and has now been shown to apply for prescriptions drugs [14]. This understanding is important for two reasons. First, a lot about aberrant drug use in a group or a country can be learned from sales statistics. We do not always need clinical investigations to look for aberrant drug use: the sales figures can give a good indication of the problem. And second, preventive measures can

Table 22.5 Prescription drugs are, according to US health authorities, classified after their potential for harm, including abuse

Schedule	Definition	Most central drugs included
I	Drugs with no currently accepted medical use in treatment in the United States and high potential for abuse and dependence	Cathinone, GHB, heroin, LSD, marijuana, MDMA, most hallucinogens, methaqualone (Quaalude)
II	Drugs with currently accepted medical use in treatment with severe restrictions in the United States and high potential for abuse and dependence	Cocaine, amphetamines, other opiates than heroin, some opioids, some synthetic cannabinoids, barbiturates
III	Drugs with currently accepted medical use in treatment in the United States and with a lower risk for abuse than drugs in schedules I and II and low to moderate dependence risk	Anabolic steroids, some barbiturates, buprenorphine, codeine, ketamine, GHB as Xyrem, some synthetic cannabinoids
IV	Drugs with an accepted medical use in treatment in the United States and with a low risk for abuse and dependence (lower than III)	Benzodiazepines, benzodiazepine-like z-hypnotics, some barbiturates, carisoprodol
V	Drugs with a currently accepted medical use in treatment in the United States and with a low risk for abuse and dependence (lower than IV)	Codeine, pregabalin, lacosamide, atropine

Some but not all drugs in this list are prescription drugs

be any procedure that will limit the prescribing and sales of a drug. Such measures must always be weighed against what is good treatment. But this also teaches us that guidelines which allow for liberal practices may have this downside.

We know that some doctors, independently of the profile of their patients, prescribe more drugs with abuse potential than others. This can be due to local traditions and to countrywide regulations but also has to do with the doctor's own beliefs and ideas. Doctors with a liberal view on these drugs tend to prescribe more. This is also reflected in the doctors' own use of these drugs; doctors more willing to use these drugs themselves are also more willing to prescribe them to their patients [83].

Prescription drugs should only be prescribed after a consultation and a review of the patient's problems. There is, however, an increasing sale of prescription drugs via the Internet. The police and customs face an almost impossible task trying to stop this import. Patients who buy drugs from Internet pharmacies and the Internet pharmacies themselves are operating in a gray zone. We do not know the extent of this Internet market, but different estimates usually suggest large figures. There is a thin line between these sources and a true black market. The only way to deal with this is to appeal to people's reasoning and warn against the dangers of receiving a suboptimal product. Some of the products are of good quality, but others contain little or no active ingredient or even toxic material.

22.6 Treatment

The boundary between prevention and treatment is often obvious but can sometimes become unclear. Some preventive measures will be embedded in treatment, and some experiences and views from treatment will be reflected in prevention.

Tackling the Drug-Seeking Patient What kind of drug-seeking behavior physicians will encounter may vary according to their field, but also according to their place, region, or country of work. Some common features can, however, be mentioned. Beware of lost prescriptions, lost medicines, or other reasons patients give for needing a prescription earlier [38, 48]. Also be cautious prescribing drugs with abuse potential to patients you do not know. Optimally, only one doctor should prescribe drugs with abuse potential to the patient. If other doctors need to write prescriptions for patients that they do not know, they need to do a proper workup and confirm diagnosis. If prescriptions are given, prescribe drugs with the lowest abuse potential in the smallest possible quanta. Remember that you do not have to prescribe a whole package, even of the smallest package. The crux is to give your patients appropriate care. Withholding effective medication to needy patients is not an optimal alternative. Some institutions have policies for not prescribing drugs with an abuse potential to patients at certain times or under certain conditions. These institutions can report that they avoid a lot of drug-seeking patients because word often spreads quickly if you cannot get what you want, but the institutions also risk not providing adequate treatment in some cases.

Minimal Interventions If you are worried about a patient's use of prescription drugs, the first step is to discuss this with your patient. Open communication is of the essence. Even if the patient does not admit to problematic drug use, just verbalizing the issue may give them food for thought. Some doctors regularly review their patient lists and try to get a grip on who they should be concerned about. One strategy would be to send a letter or e-mail of concern to the patients in question, just informing them of the potentially problematic sides to their drug use. Such interventions have proven efficient in stopping or reducing aberrant drug use [69]. Further support may be needed ("stepped care"), and follow-up could include information meetings (pharmacology education), psycho-educative programs (information about the underlying disease and alternatives to pharmacological treatments), support groups, or even group therapy [97].

Tapering in the More Difficult Cases (Inpatient vs. Outpatient) Gradual tapering of the medication is preferable to abrupt discontinuation [28, 71]. The use of anticonvulsants like carbamazepine or valproate can be of use for benzodiazepine withdrawal and clonidine for opioid withdrawal. Also some authors suggest the use of benzodiazepines for withdrawal from opioids, even if this can mean substituting one addiction with another [30]. The main principle is to substitute short-acting drugs with longer-acting drugs in order to have more control over the withdrawal symptoms.

Tapering the Patients with Benzodiazepine Dependency A thorough evaluation of the dose should be done. All the different benzodiazepines and benzodiazepine-like drugs should be reduced to two different drugs at the most. Switch to a longer-acting drugs like diazepam (in most people) or a drug with fewer reinforcing effects like oxazepam (in drug abusers or the elderly). Remember that some benzodiazepines (e.g., alprazolam, clonazepam, and flunitrazepam) are 10–20 times more potent and need to be converted to equivalent diazepam doses. For good cooperation between you and your patient, you need to assure the patient that he/she will be adequately covered. For outpatient treatment, you may want to taper by reducing 20% of the total daily dose during the first months and then 10% of the dose later, reducing to 5% or less for the last weeks. Allow the patient to reach a steady state between dose reductions and allow for time to tackle the withdrawal symptoms. For adults with a $T_{½}$ of 1–1.5 days of diazepam, one step can be performed every second week, but for older people, the $T_{½}$ of diazepam increases, and more time should be allowed for each step. A lot of support and encouragement may be needed, sometimes in support groups, sometimes individually. For inpatient treatment, a more aggressive approach is recommended. Often, the patient will not be given enough time for a slow taper. The amount of withdrawal the patient needs to manage is constant either with short- or long-term tapering. Thus, in the inpatient situation, a tapering of the whole dose within 2–3 weeks is recommended. You must then be aware of benzodiazepine delirium.

Tapering/Detoxifying the Patients with Opioid Dependency The tapering of prescription opioids should always be done after a thorough workup on pain and consideration of adequate pain management. For this, we refer to textbooks on pain management. Even if inadequate pain management is the cause of the patient's problem, reduction or removal of the drugs will be needed. This would involve tapering. Such tapering can be more manageable using a long-acting opioid such as methadone or buprenorphine as a tool, even supported by clonidine to tackle the worst withdrawal symptoms. For further information on opioid detoxification, we refer to other chapters in this book.

Intoxications Acute treatment of intoxications with prescription drugs should be handled as other emergencies. Life support including airways, breath, and circulation should be observed. Gastric lavage can be performed if necessary and when done within a limited amount of time. For opioids and benzodiazepines, there are antidotes such as naloxone and flumazenil. Otherwise, drugs should be given on indication.

Benzodiazepine Delirium This should be treated like an alcoholic delirium tremens. Reinstating benzodiazepines and tapering them at a slower pace would be the preferred mode.

22.7 Brief Summary

Many drugs can be abused, but sedatives, painkillers, and central stimulants are the most prevalent prescription drugs to be abused. We have seen an opioid epidemic, especially in the States during the latter years, mostly due to overprescribing and underestimation of the problematic sides of this. All prescription drugs with an abuse potential need to be used with care to ensure the right treatment for the maladies, avoiding use that could lead to addiction. Treatment is as for many other drugs, but special emphasis should be put on tapering from high doses.

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Part III

Behavioural Approaches

Richard Rawson and Marc Galanter

Behavioral Approaches: An Introduction

23

Richard A. Rawson and Marc Galanter

Contents

Abstract

Behavioral approaches are the most widely used clinical strategies for treating individuals with substance use disorders (SUDs). This introduction provides an overview of the chapters in this section on behavioral approaches to SUDs, including motivational interviewing, cognitive behavioral therapy, contingency management, couples and family therapy, trauma-informed therapy, network therapy, community reinforcement approach, mindfulness, psychodynamic psychotherapy, group therapy, and physical exercise. In addition, this section includes chapters that describe strategies for managing the acute and chronic pain of individuals with SUD, address the application of technology in delivering behavioral treatments, and discuss the importance of adapting approaches in culturally sensitive ways while maintaining fidelity to the original model.

Keywords

Behavioral approaches · Therapies · Psychological approaches

23.1 Introduction

Behavioral approaches, including "talk therapies," are essential components in the development of treatment systems for treating individuals with substance use disorders (SUDs). In their most rudimentary form, behavioral treatments consist of advice-giving or commonsense generic counseling. While these nonspecific methods can serve as humane, compassionate activities, there is little, if any, evidence of their effectiveness in helping people reduce or eliminate their drug use. As the addiction treatment field has developed,

R. A. Rawson (✉)
Vermont Center for Behavior and Health, University of Vermont, Burlington, VT, USA

Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles (UCLA), Los Angeles, CA, USA
e-mail: rrawson@mednet.ucla.edu

M. Galanter
Division of Alcoholism and Drug Abuse, Department of Psychiatry, NYU School of Medicine, New York, NY, USA
e-mail: marcgalanter@nyu.edu

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there has been an increasing emphasis on promoting the use of behavioral strategies with empirical support for their effectiveness (aka "evidence-based practices").

In recent years, a collection of behavioral interventions and approaches, developed and evaluated in research trials, have gradually been adopted into a wide variety of treatment settings. As outpatient settings have increasingly become the primary setting for SUD services, two key guiding principles in assessing the impact of these approaches are: do they retain people in treatment and do they help people reduce/eliminate their unhealthy use of drugs and alcohol? Unlike the harsh, confrontational approaches previously used in the early years of addiction treatment, many of the approaches described in this section make extensive use of positive reinforcement to enable behavioral change, including retention in treatment.

The behavioral approaches and strategies described in the section now represent the foundational treatment paradigm for much of the SUD treatment delivered in the world. For the treatment of SUDs that have effective pharmacotherapies, including the treatment of opioid and alcohol dependence, these behavioral approaches are frequently employed in combination with these medications. For other SUDs, such as stimulant dependence, these approaches are the only empirically supported techniques currently available. A limiting factor to increasing access to these therapies is the need for a well-trained workforce, requiring a significant training effort necessary for the successful transfer of the knowledge and skills needed to deliver these treatments.

Section IV includes a comprehensive set of chapters on the behavioral approaches that have been developed and evaluated for the treatment of SUDs. During the past 25 years, three behavioral approaches, motivational interviewing, cognitive behavioral therapy, and contingency management, have been the most extensively researched, evaluated, and widely disseminated behavioral approaches. Motivational interviewing (MI), conceived and first presented in a 1991 text authored by Miller and Rollnick, is reviewed in Chap. 24 by Kouimtsidis and colleagues. MI is arguably the most important behavioral strategy ever developed for the treatment of SUDs, as it has been applied in a very extensive array of settings and with a wide variety of patient populations. Chapter 24 reviews the rationale for MI and the skills needed by therapists to effectively employ the MI approach. In Chap. 25, Lee and colleagues review the learning-theory underpinnings of cognitive behavioral therapy (CBT), some of the practical considerations for the use of CBT, and the skills needed by therapists to effectively deliver CBT. They also provide a comprehensive array of CBT models and variations as developed by various authors/researchers, and Lee et al. review the evidence that supports the efficacy of CBT. In Chap. 29, Roll and colleagues describe the operant-conditioning foundational principles for contingency management (CM) and theoretical rationale for methods used to apply CM principles in the treatment of addiction. They review some prototypic examples of how CM has been practically applied in clinical settings. Of all the behavioral approaches, CM has the strongest empirical evidence of efficacy. Roll and colleagues organize their review of the research evidence to reflect the key factors that impact the effectiveness of CM interventions. They finish their review by addressing the implementation barriers and limitations of CM and new work on the implementation of CM using technology to deliver CM remotely.

Two of the chapters in Section IV describe behavioral approaches where there are multiple individuals involved in participating in the treatment process. In many parts of the world, group therapy plays a major role in addiction treatment. In Chap. 30, McHugh and colleagues review the variety of group therapies used in SUD treatment and the data that supports the value of group therapy. They provide practical information on which models of group therapy are appropriate for which patient groups, including for patients with co-occurring psychiatric disorders. In Chap. 31, Klosterman and O'Farrell present a review of couples and family therapy. They discuss the impact of substance abuse on the family, and they describe the models, techniques, and principles

of couples and family therapy that have been used with substance-abusing patients, their partners, and extended family members. They also discuss the potential barriers to implementing partner- and family-involved approaches for substance use and explore future directions with respect to partner- and family-involved therapies for SUD.

Section IV also includes three chapters that describe multi-element outpatient approaches. In Chap. 32, Galanter describes the rationale and elements of network therapy and the importance of employing the support of family and close friends for the treatment of addictive disorders. The chapter provides clinical examples of how network therapy is applied and research to support the approach, as well as a role for the use of twelve-step facilitation in conjunction with this approach. In Chap. 33, Roozen and Smith describe the Community Reinforcement Approach (CRA) and Community Reinforcement and Family Training (CRAFT) therapy models. These models are predicated on the behavioral principle that a non-drinking/non-drug using lifestyle must be experienced by individuals as rewarding in order for them to choose it consistently over substance use. The chapter describes elements of the approaches and how they can be applied with unmotivated individuals and with adolescents. Research evidence on the efficacy and effectiveness of the approaches is also presented. In Chap. 28, Brown provides a comprehensive review of the role of trauma as a contributing factor to SUD and mental health disorders. Brown describes the rationale and techniques used in trauma-based therapy and trauma-informed care. She also describes how traditional treatment methods can re-traumatize patients (and staff) and how this can be avoided. Data are presented on the benefits of trauma-based care.

Two innovative behavioral techniques that are generating considerable interest are mindfulness meditation and physical exercise. In Chap. 27, McClintock and Marcus describe the foundations and types of activities that make up mindfulness. They describe numerous therapy models in which mindfulness is a component and a variety of applications for mindfulness approaches. They review the research evidence for mindfulness as it is applied to specific SUDs. In Chap. 34, Mooney and Rawson review the extensive set of research that documents the robust positive health benefits of exercise. The chapter documents the rapid expansion of exercise research on exercise for SUD and provides a summary of the research findings. They describe in detail the study methodology and results of a randomized clinical trial of exercise for individuals in early recovery from methamphetamine.

In Chap. 26, Khantzian describes how drugs and alcohol are used to cope with suffering and emotional pain. Psychodynamic psychotherapy has long been used to understand how people use drugs and alcohol to modify hedonic states and self-regulate moods. The chapter describes the concept of "disordered self-care" and the implications of this concept to the psychotherapeutic process. In addition, the chapter emphasizes the importance of the therapeutic alliance as an important element in promoting change and describes the key elements of this alliance as kindness, support, empathy, respect, patience, and instruction. In Chap. 37, Krashin and colleagues describe the complex and challenging interface between pain and its treatment and SUDs and their treatment. They recommend a multimodal approach that is personalized for each individual. They review current treatment recommendations for the treatment of acute and chronic pain within SUD settings and for different patient populations. They provide a discussion of palliative care and strategies for risk management in the use of opioid medications.

In Chap. 35, Lemle and Marsch provide an excellent overview of the new world of technology applications to the treatment of SUDs. Because there are a variety of factors that limit access to in-person clinical service delivery (e.g., distance, cost, lack of trained personnel), digital strategies to bring treatment information and programming via digital technology are being rapidly developed and implemented. The chapter presents a review of the types of interventions developed and an overview of the research evidence concerning their effectiveness. In Chap. 36,

Castro and colleagues have contributed a chapter on the importance of culturally adapting behavioral approaches in a systematic manner for their application in other languages and cultures. They describe a systematic methodology for balancing the fidelity to the original evidence-based model while allowing for adaptation of the model to address specific cultural issues of importance. They describe the challenges of effective language translation as well and cautions about misadaptation. This chapter is of tremendous value in assisting in the adaptation of evidence-based practices developed in Western cultures to other parts of the world.

23.2 Summary

Section IV includes a collection of chapters, written by experts in the topic areas that provide a comprehensive overview of the major evidence-based behavioral approaches to the treatment of SUD. This is an area of tremendous change as extensive work continues to develop, scientifically examine the efficacy and effectiveness of new approaches, and implement these strategies in applied treatment settings around the world.

24 Motivational Interviewing, Behaviour Change in Addiction Treatment

Christos Kouimtsidis, Claudia Salazar, and Ben Houghton

Contents

Abstract

In this chapter, we discuss the concept of addiction and the most influential theories of behaviour change under a common theory framework, including theories on motivation such as the PRIME theory.

C. Kouimtsidis (✉)
Imperial College, London, UK

C. Salazar
Central North West London NHS Foundation Trust, London, UK

B. Houghton
St George's University of London, London, UK

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Motivational interviewing (MI) has been an influential therapeutic approach proposed by Miller in 1983. MI is a way of interviewing people with an addiction problem, which goal is directed and aims to empower the person to explore their ambivalence, mixed feelings, and thoughts about their addictive behaviour and develop their own plan of action to address it. We discuss the main components of MI and how to use it in everyday clinical practice.

MI is the major ingredient of brief interventions for alcohol use disorder and other substance use disorders. MI can also be a component of other structured psychological interventions (such as cognitive behavioural therapy) for people with dependence on alcohol or other substances. Finally, we discuss the evidence supporting the effectiveness of MI from the early individual trials to the most recent systematic reviews.

Keywords

Addiction · Addiction theories · Motivation
Motivational interviewing

24.1 Introduction

What is the best way that we can help people change behaviour has been and still is one of the major challenges for health and social care professionals. In substance use disorder treatment, the role of motivation and the professionals' skills in influencing change are central across all approaches. Motivational interviewing (MI) was described by the psychologist William Miller [1] and later expanded on though collaboration with Stephen Rollnick. Through consultation with other researchers and clinicians working in the 1980s, there were concerns about confrontational and cohesive approaches that were commonplace in addiction treatment, that were based on little evidence and that were observed to have poor outcomes. Miller and Rollnick collaborated in combining the emerging evidence about motivation and behaviour change research as well as their experience in psychology and counselling those with substance use disorders. They put forward their approach in their first edition of their book that focused mainly on illicit substance and alcohol treatment, describing the approach and techniques involved in having a different kind of conversation about change that avoided conflict and judgement of the person. As MI became more widely applied and processes better understood across a range of health and social care settings, in their second edition, they include applications across a wide range of problem areas and begin to propose possible mechanisms on how MI works. In their third edition [2], they bring together the key evidence from randomised controlled trials in the intervening decade, and they clarify and redefine some of the skills and processes involved, in particular emerging evidence on the importance of paying selective attention to particular types speech MI that strengthens commitment to change.

24.2 Addiction and Choice Theories of Behaviour Change

Addiction is a social phenomenon. Across diagnostic classification systems and across the years, the definition has three main components/aspects. It is described as (i) a reward-seeking behaviour, (ii) that has become out of control and (iii) which impaired control is leading to harm [3]. To that effect, addiction includes any behaviour that satisfies the above three criteria, such as substance use, drinking alcohol, smoking, gambling, gaming and others. The above behaviours per se do not equal addiction unless there is loss of control and associated harm. It could be argued that addiction sits at the core of human species, defined as a 'social animal' by Aristotle. Addiction is an inherent biological phenomenon, related with the existence of the brain pathways of reward, aiming to maximise the chances of the individual to survive and multiply within a challenging physical and social environment.

Over the years, several theories were developed with the aim to understand and explain the

aforementioned components of the definition of addiction. The multitude of existing theories is an example of pluralism of approaches. This pluralism is necessary for further development of our understanding of addiction. Furthermore, it is considered important that phenomena are understood under the framework of a single theory because fewer axioms have to be accepted as true, concepts can be shared, and testable hypotheses can be generated. To that effect for human behaviour, the theory of evolution is considered the master theory that provides the framework to acknowledge the reciprocal and dynamic interaction between living organisms/humans and the environment. All theories trying to understand a specific phenomenon (such as addiction) should be conceived under and be compliant with the theory of evolution.

All the theories of addiction that aim to explain the process of how the reward-seeking behaviour is initiated, then becomes out of control and is maintained irrespective of the harm experienced could be seen under a common theory framework that focuses on the principle of choice. The therapeutic interventions (pharmacological, psychological or social) based on these theories conceive addiction as a decision-making process which is conscious to start with, later on becomes unconscious and in order to be modified needs to become conscious again. For this theory framework to be consistent with the evolution theory, there is a need to identify and understand the potential advantage of having reward pathways that become out of control and the cognitive process of choice becoming unconscious.

Under the common framework of choice theories, we could include early basic theories and their more recent adaptations such as operational conditioning [4], as well as the very influential social learning theory [5], and the expectancy theory.

Social learning theory is a generic theory of human behaviour and focuses on the individual and his/her choices within a social environment. Behaviour is regarded as the result of a continuous interaction between personal and environmental variables. Social learning theory introduces two main concepts: (i) outcome expectations, which are 'the person's estimate that a given behaviour will lead to certain outcomes', and (ii) efficacy expectations (or self-efficacy), which refer to a person's belief 'that one can successfully execute the behaviour required to produce outcomes' ([5], p.193). Self-efficacy is relevant to all stages and aspects of human development (family environment, school, career development and pursuits, health-promoting behaviour). The theory was expanded later to the social cognitive theory in order to conceive the person as an agent of change that affects the person and the social environment [6].

Originally, expectancy theory placed emphasis on initial conscious cognitive processes, which are related to the experience of craving. Evidence though suggested that subjective report of craving is only moderately linked with substance use and relapse. As addiction progresses, substance use is regulated by automatic cognitive processes, while craving represents the activation of non-automatic processes. These non-automatic processes are activated to either aid in completing interrupted substance use or block automatic substance use sequences [7]. As addiction develops, the expectancy-based control system of behaviour becomes unconscious, and therefore, behaviour is influenced less by conscious expectancies involving controlled processes and more by unconscious expectancies involving automatic processes. Furthermore, cognitive bias theory introduces the concept of biases that affect conscious functions such as beliefs, attention and memories as well as unconscious processes in information recall from memory [8]. Over time, activation of one part of the 'network' (e.g. alcohol representations) automatically triggers propositional links in other parts (e.g. relaxation concepts) and vice versa; however, it is hypothesised that this information is less accessible and relies more on effortful and non-automatic cognitive processes; therefore, its moderating impact on behaviour is compromised [9].

Hybrid models which provide a synthesis between biological and psychological models could be placed under the choice framework. Such models include the hedonic homeostatic

dysregulation model [10] and more recent ones such as the incentive-sensitisation model [11] and the inhibition dysregulation model [12], which attempt to explain the progress from choice to compulsive use.

In summary and in order to address the question of the evolutionary advantage of addiction, it could be argued that the phenomenon of addiction is related with the ability of humans to test new behaviours, those considered important for surviving to become automatised and therefore replicated fast without ongoing review of their appropriateness. Therefore, it could be argued that addictive behaviours are the price paid by humans for having the ability to learn and to adapt to environmental changes.

24.3 Theories of Motivation

24.3.1 Trans-theoretical Model of Change

The development of motivational interviewing coincided with the appearance of the extremely influential trans-theoretical model of behaviour change or stages of change model, developed by Prochaska and DiClemente in 1986. The focus of this model is the motivation to change and the process of change itself. Although it is described as a model, it proposes new theory concept; therefore, it could be seen as a theory.

'Stages of change' (as it is often referred to) has been used in everyday clinical practice alongside MI although MI was never based on this model as argued by Miller and Rollnick in the second edition of their book in 2009. People are rarely in a state where they do not view some aspect of their substance use or other behaviour to be problematic, or in need of change, even more so when they are encouraged to reflect on the impact of the addictive behaviour on their life. To that effect, stages of change helps the person to define or acknowledge the state of their commitment to change.

The model proposes that the process of recovery from an addictive behaviour involves transition through five stages: (i) pre-contemplation stage in which no change is contemplated; (ii) contemplation in which change is contemplated for the near future; (iii) preparation, in which plans are made on how to change behaviour in a definite way; (iv) action stage in which the plans are put into action and change takes place; and (v) maintenance in which the new pattern of behaviour emerges, establishes and is maintained. There is a sixth stage, that of termination, which was added more recently and in some way overlaps with the maintenance stage. In this stage, the individual has adopted and consolidated the new behaviour. The model proposes that individuals can move forwards or backwards through the stages.

The model has enjoyed great popularity although it has received major criticism. The popularity might be explained by the seemingly scientific approach of diagnosing the stage of change and the perceived relation to a specific treatment plan, as well as the provision of categories to place people rather than use everyday language. The criticism relates to several aspects of the model, such as the definition and validity of the proposed stages, the proposed linear progress through the stages as well as the inability of the model to account for the unconscious decision-making processes [3].

24.3.2 Identity Shift Theory

Identity shift theory [13] takes into account the principle of unstable preferences, which is considered a fundamental feature of human motivation, and proposes that increasing distress caused by behaviours results to value conflict. This prompts to a small step towards behaviour change, which if successful begins to lead to an identity shift. Increased self-awareness and self-confidence then fuel continued change. At the core of the model is the ongoing evaluation of benefits, costs and the build-up of dissatisfaction with the current situation. Then a trigger, small or major, results in an immediate and unplanned step of change that initiates the process of behaviour change.

24.3.3 PRIME Theory of Motivation

West [3] proposed a new theory of motivation called PRIME, an acronym standing for the proposed five levels of motivation: plans, responses, impulses/inhibitory forces, motives and evaluations. Although it is described as a theory of motivation, it could be regarded as a theory of addiction in general. According to this theory, addiction is conceived as a chronic condition of the motivational system in which the reward-seeking behaviour has become out of control. This is a synthetic theory that aims to encompass all the elements of the previously discussed theories. The levels of motivation are hierarchical from low levels of responses that involve reflexes and automatic behaviours to higher responses that include evaluations, plans involving expectancies and the concept of identity.

The theory proposes that there are three types of abnormalities of motivation: (i) abnormalities of the motivational system that exist independently of the addictive behaviour such as a predisposition to anxiety or depression; (ii) abnormalities of the motivational system resulting from the development of the addictive behaviour itself, meaning the process of developing a habit; and (iii) abnormalities in the individual's social or physical environment such as the presence of strong social or other pressures to engage in an activity such as drinking or drug taking. This means that an activity becomes addictive if it affects an already unbalanced system (comorbid anxiety, traits of impulsivity) which operates within an unbalanced environment (belonging to a social group that activity is considered normal), in such a way of undermining the normal checks and balances that operate to prevent undesirable behaviour (activity becoming continuously rewarding).

The theory is based on the principles of chaos theory. This means that the motivational system is inheritably unstable in the sense that it is susceptible to continuous influence of smaller or bigger internal and external stimuli. This notion can explain both the development of an addictive behaviour and the need for change. Therefore, any event that could be seen as significant or insignificant can potentially send an individual down to a specific path (use of a substance) or could set up an environment which is liable to facilitate for the addictive behaviour to develop. The theory also accounts for the co-occurrence of several addictive behaviours as long as they are mutually reinforcing in terms of their effect on the balance of the motivational system or the individual's environment. According to the theory, triggers for urges (impulses) or desires are not simply the consequence of associative learning but are responsive to higher level expectations and interpretations.

24.4 About Ambivalence

Ambivalence is a natural part of change process for humans, and the way people have to talk to themselves and others about the benefits and costs of change influences those decisions to make that change or not to. Having a dilemma about change is common in people facing psychological difficulties. Statements about *wanting* to change (change talk) and *not wanting* to change (sustain talk) coexist, and for some people, this ambivalence can go on for a long time [2]. It is natural for those working in alcohol and other substance use treatment to want to persuade or convince the person on the arguments for change, but instead this has the opposite effect and provokes people to voice arguments against change. Humans do not like to see other people suffering, especially when they are visibly so unwell, and there can be a want to 'fix it'. This is referred to as the 'righting reflex', a person's desire to help urging the giving of immediate advice without permission, voicing of the counter-arguments with the effect of increasing the sustain talk. The behaviour of the practitioner predicts the outcome, and the more directive and confrontational the practitioner becomes, the more resistance this raises from the person being helped [2]. What influences change is complicated and fluid. Change is not easy, people change when they think change is of value and achievable, and often, change requires several attempts to do so, with lapses and relapses being necessary

for success to be achieved [14]. People are more persuaded by their own arguments, and the skill of the practitioner is to develop a style of communication, characterised by active listening and avoiding being directive, that helps the person make decisions for themselves. This is referred to as a guiding style of communication [15]. The practitioner's task is to support a person led shift in favour of behavioural change and to recognise the discrepancy between their view of self and their behaviour.

24.5 What Is Motivational Interviewing?

MI has evolved from the person-centred approach of Carl Rogers [16], but it is distinct from the 'non-directive' role of counselling as it has direction in that it is goal orientated with an intentional focus towards change. Using this guiding style of communication (somewhere between a directive and non-directive style), the practitioner pays selective attention to certain forms of speech (change talk). The more the practitioner is able to recognise, draw out, reflect and amplify change talk, the more likely this is to strengthen commitment to change that in turn predicts positive outcomes [17]. This needs to be done in a particular atmosphere that requires specific attitudes as well as skills.

The technical definition:

> Motivational interviewing is a collaborative, goal orientated style of communication with particular attention to the language of change. It is designed to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion [2].

24.6 How to Create Atmosphere for Change?

The values and attitude of the practitioner, referred to as the 'spirit', are the central component of this way of interacting. In the early applications of MI, researchers and practitioners focused on improving fidelity to the approach by structuring the techniques into structured feedback or manualised treatment such as motivational enhancement therapy. However, manualised and structured approaches have been found to be less effective [18], so over the last decade, the practice has refocused on the relational components in the interaction as having the most impact [19]. There are four vital aspects of the 'spirit' [2]:

Partnership The practitioner always involves the person in every aspect of the process, from deciding on what to change and then how to go about this; information and advice are offered but not imposed, with the understanding that the solutions and ideas lie as much with the person as with the practitioner. The practitioner is honest about what could be focused on and what has been noticed but involves the person in deciding the next step.

A question such as 'I would like to know what your thoughts are about your drinking' would help to open a dialogue and an assessment process.

> Should we look into this in more detail?
>
> What do you think you should do about this? What do you think might be possible for you to achieve?

Acceptance The practitioner's focus should be on the person's strengths, affirming their efforts and intentions, staying neutral and avoiding either positive or negative judgements. The practitioner should have empathy towards the person and believe the person to be trustworthy, emphasising their freedom to choose and the ability to make the best decisions for themselves.

> I don't have a ready-made recipe of how to resolve your challenge. We can understand this together. You know yourself better, what you can do and what might be extremely difficult to do at this point.

Compassion Actively promoting the other person's welfare, acting in their best interest, and maintaining hope that change is possible. This is fundamental for ethical practice.

> I could help you though using my science and my experience of what might be easier or advisable. Two people working together is better than one.

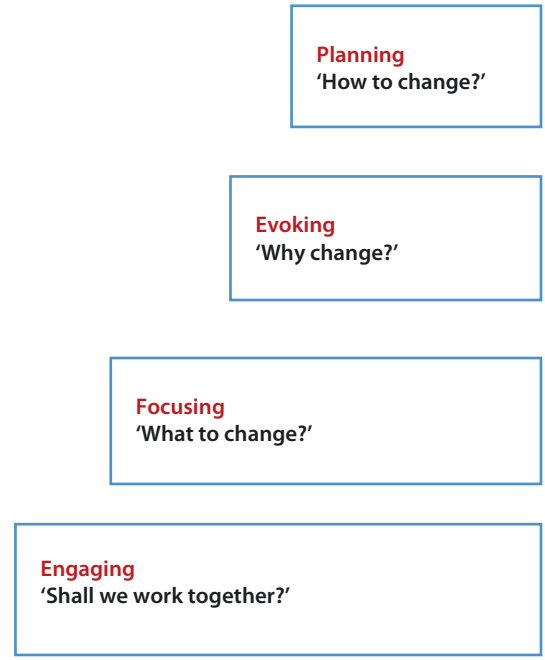
Evocation The practitioner role is to draw out ideas and thoughts from the person, believing in their wisdom and the importance for the person to voice their thoughts and to listen to their own change talk, as being crucial. The practitioner avoids taking the expert role, as the belief is that people are the best experts in their experience and they have the best ideas and solutions that will work for them. The practitioner role is one that facilitates the exploration of answers that lay within the individual.

> So let us start with what do you think has worked for you in the past. What are your observations?

These four elements describe the way of being, the values that an MI practitioner working with substance use disorders should seek to establish to maintain collaborative and empathic relationships with the people they are trying to help. Continuing working throughout the lapses and relapses, believing in their ability to change and succeed in maintaining change, affirming their strength to persevere, normalising how hard change is and helping them maintain the hope that they will succeed.

24.7 The Processes and Skills in MI

In the practice of MI, there is now an understanding that there are four processes in the journey of helping people change and that the practitioner guides the person through them [2]. Each process is a stepping stone to the next that helps the practitioner concentrate on the skills and techniques to guide the person through each step beginning with engaging them to ultimately making a robust plan for change. The core skills are known by the acronym of *OARS, open-ended questions, affirming, reflecting and summarising*, and are derived from person-centred counselling. These skills are used throughout the four processes in developing and maintaining momentum, forming a central part of becoming a skilled practitioner [20].



24.7.1 Engaging

The first task is establishing a good therapeutic relationship to develop trust and collaboration as quickly as possible. The first few minutes of any interaction can be crucial in this process [21], and it requires the practitioner to concentrate on active listening skills and focus on the OARS.

Open-ended questions This type of questions cannot be answered by 'yes', 'no' or a 'fact' but is explorative. These questions are encouraging the respondent to think and elaborate and to voice their wisdom, their *change talk*. In engagement, we want to understand their perspective without pursuing particular answers or assuming that the person has made a decision to change.

'How long have you had an alcohol problem?' is a closed question that is already labelling a problem as opposed to 'Tell me about your drink-

ing?' which is an open question that is encouraging the person to tell you their story.

Affirming MI is strength focused and requires the practitioner to concentrate on valuing the person's perspective, with the practitioner making a conscious bias to notice and voice the person's strengths, insights and abilities to promote engagement, reduce defensiveness and raise confidence. There is active effort not to focus on what is wrong, the pathology, errors or deficits [22]. Making people feel better about themselves enables them to have the strength to address their problems and retains people in treatment. Acknowledging the potential embarrassment associated with the realisation that the behaviour is self-inflicted is important. Be clear about having no right to make judgements as we are all made from an evolutionary point of view to develop habits and addictions. Emphasise that what matters is the willingness to consider change.

Reflecting Listening Reflective statements are a key skill in MI, allowing the practitioner to voice their guess at what the person means, to check understanding, to convey empathy as well as to allow the person to hear their thoughts and ideas. Hearing reflections makes people feel encouraged to continue talking. The skill of forming reflections is key, from simply reflecting what the person said to more complex reflections that attempt to convey an understanding of meaning and feeling. There is a selective use of reflections, and so the ability to recognise and reflect *change talk* is key to encourage the person to decide to commit to change.

Simple Reflection: One strategy is simply to reflect what the client is saying. This sometimes has the effect of eliciting the opposite and balancing the picture.

Client:	*I'm fed up of talking about my drinking!*
Practitioner:	*You're fed up of talking about your drinking. Ok what else would you like to talk about?* (The aim is to return to a discussion about the drinking through a different indirect route.)

Reflection with Amplification: A modification is to reflect but exaggerate or amplify what the client is saying to the point where the client is likely to disavow it. There is a subtle balance here because overdoing an exaggeration can elicit hostility.

Client:	*But I'm not an alcoholic or anything like that.*
Practitioner:	*I understand. You don't want to be labelled. There is no need for labels, but what do you mean about being an alcoholic? What alcoholics do?*
Client:	*I don't think I have a drinking problem.*
Therapist:	*So you think there haven't really been any problems or harm caused by your drinking.*
Client:	*Well. I wouldn't say that.*
Practitioner:	*I see; you don't like the idea that you have a drinking problem* (pause); *but you think your drinking has caused you problems. Could we investigate this?*

Double-Sided Reflections:

Client:	*But I can't stop drinking. All my friends do it!*
Practitioner:	*It's difficult for you to imagine not drinking with your friends (pause); but you also worry what it's doing to you. I think that I understand.*

Then you might want to break down the two components (friends and stopping) of the above statement and see what would be easier and more productive to challenge. For example, *Are there situations that you don't drink with your friends? May I ask if your drinking is similar or different to this of your friends*? *Maybe we don't need to stop drinking. Maybe reducing the amount would be easier. What do you think?*

Summarising Bringing together key statements voiced by the person is particularly important; a summary can help collect various statements together to help clarify ideas. Often, if there is ambivalence when you are trying to engage with the person, it is very helpful to summarise the arguments that they have voiced for and against change. Summarising not only helps clarify their thoughts but can make them more real and conveys the desire to understand their dilemma.

> Let me see if I got this right. So far you have told me that you don't think you are an alcoholic but you think that your drinking has caused you some problems.

A part of the engagement process, Miller and Rollnick [2] describe how important it is to avoid various traps that may interfere and lead to disengagement from treatment, such as ***assessment trap*** (focusing gathering of facts), ***expert trap*** (having all the answers), ***premature focus trap*** (working on solutions before you have engagement), ***labelling trap*** (*diagnostic labelling*), ***blame trap*** (focusing on who might be to blame) and ***chat trap*** (not having a focus to the session).

24.7.2 Focusing

Once good rapport has been established and there is engagement, it is important to clarify the change direction towards defining a specific goal. Often, a person may be facing several areas in their lives they are considering changing and feel overwhelmed, for example, it may be illicit substance or alcohol use, smoking or domestic violence, or conversely, they may be unclear about what needs to be changed. The 'agenda mapping' tool may be used to explore possible options for change to help prioritise what may be most important. The key is to maintain a guiding style to decide collaboratively on a change direction and help the person maintain this.

'So what would you like to talk about? Should we make a list together?'

24.7.3 Evoking

Drawing out the person's motivations for change is a process that is most unique to MI. There is a need to explore how ***important*** the change is and how ***confident*** the person feels about making a change, and this may need to be strengthened if it is low. For change to happen, the change has to matter to the person, and they need to have the confidence to do so. The focus is to ensure, through selective use of OARS, that there is an increase in the amount of change talk and any self-expressed language that is an argument for change [2] whilst paying attention to the different types of change talk that indicates a person is ready to make changes [23]. Amrhein differentiates ***preparatory change talk***, statements that express *desire*, *ability*, *reason* or *need* to change from ***mobilising change talk***, statements that indicate that the person has made a *commitment* 'I will stop' or activation 'I am ready to set a quit date' or *taking steps* 'I've started cutting down'. By listening and affirming change talk, the practitioner strengthens commitment to change. Miller and Rollnick [2] suggest that those people who present to treatment ready to make changes may need to go straight to planning and skip evoking.

24.7.4 Planning

The final step in the process is guiding the person to develop a specific plan, and this is seen as the beginning of change. For some, the plan may be about how to take the first step that will begin a process. Some people may have a clear plan, others may need to consider choices as part of the process, and some may need to start from scratch as it may be all new. The important practice point is to stay within the collaborative spirit and actively listen. It is important to allow the person to lead and choose from options and for practitioners to avoid becoming directive and prescriptive, remaining open to new ideas. The practitioner may offer suggestions, information or ideas, but most importantly, they should help the person explore theirs first. Miller and Rollnick [2] sug-

gested a template for change plan that has the component to have a guided discussion to help someone arrive at a robust plan.

Miller and Rollnick [2] initially described five basic motivational interviewing practices underlying such an approach:

1. Express empathy
2. Develop discrepancy
3. Avoid argument
4. Roll with resistance
5. Support self-efficacy

24.7.4.1 Express Empathy

Empathy refers to the ability of the practitioner to make sense of the person's experience. Contrasted with approval or identification, empathy is the process of communicating to the person that the behaviour in question has its own rationale. This is different from sympathy, which implies a sense of inevitability and feeling sorry for the person. Empathy is communicated by the practitioner through reflective listening and selective reinforcement, through affirmation and the way that the practitioner summarises a person's position.

24.7.4.2 Develop Discrepancy

Motivation for change occurs when people perceive a discrepancy between where they are and where they want to be. The approach seeks to enhance and focus the person's attention on such discrepancies with regard to drinking. In certain cases, it may be necessary first to develop such discrepancy by raising the person's awareness of the personal consequences of the behaviour. Such information, properly presented, can precipitate a crisis of motivation for change. As a result, the individual may be more willing to enter into a frank discussion of change options in order to reduce the perceived discrepancy and retain emotional equilibrium.

24.7.4.3 Avoid Argument

If handled poorly, ambivalence about the current behaviour and discrepancy between the consequences of the behaviour and person goals or aspirations result in defensive coping strategies that reduce discomfort but do not alter the behaviour and related risks. An attack on the person's drinking or substance using behaviour tends to evoke defensiveness and opposition and suggests to the person that the practitioner 'does not really understand'. MI explicitly avoids direct argument. No attempt is made to have the person accept or admit a diagnostic label. The practitioner does not seek to prove or convince by force of argument. Instead, the practitioner employs other strategies to assist the person to see accurately the negative consequences of the behaviour and to begin devaluing the perceived positive aspects of it. In essence when MI is conducted properly, *the person and not the practitioner* voices arguments for change [2].

> You are worried about having to decide right now. Let's just carry on understanding together where you are at the moment (pause). Later on, we can worry about what, if anything, you want to do about it.

24.7.4.4 Roll with Resistance

How the practitioner handles person resistance is a crucial and defining characteristic of MI. Motivational strategies do not meet resistance head on but rather roll with the momentum, with a goal of shifting person perceptions in the process. New ways of thinking about problems are invited but not imposed. Ambivalence is viewed as normal, not pathological, and is explored openly. Solutions are usually evoked from the person unless specifically requested of the practitioner.

> Okay, that's where you're at now (pause). That it's too difficult to make a change. Maybe you'll decide that you want to keep on drinking. That's up to you.

24.7.4.5 Support Self-Efficacy

People who are persuaded that they have a serious problem will still not move towards change unless there is hope for success. Self-efficacy is a critical determinant of behaviour change (see social learning theory above). In this case, people must be convinced that it is possible for them to change their own drinking and thereby reduce related problems. Unless this element is present, a discrepancy crisis is likely to resolve into defen-

sive coping (e.g. denial, rationalisation) to reduce discomfort without changing behaviour. This is a natural and understandable protective process. If one has little hope that things could change, there is little reason to face the problem.

Learning practising motivational interviewing requires practitioners to acquire skills identified in 12 learning tasks that are illustrated and explained in detail in the third edition of the textbook [2]:

1. Understanding the underlying spirit
2. Developing skill of reflective listening and person-centred OARS skills
3. Identifying change goals towards which to move
4. Exchanging information and providing advice in MI style
5. Being able to recognise sustain talk and change talk
6. Evoking change talk
7. Responding to change talk to strengthen it
8. Responding to sustain talk and discord so it does not increase
9. Developing hope and confidence
10. Timing and negotiating change plan
11. Strengthening commitment
12. Flexibility in integrating MI with other clinical skills and practices

24.8 About Information and Advice

Interactions in healthcare often require practitioners to give information and advice that often makes the practitioner assume the expert role and employ a directive style. In MI, there is an acknowledgement that clinical interactions involve information exchange but that this needs to be done skilfully. Principles of good practice outlined by Miller and Rollnick [2] start with suggestions that we need to make this process personalised and strength driven, starting with finding out what the person already knows and offering information on what they would like or need to know whilst encouraging autonomy on decision-making. One strategy for information exchange is termed 'elicit-provide-elicit':

- ***Elicit*** – Ask the person to offer information, finding out what the person already knows and what they would like to know.
- ***Provide*** – Prioritise the information that the person is asking for. Be clear, use everyday language and avoid jargon, presenting information in a neutral manner avoiding the need for the person to interpret.
- ***Elicit*** – Ask the person what they think about the information, allowing time to process and ask further questions.

Offering **advice** is a special kind of information, as it usually involves recommendations that suggest action to be taken, for example, reducing alcohol consumption to low risk levels. For advice to be heard and followed, this needs to be offered following the elicit-provide-elicit strategy and can only be given if you have engagement with the emphasis of personal choice and control.

24.9 How Effective Is Motivational Interviewing for Substance Use Disorders?

An early body of evidence exists about the effectiveness on motivational interviewing, how it works and how it compares with other approaches. The original research mainly focused on those with alcohol problems and the positive effect of one session of MI on follow-up [24]. Brief intervention studies in alcohol across the world were showing positive outcomes, and a review of controlled trials found brief interventions in alcohol to be better than no treatment and as effective as more intensive interventions [25]. This review highlighted common components that were further developed MI practice. A feedback component was added to subsequent MI research that was defined as an adaptation of MI (AMI). Significant benefits have been also found in outcomes in drug treatment, and single-session

interventions also continue to demonstrate effectiveness [26].

Two major randomised controlled trials (RCT) in the alcohol use disorder have taken place in the 1990s and merit special mention. Project MATCH [27] was the first multisite RCT in the USA. It has used a feedback-based approach referred to as *motivational enhancement therapy*, which combined the clinical style of MI with structured assessment feedback in four sessions over 12 weeks. This was compared to 12 sessions of 12-step facilitation and 12 sessions of CBT, with all three showing similar outcome measures. Another multisite RCT in the UK, trial in the late 1990s [28], compared outcomes of MI with other two approaches, and although no differences in efficacy were found, MI was just as good as more intensive, evidence-based interventions.

More recently, though, Cochrane systematic reviews did not support the efficacy of MI for substance use disorders. A consistent finding across these Cochrane reviews was the low quality of evidence available. This limitation is common across research for all psychological interventions in the field of substance use disorders. There are two points of note: (a) MI is a tool to be used to resolve ambivalence, and studies do not identify whether participants are ambivalent; therefore, it may not be the right tool to be used which would skew efficacy data; (b) MI was developed for alcohol use disorders which is where the evidence for efficacy appears strongest from individual studies.

For example, in smoking cessation, a systematic analysis including 15,000 participants found insufficient and low-quality evidence to recommend MI as a tool to aid smoking cessation despite a slight increase in likelihood to quit smoking if MI was provided [29]. In benzodiazepine, no efficacy was found for MI [30], whereas in gambling behaviour, there is preliminary evidence for the use of MI although CBT would appear to be more effective [31]. Very low-quality evidence was also found for the efficacy of MI versus other treatments in Cochrane review of people who inject drugs with concurrent alcohol use. Within this review, one study of 187 participants found that a brief motivational intervention reduced alcohol use versus assessment only [32]. Furthermore, MI for people with severe mental illness and substance use disorders may increase attendance at aftercare appointments but does not seem to have an advantage against other treatments in reducing dropout rates or abstaining from substances other than alcohol [33]. There were no observable changes in mental state following MI in this population though it should be noted the quality of evidence included in analysis was thought to be very low. These results were replicated in a review of drug-using offenders with co-occurring mental disorders [34]. Similarly, Cochrane review of 84 trials in young adults aged between 15 and 24 years with alcohol-related problems concludes that MI does not appear to have substantive and meaningful benefit, despite limited efficacy for reducing alcohol-related problems, but no effect for binge drinking or drink driving was found [35].

In contrast to Cochrane reviews that consistently found methodological quality a concern with MI studies, a review by DiClemente and colleagues [36], which included six Cochrane reviews, concluded that there was strong evidence of effectiveness for motivational enhancement interventions with alcohol and tobacco users, brief interventions showing the strongest efficacy. There was some efficacy in gambling and strong support with cannabis use but insufficient evidence for methamphetamine and opiate use disorders. Critically, this review was not recommending MI above other therapies but simply concluded it was more effective than no therapy at all.

Another systematic review regarding the efficacy of MI for adult behaviour change in health and social care settings comprising 104 reviews and 39 meta-analyses also found low-quality evidence. Evidence was graded moderate for the short term (<6 months) statistically significant beneficial effects for reduced binge drinking, frequency and quantity of alcohol consumption and substance abuse in people with dependency or addiction [37].

Beyond conventional face-to-face delivery of MI, there is promising efficacy in alternate methods such as telephone, Internet based and text

messaging [38]. Whilst the latter two findings remain controversial and inconclusive given the small number of studies, telephone-based delivery of MI may be considered a viable alternative for substance use disorders.

24.10 Clinical Relevance

- MI is a general way of approaching the interaction with our client and less so a detailed therapy model. It is more about how we do something rather than what we do. It is about how we approach an assessment appointment, how we develop an understanding of the given problem, how we develop and how we implement a change plan. This 'WE' involves the practitioner, the individual and when appropriate their immediate social environment.
- MI is not just a technique but instead an integrated set of interviewing skills, centred on particular values and attitudes to be conducted with the person in guiding them towards change and choice.
- MI is the main component of any brief or extended brief intervention, which could be the sole intervention for smoking, non-dependent alcohol use or a light to moderate drug misuse and can be implemented by any professional not necessarily a specialist. For more severe substance use disorders or other behavioural disorders, MI could be an important component at all stages of treatment.
- Use of MI can be challenging for professionals, as they might have to distant themselves from approaches and attitudes well impeded into their basic professional training, especially doctors, when they are called to resolve a problem using an authoritarian approach. It could be though equally challenging for a counsellor who s/he might over-rely on his/her model or a peer mentor in recovery who can only share his/her way of changing his life. For the professional to develop an MI-based approach, he or she needs to accept the relative effectiveness of his/her treatment approach and to appreciate the fundamental role of the individual who needs and decides to change.

24.11 Conclusion

In motivational interviewing (MI), the aim is to walk alongside the person to the point where they propose goals to change their addictive behaviour, through a process of helping them to explore the positive and negative aspects of the behaviour, recognising the discrepancy between their view of self and their behaviour with the aim to enhance the need for action to change the addictive behaviour and hence resolving this discrepancy. This process is similar to the cognitive restructuring process of cognitive behavioural therapy models which put major emphasis on evaluation of positive expectancies and negative effects and expectations of the addictive behaviour.

Despite the mixed evidence for its efficacy and the link with the process of change model, which has received major criticism, MI has been proven extremely popular and influential. It has helped the field of addictions to move away from the concept of 'denial', to reduce barriers for accessing treatment and open the door to professionals, specialists in addictions or not, to work with persons not ready yet to commit to major change of their lifestyle. It has somehow shifted the responsibility from the person with the addictive behaviour to find a way to commit to a change towards the professional who now has the tools to facilitate this change. MI has provided an easy way to intervene earlier and with populations not considered appropriate for more structured and expensive treatment options.

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25 Cognitive Behavioural Therapies for Alcohol and Other Drug Use Problems

Nicole K. Lee, Paula Ross, and Richard Cash

Contents

N. K. Lee (✉)
National Drug Research Institute (NDRI), Curtin University, Bentley, WA, Australia

360Edge, Melbourne, VIC, Australia
e-mail: nicole@360edge.com.au

P. Ross · R. Cash
360Edge, Melbourne, VIC, Australia
e-mail: paula@360edge.com.au; richard@360edge.com.au

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Abstract

Cognitive behavioural therapy is an umbrella term that describes an expansive group of therapies. Although many in number and broad in their approach, they have in common a focus on 'cognitions' (including thoughts, beliefs, schemas and metacognitions) as the central driver of, and the solution to, effective emotion regulation. The early cognitive behavioural therapy models grew from behaviour therapy and introduced the concept of cognition into the behavioural models. The most well-known of these models were developed by Aaron Beck (Cognitive Therapy) and Albert Ellis (Rational Emotive Behaviour Therapy). More recently, mindfulness-based therapies, such as Mindfulness-Based Relapse Prevention, Acceptance and Commitment Therapy and Dialectical Behaviour Therapy, have contributed to the evolution of cognitive behavioural therapies. This chapter describes how these models work and how they have been adapted to alcohol and other drug use treatment, ranging from intensive to brief and low-intensity interventions. The evidence shows that cognitive behavioural therapy is one of the most effective interventions for alcohol and other drug use issues, as well as for co-occurring alcohol and other drug use and mental health problems. It has been adapted and applied across a range of cultures and countries.

Keywords

Cognitive behavioural therapy · CBT · Alcohol and other drug treatment · Alcohol and other drug use disorder

We are what we think. All that we are arises with our thoughts. With our thoughts we make the world. Shakyamuni Buddha

25.1 Introduction

25.1.1 What Is Cognitive Behavioural Therapy and Where Did It Come from

Cognitive behavioural therapy (CBT) has evolved significantly since its beginnings in the 1950s. At that time, psychology more broadly had begun to shift from its psychoanalytic roots into a science-based discipline with an emphasis on the scientific method, and therefore the measurable. A branch of psychology called behaviour therapy began to form driven by scientific enquiry [76].

By the 1960s, two psychoanalytically trained therapists, psychiatrist Aaron Beck ('Cognitive Therapy') and psychologist Albert Ellis ('Rational Emotive Behaviour Therapy', usually referred to as simply REBT), had almost simultaneously began to look beyond behavioural principles to the role of interpretation of events, drawing on ideas from cognitive psychology [53] and social learning theory [4]. What most people

refer to as traditional 'CBT' is usually some version of one of these two styles.

The next major development began in the 1990s with the mindfulness-based therapies such as Dialectical Behaviour Therapy (DBT) [41], Mindfulness-Based Relapse Prevention (MBRP) [13] and later Acceptance and Commitment Therapy (ACT) [27].

Thus, cognitive behavioural therapy is not a single therapy. It is an umbrella that encompasses a large group of therapies that have in common a focus on cognitions and behaviour as both the cause of, and the means to resolve, emotional and behavioural dysregulation. Perhaps more accurately referred to as cognitive behavioural therapies, this group of therapies is based on well-researched theoretical models; they share the underlying assumption that our thoughts, behaviours and emotional reactions are learned and that the path to well-being is through managing thoughts and beliefs and to some extent behaviour.

Cognitive behavioural therapies are the most researched group of therapies in the world, and due to the extensive evidence base, they have become a core competency for people in the alcohol and other drug workforce.

25.2 Assumptions Behind Cognitive Behavioural Therapies

25.2.1 Thoughts, Behaviours and Emotions Are Learned

From a cognitive behavioural perspective, alcohol and other drug use, and dependence is complicated by genetic, biological and temperamental factors, but these are risk factors rather than determinants. In much the same way as certain people may have a biological or genetic history of heart disease that puts them at higher risk of heart problems, environmental and learned factors such as eating habits, ability to control stressors, and exercise can prevent or lead to the development of a heart condition.

Both alcohol and other drug use and dependence are considered to be learned behaviours that emerge over time and can therefore be 'unlearned' [50]. They are assumed to operate within a context of a range of environmental influences, including family and friends, availability of alcohol and other drugs and sociodemographic circumstances. Cognitions and emotional responses are also considered to be learned.

25.2.2 Therapeutic Alliance Is a Necessary but Not Sufficient for Change

Cognitive behavioural therapies are often accused of ignoring the therapeutic alliance, but this is not the case. It is true that, unlike the analytic style therapies, cognitive behavioural therapies do not rely on the therapeutic alliance to create change. It is viewed as a necessary (but not sufficient) condition for change [8]. Leahy [39] describes it like an anaesthetic in surgery. Without it, surgery would be difficult and painful, but if you *only* had the anaesthetic, the problem would not be rectified.

Cognitive behavioural therapies build alliance in multiple subtle ways. Collaboration and active participation by individuals in their own treatment is viewed as essential and an important vehicle to developing a positive therapeutic alliance.

Clients' negative attitudes to treatment predict poor alliance in cognitive behavioural therapy [6], so a good effective treatment experience can improve therapeutic alliance. Cognitive behavioural therapies are goal oriented and problem-resolution focused. Whilst treating the whole person is important, addressing the client's immediate goals through developing problem-solving skills is the initial focus of treatment. In the process of resolving the client's problems, therapeutic alliance is naturally developed.

In addition, alleviating the clients' problems, good counselling skills, a flexible adapting style, a collaborative approach and seeking feedback

from the client all contribute to the development of therapeutic alliance [8].

25.2.3 Focus on the Here and Now

Cognitive behavioural therapies emphasise the present, at least initially. This is especially important because for many people who have problems with alcohol and other drugs, focusing on resolving past difficulties, especially those associated with the development of alcohol and other drug problems, is often of little benefit unless the day-to-day issues of drug use are addressed [50]. For example, there is little benefit in addressing childhood trauma, which may have contributed to the development of a drug problem, if the client is attending sessions intoxicated.

25.2.4 The Client as Their Own Therapist and the Importance of Homework

Cognitive behavioural therapies focus on developing skills in the client to enable them to be, in a sense, their own therapist. The session is designed to help clients to develop skills in reflection and self-management, and the emphasis of therapy is what happens outside the session, rather than in it. Hence, skill practice (sometimes referred to as 'homework') in between sessions is critical.

In one meta-analysis, the overall effect size between homework compliance and treatment outcome was 0.26; completing homework is associated with improved treatment outcome [47]. This effect size is similar to the effect of therapeutic alliance on outcomes [33], further emphasising the importance of homework.

25.2.5 Guided Discovery as a Self-Reflection Tool

Guided discovery, based on Socratic questioning, is the primary tool of cognitive behavioural therapists to support self-reflection. Socratic questioning is drawn from Socrates' teaching method of asking questions to promote thinking and reflection. The key difference between Socratic questioning and guided discovery is that Socrates usually had an end in mind, whilst this is not necessary for guided discovery. In fact, guided discovery requires genuine collaboration and curiosity [56] which preclude having an outcome in mind. The assumption behind the use of guided discovery is that the client has the answer to their problems, or at least the means to find answer. The therapist's role is as a guide or coach rather than the expert.

25.2.6 The Scientist-Practitioner Approach and Collaborative Empiricism

Cognitive behavioural therapies are driven by the scientist-practitioner approach. That is, the practitioner applies the scientific method to understanding and addressing client issues. Therefore, there is a constantly evolving cognitive behavioural case formulation that poses hypotheses that are then collaboratively tested. This is referred to as 'collaborative empiricism'.

The scientist-practitioner approach also necessitates undertaking and utilising research about outcomes, which is why cognitive behavioural therapies are the most researched group of therapies. In the scientist-practitioner approach, cognitive behavioural therapists use science in their practice, continually review science to maintain best practice and contribute to science through research [66].

25.3 Cognitive Behavioural Therapy in Practice

25.3.1 Length

In general, cognitive behavioural therapies are relatively brief (usually not more than 12–16 sessions), and even briefer versions have been developed that are designed for delivery between one and six sessions [3].

25.3.2 Structure

Typically, cognitive behavioural therapies use a structured session plan broken into three or four interconnected sections. Within those sections, the work is tailored to the client's needs, so the session format is both structured and flexible.

Carroll [14] uses the '20-20-20 rule': 20 minutes on review of the week, homework tasks and issues arising during the week; 20 minutes on discussion and practice of a particular skill or topic linked to an issue from initial assessment or something that has arisen during the week (e.g. 'since you've had a couple of close shaves this week, I thought we'd talk about high-risk situations today'); and then 20 minutes on recapping the session, agreeing on homework tasks and planning for the next week. In reality, sometimes the middle 20 minutes takes up slightly more time than the first and third 20 minutes, and it may become a 15-30-15 rule.

Mitcheson et al. [50] use a four-part structure: (1) setting the agenda and recap of previous session, (2) dealing with the specific agenda items (the focus of the session), (3) planning for the next session and (4) session review.

Structure of some sort is needed because often clients do not have well-developed skills in structuring their own lives, and this serves as a model to assist them to learn these skills. The structure is outlined to, and agreed with, the client at the beginning of each session. This practice is referred to as 'setting an agenda'.

'Structured' does not mean 'inflexible'. If issues arise, they are incorporated into the agenda as appropriate. Practitioners still need to use their clinical judgement and skills to determine what happens within the structure and when the structure may need to adapt to the immediate circumstances.

The purpose of the structure is both to help the client learn how to apply structure to their own world and to focus the session to ensure critical therapeutic work is being done, so the session is not just general counselling, or a chat.

25.4 Key Cognitive Behavioural Therapies for Alcohol and Other Drug Problems

There is extensive evidence for the effectiveness of cognitive behavioural therapies for a range of mental health problems, including alcohol and other drug disorders. McHugh et al. [48] showed moderate effect sizes (on average $d = 0.45$) with the largest treatment effects found for cannabis use disorders, followed by cocaine, opioids and then polysubstance dependence. Magill and Ray [43] showed similar results.

Overall, cognitive behavioural therapies appear to be both effective and long lasting when compared with general drug counselling, treatment as usual and no treatment controls and are effective in both individual and group formats [48].

25.4.1 Relapse Prevention

Relapse Prevention [45] is one of the earliest cognitive behavioural approaches developed specifically for alcohol and other drug problems. Its main goal is to develop skills to identifying and preparing for high-risk situations that lead to relapse to problematic alcohol or other drug use. Relapse is influenced by numerous factors including self-efficacy, outcome expectancies, craving, motivation, coping, emotional states and interpersonal factors, as well as lifestyle factors, and specific interventions also deal with each of these risk factors.

A number of studies have examined Relapse Prevention, including a systematic review of psychosocial interventions for alcohol and other drug use disorders [48], which included five studies that showed positive outcomes on retention in treatment and use. Compared to other types of behavioural therapies, Relapse Prevention was most effective in maintaining abstinence post-treatment (39% abstinent post-treatment), suggesting if abstinence is the treatment goal, relapse prevention may be the treatment of choice.

In a review of cognitive behavioural therapy, relapse prevention and contingency management, Dutra et al. [21] found that the group referred to as 'CBT therapies' (which included Cognitive Therapy and similar therapies such as Dialectical Behaviour Therapy) had lower dropout rates (35%) than relapse prevention (57%), equivalent effect sizes, but lower abstinence rates post-treatment.

Other treatments that draw heavily from the relapse prevention model have also been found to be effective. The Matrix Model [60], for example, is a 16-week manualised group focused outpatient intervention that includes many components of relapse prevention, plus a range of other behavioural interventions such as contingency management. It has been found to be effective for a range of people who use alcohol and other drugs, including amphetamine and cocaine users [64].

25.4.2 Cognitive Therapy

Cognitive Therapy of Substance Abuse, was first developed by Aaron Beck et al. [7], based on the general Cognitive Therapy model. Cognitive Therapy is often used interchangeably with the term cognitive behavioural therapy. Cognitive Therapy is a type of cognitive behavioural therapy but is not synonymous with it. Typically, in the literature, an intervention described as 'cognitive behavioural therapy' is a pure or modified form of Cognitive Therapy, or sometimes a pure or modified form of Relapse Prevention.

Not dissimilar to Relapse Prevention, the theory of Cognitive Therapy focuses on 'proximal situational factors', such as cognitive, behavioural, emotional and physiological variables that are immediate triggers for alcohol and other drug use, and 'distal background factors', such as personal history, long-standing cognitive and behavioural variables and personality traits that provide a context or set of vulnerabilities for alcohol and other drug use and may act as maintaining factors [71].

25.4.3 Coping Skills Therapy

The four main components of Coping Skills Therapy are relapse prevention training, social and communication skills training, training in coping with urges and cravings and mood management. Monti and Rohsenow [51] also used Cue Exposure Therapy to extinguish alcohol-related cues and to enable an environment to test out coping skills.

Although there are several positive studies linking cues to relapse, cue exposure has not shown the same effectiveness in alcohol and other drug use treatment as it has in other mental health areas, such as post-traumatic stress, obsessive-compulsive and panic disorders (e.g. Kavanagh et al. [36]).

Project MATCH, the largest alcohol treatment outcome study, used a modified version of Coping Skills Therapy as the cognitive behavioural arm of the study [51] and found it equally as effective as Motivational Enhancement and 12-Step Facilitation.

25.4.4 Mindfulness-Based Cognitive Behavioural Approaches

Mindfulness interventions are derived from the Buddhist practice of 'mindfulness' which involves purposeful attention to the present and an openness to accept things as they are [65]. There are a number of mindfulness-based therapies that are part of the cognitive behavioural therapy family.

Mindfulness-Based Relapse Prevention (MBRP) was developed specifically for substance use and integrates traditional relapse prevention with mindfulness-based meditation practices [74]. In a review of Mindfulness-Based Relapse Prevention [23], found significant improvements on withdrawal and craving symptoms, and negative consequences of substance use with Mindfulness-Based Relapse Prevention compared to Relapse Prevention, health education, Cognitive Therapy and treatment as usual. Studies have shown reductions in alcohol

and other drug use and craving and increases in acting with awareness and acceptance using mindfulness strategies [19].

Although Acceptance and Commitment Therapy has shown some good outcomes [40], there have been few well-conducted empirical studies from which to draw conclusions. Dialectical Behaviour Therapy, which blends traditional cognitive behavioural approaches with Zen buddhism was oroginally developed for people with borderline personality didorder but has also been found to be effective for people with alcohol and other drug problems [25].

There is a limited, but growing, research base for mindfulness-based therapies more generally. Hofmann et al. [31] argue that the proposed differences between mindfulness-based and traditional cognitive behavioural therapies do not require a separate classification of these treatments and have shown that the outcomes from both are about equivalent.

25.5 Variations in Cognitive Behavioural Therapies for Alcohol and Other Drug Problems

25.5.1 Brief Cognitive Behavioural Therapies

A number of brief cognitive behavioural interventions have been developed, primarily based on relapse prevention or coping skills therapy. In general, brief cognitive behavioural interventions are best utilised for moderate- to high-risk use and with people who are dependent but are not ready to engage in intensive treatment. They have been found to be effective for a range of people who use alcohol and other drugs, including those who are severely dependent.

Brief cognitive behavioural interventions have also been shown to assist with cocaine, alcohol and polydrug dependences and with drug-related problems such as insomnia (see [43] for a review) and drug-related harms [18].

A brief six-session intervention for cannabis dependence [34] has also been developed in Australia, using a combination of Motivational Interviewing and Relapse Prevention. Sessions include goal setting, planning to quit, dealing with lapses and relapses, refusal skills, managing withdrawal and cognitive and coping skills.

In addition, a range of brief therapies (one to two sessions) and brief interventions (5–20 minutes) for moderate- to high-risk drinking have been developed, based on social learning and cognitive behavioural therapy principles, including coping skills and relapse prevention strategies [67].

In Australia, Baker et al. [3] developed an intervention for people who use amphetamines that combined Motivational Interviewing with two or four sessions of brief Relapse Prevention, including coping with cravings and lapses, controlling thoughts about using (triggers, seemingly irrelevant decisions and pleasant activity scheduling) and relapse prevention (refusal skills and relapse planning). People with methamphetamine related problems can be difficult to engage and retain in treatment, and a briefer intervention may be more desirable for this group.

25.5.2 Low-Intensity Cognitive Behavioural Therapies

'Low-intensity' interventions are those that are low intensity for the practitioner or service and sometimes, but not always, less intensive for the client. They can be delivered face to face, usually by non-specialists in the field, for example, by medical practitioners delivering screening, brief intervention and referral to treatment (SBIRT), and through psychoeducational groups and 'advice clinics'. However, they are often delivered using a range of remote and self-directed technologies, such as books and paper-based materials, CD-ROMs and computers, and online media such as the Internet [54].

Low-intensity interventions have an advantage of increasing 'reach', access, flexibility and

responsiveness, patient choice and cost-effectiveness of evidence-based intervention [61] and can be used to address a range of alcohol and other drug use problems from prevention to tertiary treatment. Cognitive behavioural therapies are ideally suited to the low-intensity environment because they are typically brief, structured and easily manualised.

A number of different types of low-intensity interventions have been developed in recent years. Advice clinics, for example, operate in mental health services in the UK [72] as a one-off 30-minute appointment with a clinician.

Guided self-help cognitive behavioural therapies [38] involve either paper-based or Internet-based self-directed learning materials that are supplemented by lower-intensity guidance from a practitioner as required. The practitioner is available to answer questions about the material, but otherwise, the client works through a brief programme essentially on their own.

25.5.3 Digital Cognitive Behavioural Therapies

Despite the established efficacy of interventions for alcohol and other drug use disorders, a range of factors continue to limit their impact. Leaving aside considerations of quality and fidelity of treatment delivery, a range of barriers restrict the extent to which clients can access and engage with treatment. For many clients, barriers to accessing treatment stem from the availability or practical accessibility of services [17] and from considerations of anonymity and autonomy, from difficulties with recognising problematic alcohol and other drug use behaviours and from experiences of shame [57].

Digital treatments (also known as computer-delivered interventions and computer-assisted interventions) offer a means for mitigating the impact of some or all of these barriers to care. Digital treatments offer several potential advantages over traditional delivery modalities, not least being their ability to help a greater number of people access treatment [5].

Digital treatments promise much lower barriers to accessing services, facilitated via the increasingly ubiquitous availability of the Internet, and the proliferation of Internet-capable digital devices able to deliver digital treatments (computers, tablets, and smartphones). These accessibility and resourcing advantages have driven much of the enthusiasm for digital treatment approaches and are seen as methods for reaching a larger proportion of people who would benefit from alcohol and other drug use treatment but do not access it (a 2011 US survey put this number at 90%) [68].

Barriers relating to stigma and concerns around privacy and confidentiality can likewise be moderated by decoupling treatment from interactions with clinicians and services and the anonymity of accessing information online. Finally, digital treatments may assist with delivering treatments of greater consistency and fidelity, ensuring that any individual accessing treatment receives the same quality of service.

Several early reviews of computer-delivered interventions for a range of high-prevalence mental health disorders (e.g. depression and anxiety) were promising, suggesting that this modality offered similar efficacy to traditional face-to-face delivery [5]. This early enthusiasm has been tempered by methodological issues with much of the available literature, not least the large variation in how digital treatment interventions are operationalised, delivered and evaluated.

The overwhelming majority of substance disorder-focused digital treatments have been based on cognitive behavioural therapy foundations [2], albeit with considerable variation in how cognitive behavioural therapy has been implemented and how faithfully the treatment has been represented. This variation includes the format for delivery – structured as ‘sessions’ that are accessed at discrete times, or more frequent, less intensive interactions. Similarly, treatments can be offered in sequential, linear formats or offer a variety of modules that users can access flexibly [22]. Some digital treatments offer only targeted components (e.g. psychoeducation, goal setting, intake monitoring and motivational enhancement [28, 55, 70]), whilst others offer

more complete translations of traditional cognitive behavioural therapy [15].

Digital treatment approaches also vary in the degree of involvement of a clinician. Programs can be provided as completely self-guided activities (similar to traditional self-help approaches) or as combined self-guided/clinician-supported modalities. Clinician support is provided as structured or ad hoc contact via face to face, telephone- or video-based sessions, or text-based interactions. Digital treatment resources can also play a role as adjunctive elements supporting traditional face-to-face interventions (e.g. assisting with treatment adherence and homework compliance).

There have been a number of systematic reviews of the effectiveness of digital treatment approaches for alcohol and other drug use disorders, indicating broad preliminary support for these interventions as effective means for reducing rates of alcohol and other drug use compared to treatment-as-usual approaches [10, 46, 52].

It is difficult to estimate the overall effectiveness of cognitive behavioural therapy-based digital treatments for alcohol and other drug use disorders. The applicability of the available evidence is hampered by several factors. Firstly, there is a wide variety of digital intervention types, structures, populations and alcohol and other drug use types targeted. Secondly, there are variations in the terminology used to describe these interventions in the literature. Thirdly, whilst cognitive behavioural therapy or elements of cognitive behavioural therapy form the basis for most interventions, the degree to which any given intervention is faithfully translating cognitive behavioural therapy to a digital application varies, according to the treatment's intent and the inherent limitations of the digital technology being used. Finally, assessments of the actual effectiveness of digital modalities are complicated by whether or not clinician guidance or input is involved (although one recent meta-analytical review of guided and unguided low-intensity interventions for alcohol use found overall small effect sizes for these interventions overall, with no significant differences between clinician guided or unguided approaches [62]).

There may be differential effectiveness for these programmes based on substance type. A 2017 meta-analysis of the effectiveness of digital treatments for illicit substances found that when viewed across all substance types, Internet-based interventions demonstrated small but significant effect sizes in terms of decreasing use compared to control conditions, and these effects appeared to be retained at follow-up, but there was too few high-quality studies to be confident that their effectiveness was uniform across specific drug types [11]. Where meta-analyses exist for specific drug types are available, they tend to echo these findings (few high-quality studies and small but significant effect sizes). For example, a 2013 review identified only ten studies of sufficient quality assessing effectiveness of digital interventions for cannabis use and reported small effect sizes post-treatment [69]. A similar systematic review in 2016 included four studies using cognitive behavioural therapy and motivational interviewing for cannabis use and also reported a small mean effect size [29].

The evidence base for digital interventions for alcohol and other drug use disorders exhibits some methodological weaknesses, including comparatively weak or inconsistent (wait list/information/treatment as usual) control conditions and comparatively infrequent reporting of follow-up outcomes. Despite enthusiasm for the potential of digital modalities to reach larger numbers of individuals requiring treatment, and indications that these modalities are somewhat effective in modifying alcohol and other drug use behaviour, the current state of the evidence supports a prudent approach be taken to their widespread adoption as stand-alone methods of treatment.

In addition, interventions have been developed for mobile phone text messaging [63], mail [35] and online-facilitated peer support [24] (see www.theshedonline.org.au for an example).

25.6 The General Application of Cognitive Behavioural Therapies to Alcohol and Other Drug Treatment

Clients rarely present to alcohol and other drug treatment with *only* alcohol and other drug disorders. Up to 80% of clients seen in alcohol and other drug treatment have co-occurring mental health issues [32], up to 80% have been exposed to at least one traumatic event in their life with nearly half screening positive for some post-trauma symptoms [49], and an estimated 50–80% have some level of functional cognitive impairment [20].

Cognitive behavioural therapies are ideally suited to alcohol and other drug treatment populations with comorbid disorders because they are highly structured, enabling those with cognitive deficits to gain benefit from the treatment, and have been well researched both in populations where these disorders are primary and in populations where these disorders co-occur with alcohol and other drug problems.

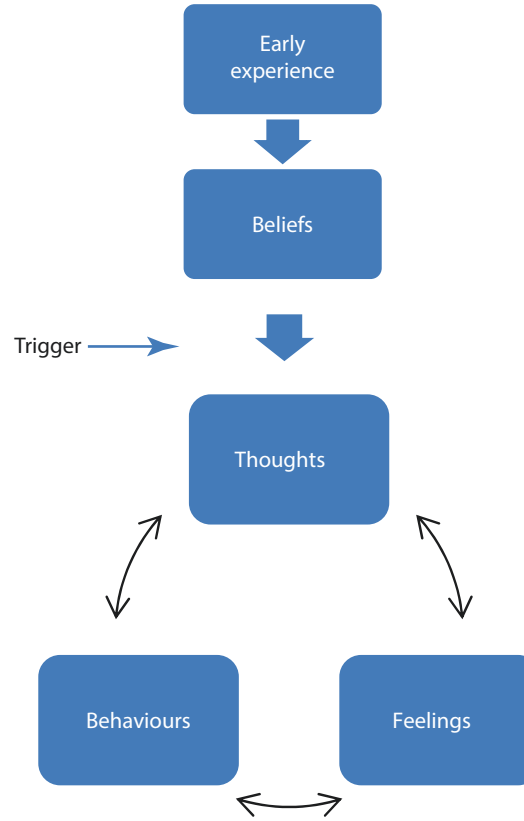

Fig. 25.1 General cognitive behavioural therapy model

25.6.1 A General Cognitive Behavioural Model for Alcohol and Other Drug Disorders

We use a generic cognitive behavioural model that is heavily drawn from traditional models but flexible enough to accommodate newer cognitive behavioural therapies. Our cognitive behavioural model is outlined in Fig. 25.1. This model allows clinicians to develop a clear formulation of a problem and flexibly implement a variety of strategies and techniques.

The model assumes that all six elements – early experience, beliefs and schemas, triggers, and a cycle of thoughts, feelings and behaviours – are important and influence each other. Understanding each element and the relationships between them is crucial in enabling change.

Despite being mostly present-focused, cognitive behavioural therapies do recognise that *early experience* is important in the development of our fundamental beliefs. Family, social, community, environmental and personal experiences early in life all contribute to people developing core beliefs about themselves, others and the world.

Everybody's early experiences are different, even those from the same family, and the development of beliefs will therefore be highly individual. These beliefs may be 'beliefs' or 'core beliefs' or 'schemas' and can be positive or negative and often feel like facts or truths to the person.

At various times, our core beliefs may be triggered by people, places or events (external) or emotions (internal) that lead to the day-to-day thoughts that are connected to our feelings and behaviours. In this model, feelings may be feelings, emotions or sensations. There is a strong influential relationship between thoughts, feelings and actions.

25.6.2 Triggers

Careful identification of triggers and the patterns of thoughts, feelings and behaviour following the triggers maximises the selection of appropriate interventions. Assisting clients to manage triggers can be a useful first step for clients to make changes and develop some sense of control over their reactions and behaviour.

Relapse prevention, one of the most well-known forms of cognitive behavioural therapy for alcohol or other drugs problems, has an emphasis on triggers. The original focus of relapse prevention [45] was to address the important issue of relapse after cessation of alcohol and other drug use [44], although it is now used in cases of controlled use and among people who use alcohol and other drugs who are not yet abstinent.

The primary focus of relapse prevention is to identify and understand 'triggers' or 'high-risk situations' (which may be locations, people and emotions) and for the client to develop behavioural coping strategies for those situations. This may involve avoiding or changing certain triggers, for example, changing activities or routines or access to substance using paraphernalia or money.

25.6.3 Thoughts and Beliefs

Substance-related thoughts and beliefs are an important focus of investigation and intervention. Broadly, the three categories of thought and belief-based interventions are *analysing*, *challenging*, and *accepting*. Clinicians need to identify problematic thoughts and beliefs with clients and then choose in collaboration with the client the approach that best suits the situation.

Analysing approaches involve identifying thoughts and beliefs and their relationship to feelings and behaviour and considering the helpfulness or unhelpfulness of these thoughts and beliefs. Traditional cognitive therapy (Beck) and rational emotive behaviour therapy (Ellis) are examples of this approach where problematic thoughts and beliefs that maintain alcohol and other drug use, 'cognitive biases', would be identified. There are a number of categories of substance-related thoughts and beliefs that may be worthy of the clinician's attention including coping and self-efficacy (e.g. ability to cope without a substance generally or in specific situations), positive outcome expectancy (e.g. enhancement of functioning as a result of alcohol and other drug use or relief from negative internal experiences such as pain or distress) and craving and withdrawal (e.g. ability to tolerate these states).

Relapse prevention approaches consider salient beliefs about the effects of using alcohol and other drugs. Thoughts such as 'I can only relax if I have a drink' can increase the risk of lapse and relapse in specific situations, for example, during periods of high stress [50]. Therefore, self-efficacy (one's belief in one's ability to achieve a goal – in this case abstinence or controlled use) and expectancies (beliefs about the effects of alcohol and other drug use) become very important and one of the main targets of treatment.

Challenging approaches involve analysing the thoughts and beliefs as described above and utilising challenging strategies such as asking for evidence for the beliefs and looking for exceptions and contradictions and then developing modified or alternative thoughts and beliefs.

An example of this approach from relapse prevention involves identifying the thoughts and beliefs that might occur should a client lapse (one instance of alcohol and other drug use following a period of abstinence) and find themselves moving towards a relapse (return to fully using alcohol and other drugs), a phenomenon known as the 'abstinence violation effect'. Thoughts underlying an abstinence violation effect are usually associated with perceived loss of control and self-blame, for example, 'I've blown it so I might as well use whatever I want...'. A challenging approach would in advance identify these thoughts and beliefs, challenge their accuracy and develop alternative less risky beliefs.

Accepting approaches involve noticing and accepting thoughts and beliefs without judgement or necessary further action. This approach

is consistent with Acceptance and Commitment Therapy that grew from the same radical behaviourist perspective as applied behaviour analysis [26]. The central components are cognitive diffusion (i.e. learning not to place a high importance on thoughts), acceptance of thoughts without judgement and commitment to action based on one's core values. It is also used in other more traditional cognitive behavioural therapies.

25.6.4 Feelings

A criticism levelled at cognitive behavioural therapies has been that the role of emotions has been undervalued. However, as stated earlier, in our model, 'feelings' are considered an essential element that influences and is influenced by the other elements. Likewise, in the relapse prevention model, negative emotional states are a focus as they both trigger and maintain alcohol and other drug use and are considered one of the main predictors of relapse [75]. Therefore, clinicians need to explore feeling states with clients and have strategies to intervene with feelings as required.

If feelings have been identified as an area requiring intervention, a number of strategies can be utilised. These include understanding emotions, identifying the relationship between emotions and alcohol and other drug use (including emotions as a trigger for and a consequence of alcohol and other drug use), emotion regulation, distress tolerance (including mood and urge surfing) and mindfulness.

Our model can be utilised to assist clients with alcohol and other drug issues to understand and identify emotions by selecting an example of the presenting issue, exploring the elements of the model and asking clients about the feeling element. We find clients may need coaching and psychoeducation about feeling states and mood monitoring homework is often of use.

With regard to emotion regulation and distress tolerance, clinicians can draw on strategies from Dialectical Behaviour Therapy, a combination of standard cognitive behavioural therapy strategies for emotion regulation and four mindfulness-oriented modules of mindfulness, distress tolerance, emotion regulation and interpersonal effectiveness. Although Dialectical Behaviour Therapy was originally developed for borderline personality disorder (BPD), it has been recommended by its developers as most suitable for very complex alcohol and other drug use disorder presentations. This includes people with co-occurring alcohol and other drug use and BPD, alcohol and other drug use disorder and chronic suicidality, and alcohol and other drug use disorder that has not responded to traditional cognitive behavioural therapy over time, especially if emotional regulation is a key factor in relapse. It is not considered a first-line treatment for uncomplicated alcohol and other drug use disorder.

Mindfulness approaches focusing on the cultivation of acceptance of negative feelings and relaxation strategies to regulate affect may also be useful where the clinician has identified that intervention is required with a client's 'feeling' states.

25.6.5 Behaviour

It is essential that clinicians consider a client's behaviour when attempting to assist them to change a pattern of ongoing alcohol and other drug use. Intervening at the behavioural level can focus on the substance using behaviour itself or on behaviours strongly associated with the alcohol and other drug use. Behavioural change can not only reduce health risks for a client but can also increase their sense of efficacy.

There are a number of alcohol and other drug specific approaches that focus on behaviour. As described above, relapse prevention identifies triggers with the purpose of changing or modifying behaviour to reduce or eliminate the impact of the trigger, for example, planning a different route home not past the bottle shop, or not listening to music associated with alcohol and other drug use. Relapse prevention approaches emphasise behavioural strategies to manage cravings, for example, relaxation, distraction or attention switching.

Coping skills therapy was developed by Monti and Rohsenow [51], initially in conjunction with cue exposure therapy, and has many similarities to relapse prevention. Like relapse prevention, it is based on social learning theory [51] but focuses more heavily on learning behavioural coping skills, and less on cognitive skills, in high-risk situations. It also teaches specific social skills to both improve relationships that have been damaged through alcohol or other drug use and to help develop healthy, non-using social networks [4].

Other cognitive behavioural approaches, not specific to alcohol and other drugs, are often useful for clients with alcohol and other drug use issues, including activity scheduling, and anger, depression and anxiety management (particularly when mood has been identified as a trigger for alcohol and other drug use).

25.7 International Considerations

Cognitive behavioural therapies have their origins in the developed world and are heavily based on western concepts and models of illness [59]. However, it is a broad and flexible model of care based on a well-grounded treatment formulation that can accommodate cultural and other influences and as a result has been adapted and successfully used across a number of cultures.

For example, in some cultures, such as many Indigenous groups, collective history is an important component of their world view [59], or in cognitive behavioural terms, 'core beliefs'. Although cognitive behavioural therapies do not delve deeply into the past to routinely reappraise it, past issues are not precluded when they are driving or maintaining current problems, and cognitive behavioural therapies can easily accommodate these types of cultural differences.

Hodges and Oei [30] have examined the compatibility of cognitive behavioural therapies with Chinese values and have identified a number of potential issues, including the value Chinese and other Asian cultures place on conformity, certainty and discipline, persistence and a strong work ethic, and respect for authoritarian systems. In Asia more broadly, there is also a high level of stigma around mental health issues and a tendency for somatisation (expressing mental health issues as physical symptoms).

Hodges and Oei [30] argue that because cognitive behavioural therapies are structured and can be adapted to a more instructive rather than collaborative style, it may suit cultural contexts needing a more directive style. This adaptation may suit the need for certainty and authority in these cultures and can also reduce the stigma of mental health treatment by using a 'coaching' style of therapy. Finally, they note that with the expansion of cognitive behavioural therapy using Eastern and Buddhist mindfulness strategies, cognitive behavioural therapies are well suited to Asian cultures.

Cognitive behavioural therapy for mental health problems has been applied successfully in a range of diverse cultures and countries including, but not limited to, Pakistan [37], Japan [12, 42], China [58], among Latina women in the USA [16], Muslims [73] and Indigenous Australians [1] using a more narrative style of delivery, sometimes referred to as 'bush Cognitive Behaviour Therapy' [9]. Although many of these studies are not specifically related to alcohol and other drug use disorders, the cross-cultural applications still apply.

25.8 Summary

Cognitive behavioural therapies encompass a wide range of therapies that have in common a focus on thoughts and beliefs as the central driver of, and the solution to, effective emotion regulation.

They tend to be relatively brief and highly collaborative, the latter the focus of the development of the therapeutic alliance, an essential component of the application of cognitive behavioural therapy. They come in a wide range of formats, including group and individual therapy, longer-term and brief therapy and low-intensity interventions such as computerised cognitive behavioural therapy.

They are among the most researched treatments in the world; both traditional and newer models have shown effectiveness for treating alcohol and other drug use disorders. The structured and theoretical base makes it ideally suited to issues that co-occur with alcohol and other drug use problems, including common mental health problems, cognitive impairment and trauma.

It has been adapted and applied across a range of cultures and countries. Cognitive behavioural therapy is ideal for adaptation to non-Western cultures because of its flexible collaborative style and its reliance on effective case formulation.

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26 Psychodynamic Psychotherapy for the Treatment of Substance Use Disorders

E. J. Khantzian

Contents

Abstract

An understanding of addiction to drugs and alcohol and their treatment is reviewed from a modern-day psychodynamic perspective drawing on ego/self-psychology and object relations and attachment theory. The author places emphasis on addictions as a self-regulation disorder. Deficits in regulating emotions, self-esteem, relationship, and self-care interact variably and cause individuals so affected to relieve their pain and suffering associated with these deficits with addictive substances and to become addicted to them. The author considers addictive drugs to be appealing not so much as pleasure producing but rather as agents that create and foster comfort and contact for individuals who are discomforted and disconnected. Alcohol and drugs, short term, relieve and/or change states of anhedonia, dysphoria, and unbearable painful emotional states. Individuals so affected discover that depending on the particular emotional pain with which they suffer, they discover a preference for a particular class of drugs. The action of each class of drugs is linked to how individuals discover these specific effects in relation to the suffering associated with their self-regulation problems. Appreciating these vulnerabilities and in contrast to outmoded psychoanalytic modes of detachment, passivity, and more strictly interpretive approaches, the author considers, from a contemporary perspective, important therapeutic elements and attitudes necessary to address the vulnerabilities such as being more

E. J. Khantzian (✉)
Department of Psychiatry, Harvard Medical School, Boston, MA, USA
e-mail: drejk26@comcast.net

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interactive and to incorporate attitudes of kindness, support, empathy, respect, patience, and instruction in order to build and maintain a strong therapeutic alliance.

Keywords

Psychodynamics · Affects · Self-medication · Self-regulation

26.1 Introduction

Psychodynamic psychotherapy rests on the principle that important psychological factors are at the root of addictive behaviors and that these factors can be identified, targeted, and modified in the treatment relationship and thus eliminate or make less likely a reliance on addictive substances. We have reviewed elsewhere [5] early psychoanalytic formulations, that with a few exceptions, emphasized the use of addictive drugs as a regressive, pleasurable adaption, whereas more contemporary formulations have placed emphasis on a progressive adaptation where addictive substances serve to cope with painful internal states and conditions and overwhelming external realities. Contemporary psychodynamic psychiatrists dating back to the 1960s and 1970s have reported on the nature of addictive vulnerability based on an appreciation of factors from structural, ego/self, and object relations perspectives. These perspectives underscore how disturbances and vulnerabilities in experiencing and processing emotions, sense of self/self-esteem, interpersonal relations, and behaviors are important if not essential factors for the development and maintenance of addiction to substance of abuse. Although there is empirical data supporting the efficacy of psychodynamic psychotherapy for a range of psychiatric disorders, including treatment of addictive disorders [4, 13, 21], there is a rich clinical literature describing how an appreciation of the underlying dynamics of addictive behavior can be fathomed and targeted in individual and group therapy to help addicted individuals understand and modify these dynamics and overcome their addictive attachments and behaviors [4]. Although individual psychotherapy is the primary focus here, this treatment modality should not or need not compete with complimentary or alternative treatments when psychodynamic findings indicate the need for additional or alternative treatment as will be discussed subsequently.

What is reviewed in this chapter derives mainly from clinical work with drug-dependent individuals. This chapter rests on the assumption that the case method and the treatment relationship (practice-based evidence) yields rich data that illuminates the nature of addictive disorders and provides keys to understand and treat patients who suffer with addictive illness. We will emphasize the more contemporary formulations that provide a basis to appreciate the vulnerabilities that underlie reliance on addictive substance and behaviors, and how individual and group psychotherapy can ameliorate addictive suffering and modify addictive behavior.

26.2 Addiction as a Self-Regulation Disorder

Addictive disorders are rooted in suffering – not pleasure seeking or self-destructive motives as early psychodynamic formulations suggested. The suffering is mainly a consequence of addicted individual's inability to regulate their emotions, self-esteem, relationships, and behavior, especially their self-care [13]. From the earliest phases of infancy through early adult development, environmental influences around parenting, safety, comfort, traumatic abuse/neglect, and peer relationships are crucial in influencing self-regulation capacities; and significantly, experiences from earliest phases of development, for which there are no memories or symbolic representations, have some of the most profound influences [8, 17, 20]. In this respect, these developmental factors weave their way through addictively prone individuals' ways of experiencing their emotions, sense of self, relationships, and behaviors to make addictions more likely. In what follows, I will elaborate on these self-regu-

lation problems and how appreciation of the dynamics involved can guide effective individual and group therapeutic responses.

26.2.1 Disordered Emotions

Contemporary psychodynamic views have placed heavy emphasis on how addictively prone individuals suffer in the extreme with their emotions. Affect life at one extreme is perplexing, elusive, cut-off, or absent, and at the other extreme, feelings are overwhelming and unbearable. Terms such as alexithymia, disaffected, anhedonia, and non-feeling states have been adopted to capture how feelings are not available, elusive, and disconnected, thus causing individuals so effected to feel empty, cut-off, and unable to use their emotions to guide their reactions and behavior [17–19]. Krystal and Raskin [18] appreciated some of the bases of these deficits when they described how feeling life has a normal developmental line (and potential for arrest or regression secondary to trauma or neglect) and how at the outset of life feelings are undifferentiated (i.e., anxiety cannot be distinguished from depression), that feelings are somatized, and without words (alexithymic). Addictively prone individuals at the other extreme suffer because feelings are intense, overwhelming, and unbearable. In this respect, more recent psychoanalytic investigators stressed defects in affect and drive defense and deficits in psychological structure to explain how substance-dependent individuals adopt addictive drugs to make intolerable feelings more bearable, especially those involving rage and aggression [10, 23, 24].

These same investigators have elaborated on how addictive drugs can stimulate and enliven individuals who are cut-off or feel vacuous or help to contain disorganizing and intense emotions when such affect is threatening or overwhelming. In these reports, the activating properties of stimulants and the releasing effects of low to moderate doses of depressants are described as correctives for individual experiencing their feelings as cut-off or vacuous [9, 11, 12]. Weider and Kaplan [23] coined the term "drug-of-choice," elaborating on how individuals self-select addictive drugs as a "prosthetic" to cope with overwhelming adolescent anxiety. The works of Wurmser [24] and Khantzian [11] emphasized the calming or muting action of opiates or obliterating doses of alcohol, especially for feelings of rage and aggression. What should be emphasized here is that these reports better focused on and appreciated how addictive drugs were used not for pleasure or self-destructive motives as early psychoanalytic studies stressed, but more precisely to selectively alleviate or make more tolerable affects that were confusing, unbearable, or intolerable.

More recently, Khantzian (2002, 2012) has considered some of the more subtle psychodynamics of addictive behavior that are insufficiently considered, namely, why so much of addictive behavior unfortunately continues to be linked to pleasure seeking (especially by neuroscientists) and how and why seeking relief from addictive drugs most usually produces more suffering than it relieves yet addicted individuals persist in their use of their drugs. In the former instance, especially those who are alexithymic and confused about their feelings, addicted individuals wittingly and unwittingly substitute the suffering which they perpetuate and control with use for the suffering they do not understand or control. The operative changes from simply relieving suffering, for one of control where they better understand and control it. In the second case, Khantzian [13] has speculated, based on clinical observations, that addicted individuals often suffer with pervasive anhedonia and that the often magical relief they first experience with their drug of choice is experienced as euphoric, which is interpreted as pleasure, when in fact it is the result of relief of the anhedonia.

26.2.2 Disordered Relations with Self and Others

Dating back to the seminal contributions of self-psychologist Heinz Kohut [15, 16], recent formulations have underscored the faulty and troubled

ways addictively inclined individuals suffer with troubled inner states of discomfort about self. Inner states of cohesion and well-being are lacking and lead to periodic and/or chronic feelings of helplessness, fragmentation, impoverishment, shame, and a low sense of self-worth; as a consequence, feelings of rage and defensive postures of omnipotence and bravado often result to mask underlying feelings of emptiness and inadequacy [13]. Dodes [2, 3] has emphasized how feelings of helplessness and compensatory narcissistic rage are major factors leading to drug use and relapse. On this basis, he formulated that addictions are a compulsive disorder and thus subject to traditional psychodynamic psychotherapy. Along similar lines, Director [6] focused on feelings of powerlessness, unimportance, and compensatory reactions of omnipotence to explain recurrent relapse to addictive drugs in her work with two addicted women.

The importance of these perspectives is that clinicians must be sensitive and fine tune to the troubled sense of self and painful lack of self-regard drug dependent struggle with and to be appreciative of how the off-putting defensive characteristics can be understood as necessary postures to avoid narcissistic collapse. Furthermore, these findings indicate the significance of appreciating how such dynamics basically interweave with the compulsion to self-medicate the emotional pain such dynamics engender.

Troubled sense of self and self-esteem issues powerfully interact with relational difficulties for substance-dependent individuals. The early psychoanalytic literature linked addictions to pathological or problematic dependency. In contrast, contemporary psychodynamic views underscore problems of interpersonal isolation and counterdependence. Although drug-dependent individuals suffer from enduring troubled, disrupted, and often traumatizing histories, experiencing or expressing their needs for connection and comfort with others that they so desperately need cannot be dared or accepted. As a consequence, feeling lonely, cut off, and alienated becomes a tragic way of life. Psychodynamic explorations of these attachment problems, more often infantile in origin, reveal how such adaptation is powerfully connected to addictive use of substance to deal with the associated distress and the pain perpetuating defenses of self-sufficiency, disavowal of need, and counterdependence ([7, 13, 22], Weegmann 2004).

Considering how these problems with sense of self, self-worth, and relational difficulties cause drug-dependent individuals so much pain and difficulty in tolerating distress and interactions with others, it should not be surprising the action of addictive drugs provides temporary relief and "solutions" to their intrapsychic and interpersonal pain and difficulties. Stimulants can counter states of helplessness, enfeeblement, and deflation in narcissistically injured individuals as well as provide a psychic boost for deflated self-esteem; or opiates can contain or offset the dysphoria that comes with disorganizing rage and make connections to others less threatening [2, 12, 13]. Low to moderate doses of alcohol can help shamefully restricted individuals, briefly, and therefore tolerably, to breakthrough and connect with others [18].

These examples offer support for the recurrent clinical observation of why and how addictive substances become so compelling in individuals who suffer with an injured sense of self, poor self-esteem, and problematic interpersonal relations.

26.2.3 Disordered Self-Care[1]

Khantzian [13] and Khantzian and Mack [14] have described a fundamental ego function involved in life and in addictive vulnerability, namely, a capacity for self-care. Self-care functions insure safety, well-being, and survivability. They are underdeveloped or deficient in substance-dependent individuals. Early in his career, Khantzian [13] cites his experience working with intravenous heroin users in a methadone program wherein he describes his powerful subjective reaction to the idea of injecting oneself with illicit drugs; he realized that his reaction of

[1]The following sections on self-care and treatment are based in part on a recent report by Khantzian [14].

repugnance to that idea was one of countertransference (modern theorists would call it an "intersubjective" response, namely, patients getting the therapist to feel something that the patient is unaware or incapable of). Tactfully sharing his recoil and discomfort with the many patients he was evaluating, Khantzian consistently and monotonously elicited reactions of little or no emotions or concerns of alarm about crossing the so-called needle barrier. Subsequently, working with abstinent drug or alcohol-dependent patients in psychotherapy, Khantzian was struck by how such lack of worry or thought persisted when no longer substance dependent. He observed these deficiencies to be involved in interpersonal and physical mishaps, slip-ups around management of important matters of unpaid premiums, lapsed licenses, and preventable medical and dental problems. It is in this context that he began to conclude that a major contributing factor to the development of addictions involved deficits in a capacity for self-care. Namely, addictively prone individuals think and feel differently about potential and real situations of harm and danger. Anxiety, fear, worry, and apprehension are deficient or absent and fail to guide such individuals in risky or self-harmful situations. There is a failure to draw cause/consequence relationship in the face of risk. Where anticipatory shame and guilt might guide when self-care capacities are better developed, in addictively prone people, shame and guilt come after the fact (e.g., "I felt stupid and bad when I did that" [rather than] "I will feel stupid and bad if I do that"). It is the combination of self-care deficits interacting with the pain and suffering involved in self-regulation difficulties that make vulnerable individuals more likely to develop addictive disorders.

26.3 Implications for Psychodynamic Psychotherapy

Treating clinicians need to constantly appreciate the underlying dynamics and vulnerabilities that govern addictive behavior. Considering the difficulties addicted individuals have with regulating their emotions, sense of self/self-esteem, relationships, and self-care, therapists need to think about therapeutic elements and attitudes that would best attune and respond to the suffering and dysfunction with which patients struggle. Old psychoanalytic approaches of passivity, therapeutic detachment, and strictly interpretive methods, therefore, would not be the order of the day. In fact, such approaches could perpetuate the confusion, shame, alienation, and disconnect with which addicted patients suffer. Thus, a contemporary psychotherapist needs to be more interactive (balance talking and listening) and incorporate attitudes of kindness, support, empathy, respect, patience, and instruction in the service of building and maintaining a strong treatment alliance. These elements are essential in order to deal with and overcome the problems with inaccessible or intense emotions, shame, broken self-esteem/relationships, and poor self-care [13]. Confrontation should be avoided and used only rarely such as concerns about safety but done in a way that preserves self-esteem.

Given recent developments in use of medications in managing substance use disorders, I should emphasize here that it is clearly evident that medication-assisted treatments (MATs) are crucially important and life-saving. They should be employed to curtail and prevent the dangers of overdose, loss of control, and the emotional and behavioral instability associated with drug-alcohol problems. They also provide beneficial prosthetic support and control to safely allow the psychodynamic explorations and therapeutic interventions reviewed in this chapter.

The psychodynamic findings that have been outlined previously are considered in what follows, not only in reference to individual psychotherapy but also as they apply to considering other treatments, especially psychodynamic group therapy, as they can enhance individual therapy or be considered as alternatives when there are psychodynamic indications to do so.

Remembering how cut-off addicted patients can be with their thoughts and feelings, therapists can help significantly with these dysfunctions by actively drawing out, identifying, and labeling feel-

ings that begin to surface or seem evident to the therapist. When patients protest they do not know what they are feeling, treating clinicians should avoid concluding it is resistance or denial but rather use such interactions to invite and support the patient to consider the challenge of exploring, discovering, and understanding their feelings and emotions. Allen, Fonagy and associates [1] (2008) have coined the term *mentalization* to emphasize one of the most basic aspects of psychotherapeutic work in general, but the concept preeminently applies to work with addicted patients, namely, to persistently focus on helping patients to access feelings, put them into words, and sustain them. Beyond individual therapy, the narrative and storytelling traditions that occur in group therapy and 12-step meetings are often very beneficial in helping patients to develop a capacity to recognize, express, and practice their own thoughts and feelings.

For those patients who struggle with and self-medicate intense and threatening emotions, particularly anger and rage, considerations and efforts should be made to help them contain and moderate the feelings that can feel so dangerous to self and others. It is worth noting how the positive treatment relationship and the therapist's concern for the safety of the patient is in and of itself a containing influence. For those whose rage and violent feeling derive from trauma and neglect, it is crucial to acknowledge and validate the legitimacy of such reactions and help them to understand how and why they have resorted to addictive drugs to contend with such intense emotions. Carefully timed and gentle explorations of the experiences that engender such emotions can gradually diminish or resolve such intense affect. In this context, judicious use of legitimate psychotropic medications targeting these affects can significantly attenuate the intensity to make the working through of these affects in psychotherapy more doable.

The support and empathy exhibited by the therapist in response to drug patients' pervasive sense of shame and broken self-esteem (predisposing and consequential) is a vital element in engaging and retaining such patients in psychotherapy. Such an approach helps in gaining inroads on the confusing and elusive ways in which the sense of self and others is experienced by substance users. Openings are created to focus on and help identify and resolve feeling of powerlessness, defensive rage, and reactions of omnipotence that are experienced and often surface in treatment. Patience, support, and kindness remain of paramount importance and allow for opportunities to therapeutically address and help the patient and the therapist, understand, and better work out problems with off-putting characteristics. These characteristics are more often reactive and defensive secondary to feelings of helplessness as well as feelings of unimportance [2, 6]. And for those who are seemingly void of emotions and disengaged, the therapist may draw on their own energy and liveliness to help activate and enliven patients who are so affected. Again, group therapy experiences often can be invaluable in this respect in instilling and validating a better sense of self/self-esteem.

The issue of low self-esteem of substance abusers is related to their tendency to be avoidant of relationships and interpersonally isolated. They feel undeserving of the care and connection to others. Remaining interactive, engaging, and empathic is an important element in responding to patients' fear of and ambivalence about relationship. Impassivity and detached interpretations can be counter-therapeutic and devastating. Tactful focus on the ambivalence can materially stimulate possibilities of beneficial connections to others. It is in this respect that the connections stimulated by individual and group therapy are extraordinarily helpful in addressing and ameliorating the attachment difficulties and sense of alienation with which substance-dependent individuals struggle.

The thoughtless and unfeeling behaviors of substance-dependent patients that are characteristic of self-care deficits become manifest in the treatment relationship by the alarm stirred in the therapist by patients' risky or dangerous behaviors. Such reactions and interactions can alert the therapist and patient to how such deficits are major factors for patients to use and relapse to additive behaviors. The therapist should be unhesitant in using their reactions of alarm and concern that patients stir to identify the lack of such reaction in the patient. Constant attention to patients' poor self-care can help instill a growing aware-

ness of how their self-care deficits continuously leave those so affected continuously in harm's way, especially those involved with the harm and dangers associated with addictive substances. Long-term therapy often helps in getting at and understanding the developmental and environmental roots of these deficits, but a here-and-now, active, instructive approach is essential in order to stimulate and better develop a better capacity to recognize, anticipate, and avoid self-harm, particularly related to addictive substances. Finally, "We need to help patients use self-respect, feelings of apprehension/worry, relationships with others, and thoughtfulness as a guide for safe behavior and self-preservation" ([13], p.278).

26.4 Summary and Conclusion

Contemporary psychoanalytic understanding of addictive disorders has generated and documented observable, developmental, structural, ego/self, and object relations disturbances that predispose to and maintain addictive behaviors and attachments. These findings provide a basis to identify the ways in which these disturbances affect feelings, self-esteem, relationships, and self-care. They provide a basis to guide therapists in targeting these problems psychotherapeutically. Impassive and strictly interpretive approaches are contraindicated if not damaging. Modern psychotherapeutic treatments employ more interactive, supportive, and empathic attitudes and techniques to help patients and therapist to focus on vulnerabilities and dysfunction that perpetuate addictive suffering and pain. This contemporary perspective provides understanding, hope, and more effective means to overcome the compelling, self-defeating, and tragic causes and consequences of addictive disorders.

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Mindfulness-Based Approaches in Addiction Treatment

27

Andrew S. McClintock and Marianne Marcus

Contents

Abstract

Substance use disorders (SUDs) are prevalent and persistent psychiatric conditions that have damaging consequences on physical and psychological health. Recently, mindfulness-based interventions (MBIs) have been developed and tested in the treatment of SUDs. In this chapter, we discuss mindfulness concepts and practices and review the empirical literature on the efficacy of MBIs for SUDs. Our review suggests that there is substantial meta-analytic evidence that SUD populations generally benefit from MBIs. Nevertheless, when examining effects on a specific SUD (e.g., tobacco, alcohol, or opioid use disorder), the evidence base is more limited and inconsistent. Literature

A. S. McClintock (✉)
University of Wisconsin-Madison,
Madison, WI, USA
e-mail: asmcclintock@wisc.edu

M. Marcus
The University of Texas Health Science Center
at Houston, Houston, TX, USA
e-mail: marianne.t.marcus@uth.tmc.edu

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shortcomings and suggestions for future research are provided.

Keywords

Addiction · Substance use disorder · Mindfulness · Mindfulness-based intervention · Review · Efficacy

27.1 Introduction

Addiction is a chronic disease characterized by craving and impairments in behavioral control [1]. Addiction is thought to hijack reward, motivation, and memory neural circuitry [1] and, like other chronic diseases, often involves cycles of remission and relapse. Although addictions can be formed to a range of objects (e.g., gambling, sex), addictions to psychoactive substances are particularly prevalent and deleterious to physical and psychological health. The 12-month prevalence of substance use disorders (SUDs) is approximately 7.6% among US adults, with about 5.7% meeting criteria for an alcohol use disorder, 2.8% an illicit drug use disorder, and 0.8% an opioid use disorder [41]. Substance abuse is a leading cause of disability and lost work productivity and costs the United States more than $740 billion annually [36]. Moreover, each year, about 88,000 Americans die from alcohol-related causes [37], and 70,000 die from drug overdose [8]. Of particular concern is the recent mortality spike attributable to heroin, commonly prescribed opioids (e.g., oxycodone), and other synthetic opioids (e.g., fentanyl). In the United States, opioid overdose claims about 130 lives every day [8].

Given the prevalence of SUDs and the impact of SUDs on the user, those close to him or her, and society as a whole, it is imperative that SUDs be treated with demonstrably effective interventions. Over the past 25 years, there has been increasing clinical and empirical interest in the application of mindfulness-based interventions (MBIs) for SUDs. In this chapter, we will discuss the concept and practice of mindfulness, highlight the most commonly used MBIs in the treatment of SUDs, and review the evidence on the effectiveness of MBIs for reducing substance misuse and preventing substance relapse.

27.2 Mindfulness

Mindfulness refers to a mode of awareness characterized by curiosity, nonjudgment, and a present-moment focus [24]. Mindfulness involves enhanced awareness and acceptance of immediate, moment-to-moment experiences (e.g., sounds, smells, thoughts, bodily sensations). Mindfulness skills and abilities are typically developed through repeated engagement in mindfulness meditation practices [24]. During mindfulness meditation, the practitioner typically sustains attention on a meditative object (e.g., breath), notes distractions when they occur (e.g., worries about a future event), and then returns attention to the meditative object. As indicated by Segal et al. [39], if the mind wanders a hundred times during meditation practice, then the task is to simply bring it back a hundred times; the issue "is not learning to switch thoughts off, but how best we can change the way we relate to them: seeing them as they are, simply, streams of thinking, events in the mind, rather than getting lost in them" (p. 134).

There are many reasons why mindfulness may help in addiction treatment. For instance, mindfulness might facilitate increased attentional disengagement from substance-related stimuli [13], reduced cognitive preoccupation with future use [48, 49], and decreased stress, guilt, and other emotional states associated with use and relapse [4]. Importantly, mindfulness may foster *decentering* from cravings, such that cravings can be observed in a wider field of awareness, with more objectivity and less reactivity [26].

27.3 Mindfulness-Based Interventions

Over the past 40 years, mindfulness-based interventions (MBIs) have been introduced to treat various psychological and behavioral problems.

The introduction of MBIs has radically altered the trajectory of clinical theory, research, and practice. Hayes and Wilson [22] assert that mindfulness-based approaches "are not just a different way of treating traditionally conceptualized problems […] They imply a redefinition of the problem, the solution, and how both should be measured" (p. 165). As an alternative to traditional cognitive-behavioral therapies, which focus on modifying the *content* of thoughts, MBIs aim to help patients to change how they *relate* to their thoughts [11].

Among the most popular MBIs are mindfulness-based stress reduction (MBSR; [24]), mindfulness-based cognitive therapy (MBCT; [39]), dialectical behavior therapy (DBT; Linehan,1993), and acceptance and commitment therapy (ACT; [21]). While MBSR, MBCT, DBT, and ACT have been employed in the treatment of SUDs, they were originally developed for non-SUD conditions. In contrast, mindfulness-based relapse prevention (MBRP; [4]) and mindfulness-oriented recovery enhancement [12] were specifically designed for SUD populations and explicitly target the symptoms and problems associated with SUDs. Descriptions of these approaches are provided below.

27.3.1 Mindfulness-Based Stress Reduction (MBSR)

MBSR is a psychoeducational program that provides rigorous training in mindfulness meditation to improve health and well-being. Originally designed to relieve stress in medical patients, MBSR has since been applied in a variety of settings and for a variety of conditions. The traditional MBSR program is structured as an 8-week course for groups of up to 30 participants who meet weekly for 2.5 hours and a full-day session during the sixth week. Mindfulness meditation is considered to be the main therapeutic technique in MBSR [24]. Patients receive extensive training in four formal mindfulness practices: (1) sitting meditation, which involves awareness of the breath and various contents of consciousness, (2) body scan, which involves sequential focus on sensations in different parts of the body, (3) mindful hatha yoga, which involves mindful awareness of the body in movement, and (4) mindful walking, which involves mindfulness of sensations associated with walking. To foster mindfulness skills, patients are asked to engage in formal mindfulness practices at least 45 minutes per day, 6 days per week. Minimum qualifications for MBSR instructors include a master's degree in a mental health field, attendance at 2-week-long silent meditation retreats, an ongoing daily meditation practice, 3 years of hatha yoga experience, 2 years of experience teaching stress reduction, and attendance at a 5- or 7-day residential MBSR professional training [24].

27.3.2 Mindfulness-Based Cognitive Therapy (MBCT)

MBCT unites elements of MBSR and cognitive-behavioral therapy and is designed to prevent depressive relapse in patients in remission from recurrent major depressive disorder. Like MBSR, MBCT is delivered in a group format over eight weekly sessions and provides training in sitting meditation, body scan, mindful hatha yoga, and mindful walking. A primary goal of MBCT is to teach patients to recognize thoughts associated with depressed mood and to relate to them as passing, transient events in the mind, rather than to identify with them or regard them as accurate reflections of reality [39]. In this way, depression-related cognitions may continue to arise, though they may not exacerbate depressed mood or lead to a depressive relapse [39].

27.3.3 Dialectical Behavioral Therapy (DBT)

DBT was originally designed for suicidal patients and was later developed and refined for patients with borderline personality disorder. The traditional DBT format entails weekly individual therapy and group-based skills training and typically requires a 6- or 12-month commitment from the patient. While mindfulness meditation is

thought to be the main ingredient in MBSR and MBCT, it plays a considerably smaller role in DBT. That is, DBT teaches numerous skills in addition to mindfulness, including emotion regulation, distress tolerance, and interpersonal effectiveness skills, rendering the contribution of mindfulness to be somewhat diluted. Nevertheless, mindfulness is the first set of skills taught and is integrated in the other facets of the treatment [27, 28]. The central dialectic in DBT pertains to the tension between acceptance and change, whereby the patient reaches synthesis by accepting the self while working toward change and personal development. Several modifications can be made to DBT when working with SUD populations [10]. Specifically, DBT clinicians can help patients: (a) identify the antecedents and consequences of drug use; (b) avoid drug cues; (c) improve regulation of urges, cravings, and emotions associated with drug use; and (d) increase engagement in healthy behaviors. Manuals are available to guide the individual therapy [27] and group-based skills training [28] components of the treatment.

27.3.4 Acceptance and Commitment Therapy (ACT)

ACT is a manualized behavioral treatment that has been delivered in both individual and group formats [21]. Derived from a contextual theory of language and cognition known as relational frame theory, ACT employs mindfulness techniques to promote psychological flexibility and value-oriented behavior. ACT stresses the notion that attempts to control or avoid unwanted experiences (e.g., anxiety) are ineffective and counterproductive, in that they actually serve to exacerbate the distress. Thus, clients are encouraged to embrace life fully by increasing awareness and acceptance of the full range of subjective experiences, including unpleasant cognitions, emotions, and sensations [21]. Like DBT, ACT teaches a myriad of skills and emphasizes mindfulness training to a somewhat lesser extent than MBSR and MBCT.

27.3.5 Mindfulness-Based Relapse Prevention (MBRP)

Patterned after MBSR and MBCT, MBRP was developed to specifically reduce risk and severity of SUD relapse. MBRP is typically administered in a group format in eight weekly 2-hour treatment sessions. Participants are introduced to several formal mindfulness practices (e.g., sitting mindfulness of breath) and are encouraged to apply mindfulness when encountering addiction-related triggers in day-to-day life (e.g., practicing "urge surfing" and "SOBER" [stop, observe, breath, expand awareness, and respond mindfully]). The mindfulness practices embedded in MBRP aim to raise awareness of internal (e.g., cognitions, emotions, sensations) and external (e.g., friends, physical environments) cues associated with substance use and to help patients engage in more skillful, healthy behaviors. Clinicians who provide MBRP in clinical trials typically hold at least a master's degree in psychology or related discipline and have experience with cognitive-behavioral therapy and mindfulness meditation [4].

27.3.6 Mindfulness-Oriented Recovery Enhancement (MORE)

Mindfulness-oriented recovery enhancement (MORE) is a manualized, integrative treatment that is delivered in eight to ten 2-hour group sessions. MORE draws on mindfulness training, positive psychology concepts, cognitive-behavioral therapy strategies, and insights from cognitive neuroscience to address an array of factors that underpin addictive behaviors and chronic pain. Psychoeducation, experiential exercises, and at-home mindfulness practice are emphasized. Mindfulness training is thought to serve numerous functions in MORE, including (a) greater awareness of attentional fixation on pain or addiction-related cues, (b) improved ability to shift from affective to sensory processing of pain or craving sensations, (c) increased psychologi-

cal flexibility, (d) enhanced ability to reappraise maladaptive cognitions associated with negative emotions and addictive behaviors, and (e) greater savoring of naturally rewarding experiences (e.g., watching a sunset). Relative to other MBIs, MORE is unique in its focus on reward processing and eudaimonic growth. A step-by-step MORE intervention manual is available [12].

27.4 Effectiveness of Mindfulness-Based Interventions for SUD-Related Issues

A growing body of research has investigated the effectiveness of MBIs in alleviating SUD-related problems. While many studies test MBI's effects on a specific SUD (e.g., opioid use disorder), others enroll a heterogenous sample involving multiple SUDs (e.g., opioid, alcohol, and amphetamine use disorders) and test effects collapsing across SUDs. Below, we review evidence of MBI's effectiveness with heterogenous SUDs and then with the specific SUDs most commonly studied in this area of work: tobacco, alcohol, and opioid use disorders.

27.4.1 Heterogenous Substance Use Disorders

Several recent meta-analyses have documented the effectiveness of MBIs when collapsing across various SUDs. In a meta-analysis of data from 900 participants, Goldberg et al. [18] found that MBIs were superior to active control conditions in addiction-related outcomes (d = 0.27). Similarly, Li et al.'s [26] meta-analysis showed that MBIs have small-to-medium effects in reducing craving (d = 0.63) and substance misuse (d = 0.33) relative to comparison conditions.

Regarding specific interventions, Grant et al. [20] conducted a meta-analysis of nine randomized controlled trials (RCTs) that evaluated MBRP for adult participants diagnosed with SUDs (total of 901 participants). Results suggested that MBRP outperforms comparison conditions on withdrawal/craving symptoms and negative consequences of substance use but not on relapse rates, frequency of use, or treatment dropout. One recent study may help to explain some of these null effects; Roos et al. [38] found that MBRP outperformed comparators among participants with highly severe affective and SUD symptoms but did not outperform comparators among participants with less severe affective and SUD symptoms. It is possible that for patients high in affective and SUD symptom severity, MBRP may help to decouple the link between emotional distress and craving [46], resulting in fewer distress-induced cravings and relapses over time.

Lee et al. [25] performed a meta-analysis of ten RCTs that assessed the impact of ACT on SUDs. Relative to active treatment comparisons (e.g., cognitive-behavioral therapy, pharmacotherapy), ACT produced small-to-medium effects on substance use outcomes at post-treatment (g = 0.29) and follow-up (g = 0.43). Importantly, ACT has demonstrated higher abstinence rates than cognitive-behavioral therapy at 18-month follow-up [19]. Luomam et al. [31] found that an ACT intervention designed to reduce shame associated with substance-related problems was effective in reducing shame and increasing long-term treatment engagement and days of abstinence among adults in a residential SUD treatment center. Results further suggested that the effects of the ACT intervention on long-term treatment engagement were mediated by levels of shame, in that those who became less ashamed about their substance-related problems later exhibited greater treatment engagement.

Regarding other MBIs, DBT has yielded better treatment retention and substance use outcomes than treatment-as-usual (TAU) in a small sample of women with SUDs and borderline personality disorder (N = 27; [30]). There is also evidence that DBT remains effective for SUDs when it is delivered with cultural adaptations; a DBT intervention that incorporated American Indian/Alaska Native cultural and spiritual practices produced a large pre-post effect (d = 1.3) on psychosocial distress among 229 adolescents in a residential SUD treatment center [2]. Garland

et al. [16] recently evaluated the efficacy of MORE with homeless men with SUDs. Participants were randomized to 10 weeks of group treatment with MORE (n = 64), cognitive-behavioral therapy (n = 64), or TAU (n = 52). MORE was found to outperform cognitive-behavioral therapy on substance craving, posttraumatic stress, and negative affect and outperform TAU on posttraumatic stress and positive affect. Additionally, MORE was shown to have indirect effects on craving and posttraumatic stress via mindfulness skills, implying that an improvement in mindfulness skills may be at least partly responsible for some of MORE's beneficial effects [16].

Mindfulness techniques have also been incorporated into substance recovery therapeutic communities, which are highly structured groups that use social learning to promote changes in self-image, worldview, and addiction-related behaviors [9]. Mindfulness-based therapeutic communities have demonstrated significant reductions in salivary cortisol in a pre-post study with 21 participants receiving inpatient treatment for SUDs [33] and significantly greater reductions in self-reported muscle tension and emotional irritability relative to TAU at 3-month follow-up in a large quasi-experimental study (N = 459; [34]).

27.4.2 Tobacco Use Disorder

A recent meta-analysis [32] synthesized data from ten RCTs evaluating MBIs for smoking cessation. Results indicated that MBIs did not significantly differ from comparators in their effects on abstinence or cigarettes smoked per day. Notably, of the ten studies included in Maglione et al.'s [32] meta-analysis, only one [43] was deemed to be of good methodological quality. Vidrinee et al. [43] compared the efficacy of an MBCT intervention adapted for smoking cessation, group cognitive-behavioral therapy, and brief individual counseling in an RCT with 412 adults who smoked an average of at least five cigarettes per day over the prior year. Biochemically verified abstinence rates did not significantly differ across intervention conditions at 4- and 26-week follow-ups. However, among participants who were smoking at the end of the treatment, MBCT participants were more likely to be abstinent at the follow-ups relative to participants in the other conditions. This finding implies that MBCT adapted for smoking cessation may be more effective than cognitive-behavioral therapy and brief individual counseling in promoting recovery from smoking lapses.

In the aforementioned Lee et al. [25] meta-analysis, subgroup analysis revealed that ACT was superior to active treatment comparisons in facilitating smoking cessation (g = 0.42; total of five studies). Importantly, there is evidence that the smoking cessation effects associated with bupropion can be augmented with the addition of an ACT-style behavioral intervention [17]. Also of note, ACT has produced promising smoking cessation rates when delivered by telephone [5], website [7], and smartphone application [6].

27.4.3 Alcohol Use Disorder

A burgeoning scientific literature has focused on the application of MBIs for alcohol misuse. Some studies have tested MBIs with individuals in remission from alcohol misuse, while others have been conducted with individuals with active, ongoing alcohol misuse. With regard to the latter, a recent pilot RCT [45] evaluated an 8-week Internet-delivered DBT skills training intervention for suicidal individuals who engage in heavy episodic drinking to regulate emotions. Participants who received the DBT intervention showed faster reductions in alcohol use relative to participants in the waitlist control [45]. Another pilot RCT [35] evaluated a brief MBI with 76 undergraduates who regularly binge drink. The mindfulness group reported significantly fewer binge episodes and alcohol-related consequences and higher dispositional mindfulness and self-efficacy than did a no-intervention control group [35].

There is also some evidence that MBIs can help persons in remission to avoid alcohol relapse. Preliminary evidence has been obtained

from pre-post designs pilot testing MBRP adapted for the prevention of alcohol relapse (MBRP-A; [50]) and an MBI incorporating elements of MBSR, MBCT, MBRP, and ACT [44]. Building on the pilot pre-post study, Zgierska et al. [48] recently assessed the efficacy of MBRP-A in an RCT with 123 adults in early recovery from AUD. Participants received either the 8-week, group-based MBRP-A intervention plus TAU or TAU alone. Both groups exhibited improvements in drinking and related consequences over the 26-week study period, though no significant between-group differences were detected. Notably, within the MBRP-A plus TAU group, session attendance and at-home mindfulness practice time were correlated with drinking outcomes, suggesting that greater adherence to mindfulness training may be associated with less alcohol misuse [48, 49]. In another trial using RCT methodology, Garland et al. [13] compared ten sessions of MORE to ten sessions of support group with 53 low-income adults with AUD who had resided in a therapeutic community for at least 18 months. MORE was found to reduce stress and alcohol thought suppression to a significantly greater degree than did the support group. Additionally, MORE appeared to decrease alcohol-related attentional bias and increase physiological recovery from alcohol cues [13]. Thekiso et al. [42] examined whether ACT plus TAU improved outcomes relative to TAU with inpatients with AUD and a comorbid mood disorder, who at baseline were abstinent from alcohol for an average of about 50 days. Although not randomized, the two groups were matched according to diagnosis, age, and gender. The ACT intervention was an intensive (i.e., five sessions/week over 4 weeks) manualized group-based treatment tailored to problems associated with AUD and mood disorders (e.g., targeting the experiential avoidance that underpins these conditions). Compared to TAU, ACT plus TAU yielded significantly better drinking, craving, anxiety, and depression outcomes at 3-month follow-up and significantly better drinking, anxiety, and depression outcomes at 6-month follow-up [42].

27.4.4 Opioid Use Disorder

Although the effects of MBIs on opioid misuse and opioid use disorder have not been meta-analyzed to date, a few studies have investigated this topic. One RCT [29] randomized 23 opioid-dependent women with borderline personality disorder to 12 months of either DBT or nondirective therapy plus a 12-step support group. Results of urinalyses showed that opiate reductions were better maintained in the DBT group than the support group [29]. Stotts et al. [40] conducted a Stage I pilot study examining ACT as an aid in opioid detoxification. In this trial, 56 methadone-treated opioid-dependent adults were randomly assigned to 24 individual therapy sessions of either ACT or education-based drug counseling. Fear of withdrawal during detoxication was found to decrease significantly in the ACT group only. About 37% of ACT participants met criteria for successful detoxification (i.e., opioid negative urine drug screen and discontinuation of methadone treatment) compared to 19% of drug counseling participants, although this difference did not reach statistical significance ($p = 0.17$), which could be attributable to the study's small sample size [40]. Hayes et al. [23] randomized 138 opiate-addicted adults to 16 weeks of either (1) methadone maintenance alone, (2) ACT plus methadone maintenance, or (3) 12-step support program plus methadone maintenance. The ACT plus methadone maintenance group had significantly higher percentages of opiate (61%) and total drug (50%) abstinence at a 6-month follow-up urinalysis assessment relative to the methadone-maintenance-only group (28% for opiate and 12% for total drug abstinence). The ACT plus methadone maintenance group did not significantly differ from the 12-step support program plus methadone maintenance group on any of the drug outcomes [23].

Two studies [14, 47] have investigated the effects of MBIs on opioid use with non-cancer chronic pain patients, who have been shown to be at elevated risk for developing opioid use disorder [3]. Zgierska et al. [47] conducted a 26-week pilot RCT with adults with chronic low back pain who had been treated with daily opioid therapy

(at least 30 mg/day of morphine-equivalent dose) for at least 3 months. Participants were randomized to either continued opioid therapy (n = 14) or continued opioid therapy with a group-based MBI (n = 21). The MBI entailed eight weekly 2-hour treatment sessions and included MBRP techniques adapted for pain management (e.g., a "pain wave surfing" exercise, adapted from MBRP's "urge surfing"). On average, opiate use declined by about 7 mg/day (morphine equivalent dose) from baseline to post-MBI and about 10 mg/day from baseline to 18 weeks post-MBI (compared to average decreases of 1.4 and 0.2 mg/day in the control condition). However, given relatively low power due to small sample size, the conditions did not differ significantly in opiate use reduction [47]. A larger study [14, 15] randomized 115 opioid-treated chronic pain patients (72% met criteria for opioid use disorder) to 8 weeks of either MORE or a support group. Compared with support group participants, MORE participants reported significantly greater reductions in desire for opioids (d = 0.50) and were significantly less likely to meet criteria for opioid use disorder at post-treatment, although these between-group effects were not sustained at 3-month follow-up [14, 15]. Subsequent analyses with laboratory data [14] revealed that, relative to the support group, MORE led to significantly greater pre-post treatment reductions in heart rate response and self-reported craving to opioid cues, implicating reduced opioid cue reactivity as a potential mechanism underlying MORE's effects.

27.5 Conclusion

SUDs are prevalent and have serious personal and societal consequences. Accordingly, it is imperative that we identify effective treatments for SUDs through rigorous controlled research. At present, there is substantial meta-analytic evidence that heterogenous SUD populations benefit from MBIs generally [18, 26] and MBRP [20] and ACT [25] specifically. Between-group effects in heterogenous SUD populations typically fall in the small-to-medium range, suggesting modest yet reliable addiction-related improvements in MBIs relative to comparison conditions.

MBIs have been less frequently studied in the context of specific SUDs. Extant research does not convincingly show that MBIs are superior to comparators in the treatment of tobacco use disorder/smoking cessation [32]. MBIs have demonstrated some promising results in the treatment of alcohol use disorder [13, 42] and opioid use disorder [14, 15, 23], yet these bodies of evidence are still limited and inconsistent, and as such, inconclusive.

More rigorous scrutiny, using powerful, well-designed clinical trials, is needed to answer questions about the effectiveness and "active ingredients" of MBIs in SUD populations. In particular, the effects of MBIs on cannabis, benzodiazepine, and amphetamine use disorders are virtually unknown and deserving of future empirical attention. Additionally, because few studies have found maintenance of addiction-related effects over time, long-term follow-ups are needed and recommended for future research. Other study limitations include small sample size, reliance on self-reported drug use, and utilization of pre-post designs and inactive/waitlist controls, which do not adequately control for extraneous factors. Neuroimaging of the correlates of mindfulness-induced changes in addictive behaviors offers an important avenue for future research. We would also recommend the following: (1) additional standardization of treatment manuals to facilitate data pooling and replication, (2) measurement of the time participants spend in mindfulness practice to assess dose-response relationships, and (3) analysis of biomarkers of substance use, which may reveal different patterns of use than are suggested by self-report.

This review focused on a treatment for SUDs that is relatively safe and inexpensive. Past research has produced some positive results suggesting that MBIs may hold some promise in the treatment of SUDs. While more rigorous, large-scale studies are needed before unequivocally recommending MBI as a first-line treatment for specific SUDs, the clinical implications of employing a form of mental training to attenuate

substance misuse is of unique practicality to clinicians and attractiveness to patients seeking safe substance abuse treatment.

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A Trauma-Informed Approach to Enhancing Addiction Treatment

28

Vivian B. Brown

Contents

Abstract

Research during the past two decades has shown that a large percentage of clients in addiction treatment have experienced multiple traumas from childhood into adulthood. Trauma is the expectation, not the exception. This chapter describes two major studies and their impact on the movement toward trauma-informed care: the Adverse Childhood Experiences (ACE) study and the Women with Co-occurring Disorders and Violence Study. In addition to the high prevalence of trauma experienced by our client population, some of the procedures/practices in addiction treatment can be triggering or re-traumatizing. Also, staff may experience secondary traumatization or re-traumatization, particularly if they have previously experienced trauma themselves. By addressing the issue of trauma, which can lead clients to leave treatment and/or relapse, a trauma-informed program can improve engagement and retention and lead to successful outcomes. This chapter also explains the difference between trauma-specific interventions and trauma-informed care; describes the core values of a trauma-informed program; and details the components

V. B. Brown (✉)
Prototypes: Centers for Innovation in Health, Mental Health, and Substance Use Disorders, Pittsboro, NC, USA

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of trauma-informed care, including screening for trauma, multileveled training for all staff, stage-oriented treatment, trauma-sensitive supervision, and implementation of staff care/self-care. In a trauma-informed practice, staff members understand the prevalence of trauma in their clients and its impact, incorporate this knowledge into service delivery, and avoid re-traumatizing those who are seeking our help.

Keywords

Trauma · Trauma-informed care · Integrated treatment · Safety · Addiction treatment

This chapter is intended to support the work of addiction treatment providers in becoming trauma informed. Trauma-informed practice is not an additional program; rather, it is a shift in program culture and approach to service delivery. By addressing the trauma(s) that can lead clients to leave treatment and/or relapse, trauma-informed care can improve engagement and retention and lead to more successful outcomes.

Research during the past two decades has demonstrated that a large percentage of clients in drug treatment have experienced trauma at some point(s) in their lives. As defined by the Substance Abuse and Mental Health Services Administration, trauma is "an event, series of events, or set of circumstances that is experienced by an individual as physically or emotionally harmful or life threatening and that has lasting adverse effects on the individual's functioning and mental, physical, social, emotional, or spiritual well-being" [37, p. 9]. Estimates of lifetime exposure to traumatic events in the general population in the USA range from 60% to 70% [20]. In substance abuse populations, estimates range from 60% to 90% [15, 22, 33]. Overall, 20–30% of those exposed to trauma will develop post-traumatic stress disorder (PTSD). The more one is exposed to trauma, in terms of severity and duration, the higher the likelihood of a PTSD diagnosis (e.g., veterans' exposure to heavy levels of combat and trauma). However, millions of individuals who are experiencing PTSD and other sequelae of trauma go unrecognized and untreated.

This chapter begins with a focus upon two major studies from the USA and their impact on the movement toward implementation of trauma-informed care. While trauma-informed practices were developed in the USA, they are now receiving global attention, particularly in the following countries: Canada, the United Kingdom, Australia, New Zealand, and Scotland [1, 19, 21, 28, 38].

28.1 ACE Study

The most widely disseminated study of the relationship between stressful and traumatic events in childhood and long-term health effects is the Adverse Childhood Experiences (ACE) study [13], a collaborative effort between Kaiser Permanente (Felitti) in San Diego and the Centers for Disease Control and Prevention (CDC) (Anda). The study was conducted from 1995 to 1997 among 17,337 Kaiser Health Plan members. The purpose of the study was to determine the prevalence among this group of ten traumatic childhood (before the age of 18) events and the long-term effects of these experiences. The average age of the study participants was 52. The sample was almost evenly divided among men and women. Approximately 80% were White (Hispanic and non-Hispanic), 10% were Black, and 10% were Asian.

The prevalence among the group for the ten ACEs was as follows:

Psychological abuse (by parent)	11%
Physical abuse (by parent)	28%
Sexual abuse (by anyone)	22% (28% for women; 16% for men)
Emotional neglect	15%
Physical neglect	10%
Alcoholism or drug use in home	27%
Divorce or loss of a biological parent	23%
Depression or mental illness in family	17%
Mother treated violently	13%
Household member in prison	6%

An ACE score for each individual study participant was calculated by adding the number of categories of adverse events reported. Women were 50% more likely than men to have a score of 5 or higher. It should be noted that multiple incidents within a category are not scored beyond 1. This has the effect of definitely understating the findings. In addition, experiences such as encountering explicit racism and community violence were not included.

Felitti and Anda then looked at the correlation between these scores and a variety of health and behavioral health issues and risk behaviors in adulthood. In the area of addiction, the strongest relationship seen was between ACE scores and the injection of street drugs. At an ACE score of 6, there was a 46-fold increased likelihood of later becoming an injection drug user, as compared to an ACE Score of 0. The relationships between ACE scores and depression, suicidality, and chronic anxiety were also studied and showed similar results. The findings of the ACE study made it clear that traumatic events experienced in childhood have a cumulative effect on emotional state and health status, including liver disease, chronic obstructive pulmonary disease (COPD), coronary artery disease, and autoimmune disease. Later, the original ACE questions were extended to add items relevant for children living in Philadelphia, a racially diverse population. The added items were on racial discrimination and exposure to community violence. These ACE scores were higher than in the Kaiser Permanente population [40].

28.2 Women with Co-occurring Disorders and Violence Study (WCDVS)

The Women with Co-occurring Disorders and Violence Study (WCDVS), a five-year study funded by the Substance Abuse and Mental Health Services Administration (SAMHSA), was designed to look at the best practices for women who were diagnosed with substance abuse and mental illness who had also experienced violence or trauma histories. The sample, drawn from nine sites around the USA, was 2729 women, all of whom had had two or more previous treatment episodes. The women were provided either integrated services (integrating mental health, substance use, and trauma) or, in the comparison sites, treatment-as-usual (TAU).

WCDVS was one of the first studies to implement and evaluate the effectiveness of trauma-specific interventions and trauma-informed care in addressing the needs of consumer/survivors. A cross-site methodology evaluated the effectiveness of the trauma integrated interventions. Trauma integrated interventions were defined as the simultaneous provision of substance abuse, mental health, and trauma services to women in the intervention condition. Outcome measures were levels of PTSD/trauma, substance use, and mental health symptoms. Service utilization and consumer satisfaction were also measured.

The lessons learned included: (1) integrated care showed significant results in reducing substance use by 6 months and reduction in mental health and post-traumatic symptoms by 12 months; (2) consumer/peer staff played important roles in providing care and in participating in research design; (3) trauma-specific interventions showed significant results in outcomes; and (4) trauma-informed practice led to increased engagement and increased retention [3].

Morrissey and colleagues [26] also studied the characteristics of all participants to identify person-level characteristics that moderated outcomes and found that women with more severe baseline measures on behavioral health tended to report better outcomes at 6 months. At 12 months, mental health symptoms and PTSD severity showed statistically significant reductions in the intervention group. Further analyses [11] confirmed that at 12 months, treatment effects were largest for women with the most severe substance abuse and PTSD presentation.

Some specific WCDVS site data also adds to the accumulating knowledge about trauma integration into service programs. In the PROTOTYPES site [14], the rate of retention in treatment was significantly higher in the trauma-informed integrated treatment group than in the comparison group. Dropout was higher in the

comparison condition than in the intervention condition throughout the first 12 weeks of treatment. In addition, the PROTOTYPES site added a measure of coping skills. In the intervention group, women's use of coping skills increased from baseline to 12 months, but in the comparison group, women's use of these skills decreased slightly from baseline to 12 months. Three-way repeated measures ANOVA results suggested that improvement on coping skills mediated improvements in emotional distress and substance use outcomes.

28.3 Why Attend to Trauma in Substance Abuse Treatment System

The substance abuse treatment system deals with high prevalence of clients with trauma. Many individuals entering the substance use disorders treatment system have been survivors of trauma from childhood through adulthood; that is, many have experienced childhood traumatic events but also have experienced additional trauma as they participated in the drug culture. These include women forced into sex work, who experienced trauma as a result of that; those who have been in jail and/or prison and experienced significant traumatic events in those settings; those who have witnessed the death of "running buddies" from overdoses, bad drug deals, hepatitis C, or HIV; and those who themselves have been diagnosed with HIV. Many have also experienced community violence. Trauma is the expectation, not the exception, for our clients.

Kessler et al. [20] showed, using the National Comorbidity Survey (NCS) data, that PTSD was significantly associated with a diagnosis of drug abuse or dependence. In addition, they found that PTSD was more often the primary or first diagnosis. The NCS generated a lifetime PTSD prevalence estimate of 5% among men and 10.4% among women and yielded far higher estimates of lifetime prevalence of trauma exposure and of the risk of developing PTSD. Lifetime prevalence of trauma exposure was estimated to be 60.7% among men and 51.2% among women. The majority of those who reported any trauma experience reported multiple traumas. Combat was most frequently associated with PTSD in men; sexual assault was most frequently associated with PTSD in women.

More recent data show that 90% of drug users report having experienced at least one traumatic event and, often, many more than one [32]. In addition, post-trauma exposure further increases the risk for re-exposure. Peirce and colleagues [34] found that 27% of participants (registrants of Baltimore Needle Exchange Program) were re-exposed to a traumatic event each month. Women injecting drug users were more than twice as likely to report traumatic event re-exposure as were men, placing them at higher risk of developing PTSD. In a subsequence study [33] that looked at clients enrolled in methadone maintenance treatment, results showed that 97% had at least one lifetime traumatic event, with a total average of 18 traumatic events. Women were more likely than men to report histories of sexual assault at any age and interpersonal violence, as well as other threats (e.g., sexual harassment and stalking). Men were more likely than women to endorse histories of physical assault and witnessing physical assault. Traumatic re-exposure was common, with an average of 18% of participants reporting a new event each month during the study. Women were more likely than men to meet criteria for PTSD at study entry (31% vs 13%). An increase of 10% in PTSD symptom severity was associated with a 36% increased risk of treatment interruption. Interventions to reduce re-exposure or at least to ameliorate the negative effects of re-exposure on treatment would be beneficial.

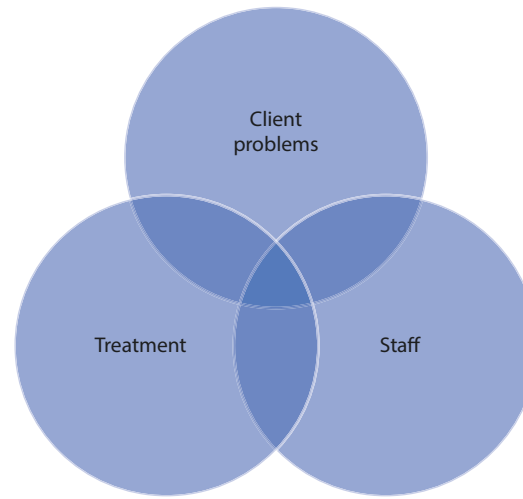
With regard to opioids and trauma, the lifetime history of PTSD was 41% among individuals with opioid use disorder (OUD) seeking treatment [25]. In 2017, 70,237 Americans died from an opioid-related overdose [7]. Medication-assisted treatment (MAT), including methadone, buprenorphine, and naltrexone, shows improved retention and decreased relapse rates for the treatment of opioid use disorder. A total of 20–50% of OUD clients also meet the criteria for a PTSD diagnosis [12]. Despite successful outcomes doc-

umented in research studies, MAT is underutilized by many addiction treatment programs and drug courts.

Some substance abuse treatment procedures are triggering. Intense, aggressive confrontation in old-style therapeutic communities can trigger negative responses (e.g., depression, a sense of hopelessness, and re-traumatization) in clients with trauma histories, and clients will leave treatment early and relapse. Many other routine treatment procedures can be triggers as well, such as urine testing, night check-ins by counselors in residential treatment, co-ed programming, and reporting to courts and/or child welfare. With regard to urine testing, the need to have someone observing the testing can be quite "triggering" for survivors. It is important to explain that we are mandated to do observed testing and that it may feel uncomfortable for the client. We need to ask, "What can I do to make you feel more comfortable (e.g., step back, but still be able to observe)?" Also, there may be messages implicit in the manner of communication between staff member and client that can be triggering for a trauma survivor if s/he experienced boundary violation, betrayal, and/or powerlessness. Such a client may experience "power over" behavior by staff as disrespectful, coercive, and threatening.

Coping deficits associated with substance use disorder-PTSD lead to poorer treatment outcomes. Coping deficits have been associated with substance use disorder (SUD-PTSD in a number of studies. Ouimette et al. [30] found that problems from substance use at a 1-year follow-up were partially explained by SUD-PTSD patients' greater use of emotional discharge coping (e.g., risk-taking, yelling) and decreased expectations of benefits from abstinence. In a subsequent study [31], emotional discharge and cognitive avoidance coping (e.g., trying to forget about the trauma) both partially explained poorer 2-year substance use outcomes. In a third study, Brown et al. [5] found that individuals with unremitted PTSD had poorer substance use outcomes and poorer coping than those whose PTSD symptoms had remitted or those who had never been diagnosed with PTSD. The study also provided support for the critical role of coping in PTSD-SUD. The authors recommend that clinicians focus on helping these patients decrease their maladaptive coping strategies and learn more adaptive coping approaches.

Higher treatment burden leads to poor retention. I have discussed [3] a multileveled picture of the level of burden in clients and staff (see diagram), including the burden on the client of a number of problems (e.g., substance use, mental illness, trauma, cognitive impairments, physical problems, domestic violence, and poverty); the burdens of treatment (e.g., waiting times for appointments, triggering by procedures such as urine testing, medications, language/literacy issues, and turnover of staff); and the burdens on staff (e.g., time pressures, electronic health records, limits on amounts of service, new priorities, staff turnover, funding cutbacks, client emergencies, and angry/hostile clients). Therefore, it is important for providers to decrease all three types of burdens; increase the use of trauma-informed practices; give additional supports to clients to help them follow through on treatment plans; understand clients' angry, fearful, disassociated responses and respond to them in a caring, supportive way; and take care of ourselves as providers.



Levels of burden

Higher levels of burden, including those resulting from experiences of trauma, are related to lower levels of retention in treatment pro-

grams. For clients who have experienced trauma, it takes time to see reductions in the anxiety, fear, and mistrust that the clients bring with them into treatment. It also takes time for these clients to feel a positive connection to providers and to other clients in the program. Although the treatment program offers a safe and supportive environment, clients with trauma histories may feel overwhelmed by the need to participate with others, to behave in a structured way, and to comply with program rules and procedures. If clients have been cognitively impaired by domestic violence (mostly women), they may not be able to understand program rules or follow them. A mother who has experienced domestic violence and who has to come into residential treatment without her children will be fearful of what is happening to the children when she is not there protecting them; this can interfere with the woman's participation in treatment and recovery. This is why residential treatment programs for mothers and children are important for both.

Substance abuse treatment providers are at risk of secondary traumatization or re-traumatization and consequent burnout. Staff may themselves be trauma survivors and, therefore, acutely sensitive to trauma issues of clients. This can lead to a sensitivity and empathic response to trauma survivors but also can lead to secondary traumatization, especially if the staff member has not dealt with his/her trauma experiences (see below).

28.4 Trauma-Specific Interventions

Trauma-informed practices are different than trauma-specific interventions. Trauma-specific interventions help the client deal specifically with their traumatic experiences and teach coping skills to facilitate healing. As part of a trauma-informed organization/system, trauma-specific interventions need to be available, either on-site or by referral. These interventions directly address the effects of trauma on the client's life and facilitate trauma recovery by helping the client understand the connections between the trauma and subsequent feelings and behaviors and teaching coping skills to help the client gain a sense of control, build more positive and safe relationships, and adopt safer behaviors. Trauma-specific interventions include both trauma-specific individual therapy and group interventions. For most treatment programs, groups are part of what they already do, so adding a new group should not be difficult.

Trauma-specific group interventions include two of the key components/principles of trauma recovery: empowerment and reconnection with others. The groups provide participants with opportunities to break down the isolating barrier of shame and to rebuild trust in others. The most frequently used trauma-specific interventions for adults are Stage 1 groups: *Seeking Safety* [27], *Trauma Recovery and Empowerment (TREM)* [16], *Beyond Trauma* [8, 10], and *Helping Men Recover* [9]. It is recommended that these groups have two co-facilitators, one of whom can be a trauma survivor or peer. This ensures that if a participant needs to leave the group because of becoming triggered, one facilitator can go with him/her. The groups also provide the learning of coping skills such as "grounding," which helps survivors calm themselves down when they are triggered by trauma memories. The secrecy and shame associated with a history of abuse may be more alleviated in a group setting than in individual treatment.

28.5 Trauma-Informed Practice

Trauma-informed practices are approaches that incorporate a thorough understanding of the prevalence and impact of trauma and are designed to avoid re-traumatizing those who seek care/help. SAMHSA has defined a trauma-informed approach as: "A program, organization, or system that is trauma-informed realizes the widespread impact of trauma and understands potential paths for recovery; recognizes the signs and symptoms of trauma in clients, families, staff, and others involved with the system; and responds by fully integrating knowledge about trauma into policies, procedures, practices, and seeks to actively resist re-traumatization" ([37], p. 9).

Trauma-informed practice expands the range of trauma sequelae; it goes beyond a focus only upon PTSD because we want to be able to prevent PTSD in patients who have already experienced trauma. It recognizes the strengths that survivors have used in dealing with interpersonal violence, i.e., that the specific symptoms such as substance abuse and/or hostility have helped the victim survive and manage the emotional and physical distress. The goal of this change in perspective is to move the fundamental question that we pose from "What's wrong with you?" to "What's happened to you?" and "How can we help?"

Harris and Fallot [17] defined the five core values or principles of a trauma-informed approach, viz., safety, trustworthiness, collaboration, empowerment, and choice.

- *Safety*. Patients/clients and staff feel physically, psychologically, and culturally safe. This means that the physical environment is safe and nurturing, that interactions between staff and client promote a sense of safety and respect, and that all procedures feel culturally safe to the patient. It is also important to be aware of the importance of language. We need to use terms that are not stigmatizing ("addicts," "borderlines"). Safe relationships are consistent, predictable, respectful, nonviolent, non-shaming, and non-blaming.
- *Trustworthiness*. Procedures are conducted with transparency; each step of the organization's processes from intake through treatment is explained in appropriate language, and patients are given enough time and respect to ask questions and receive appropriate answers; and confidentiality is explained and honored.
- *Collaboration*. There is sharing of power in decision-making between staff and clients, as well as collaboration between all providers in the system and the broader community network.
- *Empowerment*. The patient's strengths are recognized and validated, and the learning of new coping skills is provided in a respectful way. In addition, we normalize responses typically defined as "symptoms"; instead, they are seen as "adaptations." Survivors are not seen as manipulative, attention-seeking, or destructive, but as trying, instead, to cope using any means available to them. Recovery from trauma and addiction involves developing skills not only for managing intense feelings and situations but also for living a life that minimizes exposure to trauma triggers.
- *Choice*. Find ways to give clients choices. This is not "enabling" the client, as many staff in substance abuse treatment fear. Examples of choices are which groups s/he would like to start with (after all the groups available have been described) and how the client would prefer to be contacted (phone, email, or through a regular phone-in time set up for the client). Allowing the client to decide how contact with him/her will be made can be quite important for ensuring the safety of a client experiencing domestic violence. Another example is to have the client write down her/his treatment goals, while a staff member writes a separate set of goals s/he might suggest; then client and staff member work on developing the treatment plan together.

In addition to these core values, there are additional principles that are important for a trauma-informed practice. These include sensitivity to cultural issues and the inclusion of peer support.

Cultural Issues. As we have become more aware of the importance of taking culture into account as we provide care to the diverse populations in our systems, our ideas about how best to do so have moved through a continuum from cultural awareness to cultural competence to cultural humility to cultural safety. Cultural competency involves more than gaining factual knowledge about the different populations we serve; it also includes examining and changing our attitudes toward our clients. Cultural humility requires the provider to engage in continual self-reflection and to acknowledge "privilege" if that is relevant [39]. The provider must be able to overcome the natural tendency to view one's own beliefs and values as superior and, instead, be open to the beliefs and values of the client.

Cultural safety offers us one more step to enhance our understanding of the way culture affects our practices. The concept of cultural safety was first articulated in 1988 and emerged from the experiences of the indigenous people of New Zealand. The Nursing Council of New Zealand [29] furthered developed the concept: "Unsafe cultural practice comprises any action which diminishes, demeans or disempowers the cultural identity and well being of an individual." One of the key principles set forth by the Nursing Council is the need to recognize that both contemporary and historical inequities, including those resulting from colonization, affect healthcare interactions and can act as barriers to effective care. This principle, while developed for nursing, is applicable to addiction services.

This concept really helps us to understand safety through both a trauma lens and a cultural lens. There is no "post" or "past" traumatic stress when you feel your body is in danger because of your race, ethnicity, religion, gender, sexual orientation, etc. American Indian/First Nations peoples and African Americans may not feel safe when their lives can be taken by those who have been held up as their protectors. I believe that cultural safety is a key concept in understanding that although we are trying to help our patients through our addiction services, the patients may not experience our help or their safety. An essential feature of cultural safety is that the patient/client defines whether or not the practice, the provider, and the environment are culturally safe. What cultural safety asks us to do is to ask the client, "Do you feel safe here with me and in this place?"

A type of trauma that is often overlooked is historical trauma. It has been described as multigenerational trauma experienced by a specific cultural group over multiple generations. Among the many groups that have been identified as experiencing historical trauma are American Indians/First Nations people, African Americans, Jewish people, and Japanese-Americans. These populations have been traumatized by expulsion from their homelands, loss of economic status and self-sufficiency, removal of children and separations of families, loss of social ties, and torture and murder. They have similarly experienced trauma; forced relocation(s) and migrations; stolen property (including land and homes); dehumanization; forced separations from family; mass incarceration, mass murder, and lynching; torture; medical experimentation; slavery; and internment. And while there can be the sense of a "community of suffering" among these groups, there is also a distrust of others outside the groups—particularly those from historically oppressive groups. This fear and mistrust can make it difficult to trust addiction treatment providers who are of a different group.

Peer Support Services. The concept of peers helping peers is not new for addiction treatment. In 1935, Alcoholics Anonymous, the oldest of the peer programs, came into being. It was viewed as a response to the limited effectiveness of traditional services and was intended to draw on the power on individuals to offer mutual support, solace, and learning. The achievements of self-help groups such as Alcoholics Anonymous were based on the principle that people who share a disease or disability have "something to offer each other that professionals can't provide."

Reiff and Reissman [35] described the use of "indigenous nonprofessionals" as "bridgemen," who bridged the social distance between those who need services (patients) and those providing services. They described the worker as a "peer of the client (who) shares a common background, language, ethnic origin, style, and group of interests" [35]. From the 1960s through the 1980s, persons with lived experience of drugs/alcohol began many of the addiction treatment programs. In the late 1980s and 1990s, during the early years of the AIDS epidemic, peers were hired to reach injecting drug users and their sexual partners to reduce risk-taking associated with needle-using and sexual behaviors [4]. Peers serve as role models, counselors, outreach workers, recovery coaches, advocates, case managers, trainers, co-facilitators, research assistants, and directors of addiction treatment programs. They have also come to play an important role in the delivery of services within Family Drug Treatment Courts. If a client is about to embark on a potentially stressful event (e.g., going to

court or going to a medical appointment), sending a peer recovery specialist with her/him will help reduce stress.

28.6 What Does a Trauma-Informed Program Look like?

One of the consistent questions that agencies ask when they participate in trauma trainings is: "What does a trauma-informed program look like?" Because of the high prevalence of trauma within the populations entering their systems, organizations that work with children, youth, adults, and families should expect that the clients they serve have experienced some form of traumatic event.

In order to move toward trauma-informed practice in addiction treatment, there are a number of recommended organizational culture shifts and practice principles:

1. Trauma/PTSD and addiction are co-occurring disorders, and each condition is considered primary. Recovery involves moving through stages of change and phases of recovery for each condition (stabilization, motivational enhancement, active treatment, relapse prevention, recovery, continuing care) through an integrated program.
2. Implement a walk-through of your program. A trauma assessment and walk-through protocol [6] was developed and refined in the WCDVS study and a nationwide learning collaborative called the Network for the Improvement of Addiction Treatment (NIATx). The three authors of the protocol all participated in the WCDVS, and the first author was one of the first waves of NIATx grantees. Walk-throughs: enable organizations to better understand the experience of care from the clients' point of view, assist staff members to understand how they may be inadvertently re-enacting trauma dynamics, can uncover inconsistencies and limitations in systems, and generate ideas for improving organizational processes. The walk-through is a mutual data-gathering strategy that does not resemble an "audit." Trainings and technical assistance grow out of the assessment and the action plan generated by the walk-through. The assessment allows the team (managers, staff, and senior clients) to walk through the agency procedures from the first call to the agency, to the intake process, and all the way through treatment.
3. Institute universal screening for trauma (see below).
4. The risk of re-traumatization should be minimized through:
   (a) Creating a safe treatment environment (physically and psychologically). This involves ensuring that the community surrounding the treatment program is safe (e.g., there is good lighting and adequate security). It also involves the treatment program: having policies about responding to acts of violence from clients; reducing "power over" behaviors by staff; restricting visitors who might be domestic violence perpetrators or otherwise "unsafe." In addition, the program environment needs to be calming, welcoming, and culturally sensitive.
   (b) Teaching grounding strategies and promoting resilience. A group session that teaches grounding skills is relevant to both substance use and trauma. Learning to regulate intense emotions can be empowering and promotes stability.
   (c) Implementing multileveled staff training. Workforce development, including training on trauma and trauma-informed practice, trauma-informed supervision, and strategies to address secondary trauma in staff and to promote self-care, is needed to begin transformation. Training should include all staff, including support staff (e.g., receptionists, cooks, maintenance, security guards, etc.). Training should be multileveled, so that everyone receives basic trauma training, clinical staff receive additional training including trauma-specific interventions, and supervisors receive training in responsive supervision.

(d) Considering stage-oriented treatment. Residential drug treatment programs are defined as stage-oriented and most use definitions of phases. In 1992, Herman proposed a three-stage model for trauma treatments [18]. The first stage is "safety", the second is "remembrance and mourning", and the third is "reconnection". A number of the trauma-specific group curricula that have been developed focus on Stage 1; these include *Seeking Safety*, *TREM*, and *Beyond Trauma*. In this first stage, the client is supported and helped to learn the connection between trauma and addiction, as well as to learn new coping strategies and methods of symptom containment. It is recommended that one of the Stage 1 trauma-specific group curricula be started within Phase 1. If a client begins to talk about trauma memories in detail, the group facilitator should state that clients may want to talk about their memories, but that "It isn't safe for you right now." It is important that clients have a period of stabilization (including medications) and that the interventions early in treatment focus upon psychoeducation and learning to regulate emotions and impulses. In the later stages, treatment is individualized, based on the patient's strengths, vulnerabilities, and cultural factors, and focuses more on the narrative of the survivor's trauma story.

5. Provide trauma-specific interventions. These include group interventions, such as *Seeking Safety*, *TREM*, *Beyond Trauma*, and *Helping Men Recover*, as well as individual interventions, such as *CBT* and *EMDR*) [23, 36].
6. Provide trauma-informed supervision for all direct treatment staff. Supervision can provide a physically and emotionally safe place for staff to examine their work with an experienced, supportive mentor. Ongoing supervision in trauma-informed care is recognized as a major protective factor in buffering against vicarious trauma.
7. Implement self-care strategies for staff to reduce potential for secondary trauma or burnout. An important part of being a trauma-informed provider organization is an awareness that providers may also have experienced trauma. Even if they have not, working with people who have survived traumatic experiences and listening to their stories can take an emotional toll and lead to secondary trauma. Secondary symptoms may include an increase in arousal and/or avoidance reactions, re-experiencing personal trauma, sleeplessness, fearfulness, and anger. Issues of self-care need to be included in the training of staff members. (See below.)

28.7 Screening

The patient/client pathway to services is extremely important in trauma-informed practice. By improving access to services and reducing waiting times and cumbersome procedures, we enhance the patient/client experience; by providing trauma-informed care, we improve the chances that s/he will follow through with treatment, feel safe and heard, and show improved outcomes.

Identification of a trauma history is critical if a provider/program is to be able to effectively respond to an individual. All clients should be screened for traumatic experiences. Those programs that routinely use the *Addiction Severity Index (ASI)* can begin by using the trauma items embedded within that instrument. Then, the program can decide on additional screening items. Some suggested screeners are *ACE Questionnaire* (which focuses on exposure before age 18), *PTSD Checklist (PCL-C)* (which focuses on recent symptoms), *Impacts of Events Scale-Revised (IES-R)*, *Trauma History Questionnaire (THQ)*, and *Life Stressor Checklist-Revised (LSC-R)*.

The screening needs to (1) determine imminent danger (as in the case of domestic or interpersonal violence); (2) communicate that the provider/program believes trauma and violence are significant events; (3) communicate openness to a discussion of painful events; (4) determine the most appropriate follow-up; and (5) open the

possibility of later disclosure if the client is not ready at this time. Screenings are only beneficial if there are follow-up procedures in place and resources available for handling positive screens.

Survivors of childhood maltreatment and/or adult abuse and other traumatic experiences are often reluctant to talk about those experiences. If you have experienced trauma at the hands of another person, particularly someone who has been important to you and who you believed to be protective of you (e.g., parents, older siblings, teachers, coaches, clergymen), then you do not trust people—especially when they try to assure you that they want to help you and that you should trust them. For male clients, who have often learned not to show vulnerability or "weakness," ask about "exposure to violence," rather than abuse or trauma.

Facilitators for screening on trauma include the following:

1. Training providers on when and how to ask about trauma and how to respond to the answers given by patients/clients.
2. Identifying the person(s) on the treatment team who is best equipped to do the screening (e.g., intake person, admission clerk, nurse, medical assistant).
3. Keeping the screening questions short.

The reason for asking about trauma at the initial assessment is that if the questions are not asked then, they tend not to be asked at all. If the patient is too distressed at that point, then delaying the questions is appropriate. In those cases, it should be clearly recorded that the questions were not asked and the patient's file flagged for trauma screening at a later point. A trauma-informed introduction to screening might be, "I'm going to ask you some sensitive questions. If you don't want to answer, please tell me that. It's fine if you prefer not to answer" [2, 3].

There are two important points about that introduction. First, it prepares the client that there are some sensitive questions coming and that they have some importance to the provider. Second, if the client states s/he does not want to answer a question about interpersonal violence, for example, this signals to the provider that the client probably has some problem with abuse and may have important reasons for not answering the questions at this time. Reasons for not answering may be that the abuser is sitting in the waiting room, and the client is afraid to speak about the abuse; s/he is afraid you will alert the authorities, that the abuser may then be punished, and that this will make him/her even more abusive; s/he is afraid you will alert the authorities and have the children taken away; and the client simply does not trust any providers yet. It is also important to ask about present abuse and to ensure a safety plan is in place if there is any danger to the patient and/or children.

With regard to responding, validation of the client's experience(s) and of their reaction to disclosure will communicate that you understand the importance of what has happened to them, that you care about what happened, and that you are nonjudgmental. Some recommendations include affirming that it was a good thing for the client to tell you, offering support, checking the client's emotional state at the end of the session, and offering follow-up.

28.8 Intake/Reception Procedures

Reception staff should be included in the trauma training, so that they understand how to assist anxious, fearful, or hostile patients/clients. Having pamphlets in the waiting room on sexual and physical abuse can convey to patients/clients that the practice/agency is aware of and ready to help with these issues. It is also critical to ensure that our intake processes are not burdensome, repetitive, or intrusive.

During intake, clients should be informed about policies, rules, and procedures. Knowing what to expect decreases anxiety and may prevent the patient from being triggered by unanticipated events. Rules and procedures need to be repeated. Each client has her/his own pattern of situations that can trigger her/him and her/his own pattern of things that can comfort her/him. As part of the intake, staff can ask clients what upsets them and what comforts them. This impor-

tant data can be utilized by staff when the client becomes distressed. For the client, learning to recognize emotional triggers and soothing behaviors restores a sense of safety. For staff, this information can help prevent some of the disturbing events and/or help them comfort and stabilize the client when s/he is upset.

A trauma history may also impact medication adherence because the patient may fear that taking medications will result in a loss of control. Given that trauma has removed choice and control from them, whenever possible, clients should have choice and control in their treatment. For example, the provider can say: "For many people, this can all be overwhelming. We don't have to solve every problem right away. Is there one thing you would like to work on first?" Or, "We have a number of groups you could attend. Which one would you like to attend first?" And ask, "What can I do to make this easier for you?"

28.9 Reducing Re-Traumatization in Substance Abuse Treatment

When clients experience anything as a threat, the fight-flight-freeze response is triggered and results in a state of constant alertness or hyperarousal. The client is then reactive to any number of triggers. In a hyperarousal state, the individual can respond to benign stimuli as if they were life-threatening. For example, a veteran may hear a car backfire and drop to the ground, afraid he is about to be attacked as he was in combat. This prepares the individual to respond with "fight, flight, or freeze" responses; you may observe outbursts of anger (fight), clients leaving treatment early (flight), or a client with an appearance like "a deer in the headlights" (freeze). The last response is often seen in children who cannot, as easily as adults, fight or flee.

It should also be noted that, following traumatic events, survivors may also avoid "people, places, and things" associated with the event. This coping strategy is typically not available for victims of repeated child and intimate partner abuse, who are forced to continue to be engaged with the perpetrators of the abuse. Many survivors use drugs and/or alcohol to modulate their arousal. For substance abuse treatment providers, this raises the issue of "triggers" that can increase the substance use. Triggers are quite relevant to trauma work, as well as to substance abuse treatment.

There are certain procedures that can be re-traumatizing for many clients, such as urine testing, aggressive confrontation, and sudden discharge from treatment. Supervised visits with children who may be in foster care and the presence of child welfare, combined with a trauma history and a fear of losing children, place parents, particularly mothers, at high risk for acute trauma responses. Some recommendations to drug abuse treatment staff to reduce re-traumatization and to become trauma-informed are as follows:

- *Motivational interviewing (MI)* [24] states that motivation for change is cultivated within the collaborative relationship between provider and client. The focus is understanding what each client values while evoking his/her reasons for change. *MI* is completely compatible with trauma-informed care.
- During urine testing, try not to stand too close to the client, assure the client you know this procedure can be uncomfortable, and ask, "What would make this more comfortable for you?"
- Have separate groups by gender.
- If a client is triggered in a group session, stop the action and introduce grounding strategies (see [8, 27]).
- Help decide on which trauma-specific intervention (e.g., *Seeking Safety*, *Beyond Trauma*, *TREM*) fits best in your program. Participate in the training for the intervention selected.
- Link "triggers" for using drugs and alcohol to "triggers" for re-experiencing traumatic events.
- Acknowledge client's strengths ("still standing").
- Ask, "Since the last time we spoke, has anything happened that was upsetting to you?"
- In residential treatment, prepare clients for staff entering the rooms at night (for monitoring).

Then, when monitoring, knock on the door; identify yourself; say, "I'm coming in," and ask if clients are okay.

- In addition to clients with co-occurring disorders, including trauma, clients with cognitive impairment may have diminished capacity to adhere to treatment rules and procedures. In our work at PROTOTYPES, we found that a number of our clients showed cognitive impairment when tested. This is not a topic typically discussed in addiction treatment. However, some treatment practices that can help these clients are providing clear explanations; using concrete language, short sentences, and visual aids (drawings, photos); and frequent repetition. In addition, assign an advanced residential client to read any written information to the client.
- Residential treatment offers a community experience with clear structure and a set of norms and boundaries. This can promote a sense of safety for some clients. For others, this environment may feel overwhelming and threatening. Behaviors such as hostility or aggression on the part of other clients can affect the group's feeling of safety.
- In outpatient treatment, it is extremely important to assess each client's safety at home/in the community. Also, safety plans for the children of clients need to be addressed.

28.10 Staff Care/Self-Care

There are a number of practices that can help in preventing and/or lessening secondary traumatization and burnout in staff members. First, the treatment agency needs to ensure that caseloads are balanced and *not overwhelming*; supervision is available to all staff and is trauma-sensitive; staff members have a place and time to debrief with colleagues and take breaks; and procedures are in place to assure safety for staff. In addition, staff members need training on self-care, including increasing self-awareness and the ability to process negative emotions; using supervision to share how it feels to work with certain clients; setting limits with clients; staying connected with colleagues and asking one another, "What was the hardest thing you had to handle today?"; becoming part of a team activity (e.g., sport); and being able to "leave work at work" and enjoy pleasant time with family and friends.

In conclusion, in order for addiction treatment to meet the needs of our clients, our approach needs to address the impact of trauma on clients' lives/substance use and on staff. The suggested practice changes discussed in this chapter are the beginning of a cultural change in our addiction treatment. Trauma-informed practices can address a variety of adversities that affect our clients. Addiction treatment can provide (1) a safe and supporting environment for clients and staff; (2) understanding of the link between trauma and substance use; (3) training in new coping skills; (4) parenting skills training to reduce the likelihood that clients' children will be impacted by child neglect or maltreatment; (5) assistance to the children in developing resilience; (6) training in developing positive relationships and connection; and (7) access to other supportive services, including employment, housing, education, and family treatment. As is discussed throughout this chapter, trauma-informed care incorporates gender-informed care, person-centered care, and cultural safety. It values continuous improvement and encourages staff and clients to propose ideas for improvement without fear.

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29 Contingency Management as a Behavioral Approach in Addiction Treatment

John M. Roll, Sterling M. McPherson, and Michael G. McDonell

Contents

Abstract

Contingency management is a well-documented intervention for initiating abstinence from abused drugs. The technique is rooted in a long tradition of operant psychology and has copious amounts of foundational and applied research supporting its use. This revised chapter describes the background research, reviews the history of using contingency management, and provides basic information on implementation. This revised chapter includes a new section on technology support for contingency management. The reader will hopefully find this chapter to be a useful basic introduction of the topic.

Keywords

Behavioral treatment · Operant psychology · Supportive technology

J. M. Roll (✉) · S. M. McPherson · M. G. McDonell
Washington State University, Spokane, WA, USA
e-mail: johnroll@wsu.edu; sterling.mcpherson@wsu.edu; mmcdonell@wsu.edu

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29.1 Introduction

At its heart, drug abuse—addiction—is an easy concept to understand. People misuse drugs because the drugs make them feel good. This occurs either by inducing euphoria or by eliminating an unpleasant state, for example, pain or withdrawal. The effects of drugs are usually short-lived. That is to say that the euphoria or relief usually lasts for hours, not days. In order to regain the sought-after effect (feeling good), the drug must be taken repeatedly and over time. This repeated consumption quickly turns into addiction. Addiction is a vicious cycle in which the original efficacy of the drug is diminished, and the drug must be taken more frequently and at a higher dose to obtain similar efficacy (i.e., tolerance and habituation occurs).

Addiction is often further characterized by damage to the physiology of the person consuming the drug as a result of the drug's pharmacologic action. The lifestyle associated with compulsive drug seeking also damages the person—they do not take care of their personal health, and their relationships with others deteriorate and often are terminated. Compulsive users occasionally engage in dangerous behaviors to acquire drugs such as engaging in sex trade work or engaging in criminal activity, and they become less interested in maintaining their physical, psychologic, and spiritual health as they become more addicted to drugs. Unchecked, the person in the grasp of this vicious cycle of addiction will most often die or at best adopt what is essentially a palliative existence. This is true for virtually all drugs of abuse, even though the cycle may be faster for some drugs of addiction (e.g., acute methamphetamine use leading to a heart attack or an overdose resulting in death) compared to others (e.g., smoking cigarettes eventually leading to chronic obstructive pulmonary disease or eventually to lung cancer and death). These tragic outcomes result from a person simply wanting to feel euphoria or seeking relief from a negative state, something every human can relate to.

Characterizing this downward spiral that starts with the universal quest to feel good in terms of a scientific framework is important if we are to fully understand, effectively treat, and eventually prevent addiction. One of the best frameworks for characterizing addiction comes from the field of the Experimental Analysis of Behavior. While this field has its genesis in the distinguished work of scholars such as the British philosophers, Lloyd Morgan, Edward Thorndike, and others (e.g., [12]), it was essentially popularized and is most closely associated with the operant psychology of B. F. Skinner (e.g., [79]; see [68] for discussion of the history and evolution of operant psychology's influence on behavioral pharmacology).

One of the seminal events in the growth of operant pharmacology was the development of laboratory preparations (operant chamber, eponymously known as a Skinner box) for the convenient study of operant behavior. Briefly (see [41] for a detailed discussion of operant psychology), organisms could be put into the operant chamber, and under tightly controlled conditions, their behavior could be studied. A common example would be to place a hungry rat in the operant chamber and allow it to press a lever for food. Rate of responding for food will increase as the rat acquires the lever-pressing repertoire and then plateau as the rat masters the behavior. This change in rate across experimental sessions demonstrates learning. The food, which maintains the responding in the foregoing example, would be considered a reinforcer. A reinforcer can be defined as a stimulus that increases the behavior it follows. In this case, food reinforces lever pressing, and the lever pressing increases until the behavior has been mastered. Most would consider the food to be an example of positive reinforcement. That is to say, the behavior produces a stimulus (food) which increases the homeostatic "good" of the rat. Another type of reinforcement that can be demonstrated in a laboratory preparation is negative reinforcement. An example of this would be a rat placed in an operant chamber that receives a shock every 2 minutes regardless of what the rat did; in other words, the shock is inescapable. However, if a lever is placed in the box and the rat presses the lever, the next scheduled shock can be avoided. As in the positive reinforcement example, the rat will acquire the lever-pressing behavior over time until it has

mastered the behavior and maintains it at a level that avoids shocks. Negative reinforcement, which is reinforcement that removes an aversive state, like this occurs when a behavior eliminates a noxious stimulus.

The forgoing is not merely a historical footnote. The use of the operant chamber opened many avenues for the study of how drugs influence behavior. Early examples of this work were conducted by Skinner and Heron [80] who examined how caffeine and amphetamine (Benzedrine) impacted food-reinforced behavior and the extinction of that behavior.

However, the aspect of operant psychology that is of most relevance to this chapter was the demonstration that naive animals would self-administer most of the same drugs abused by humans. In an early study, Thomson and Schuster demonstrated that drug-naive monkeys would self-administer morphine [86]. This was a seminal demonstration that drugs of abuse could serve as positive reinforcers analogous to other positive reinforcers like food and water. Since this demonstration, thousands of studies in which drugs are provided to organisms (human and nonhuman) contingent on an operant response have demonstrated the robustness of this phenomenon (e.g., [68]). It is one of the more unambiguous and well-accepted *facts* that drugs of abuse act as sources of positive reinforcement. Similarly, it has been demonstrated in laboratory paradigms that drugs of abuse can also serve as powerful sources of negative reinforcement (e.g., [31, 34, 46, 47, 87]). More specifically, drug-dependent organisms will increase their responding for a drug when they are in a state of withdrawal (see especially the body of work of Negus for discussion of this). That is, the animal, or person, will increase their consumption of a drug to escape from a negative state. In situations such as this, the drug functions as a negative reinforcer.

This observation, that drugs of abuse serve as sources of reinforcement, both positive and negative, has been an important observation in our quest to understand, treat, and prevent addiction. Many would argue that the goal of treatment (and prevention) efforts should be the diminution of the reinforcing efficacy of the drug of abuse.

To relate this operant framework back to the opening discussion about a drug user's quest to feel good, we can refine that description so that instead of describing a quest to feel good, we can describe a quest for reinforcement. This could be positive reinforcement, which some might equate with euphoria, or negative reinforcement, for example, the diminution of withdrawal symptoms. This conceptualization now allows us to place drug addiction and its associated sequela into the operant psychology framework.

To appreciate the utility of this operant framework for addressing addiction, one more point needs consideration. That is that primary, or naturalistic, reinforcers are biologically important for the survival of the organism and hence the species. Food, water, and sex are crucial to survival, and these are powerful sources of natural reinforcement. Human biology has evolved to be maximally sensitive to sources of reinforcement such as these. A detailed discussion of the neurobiology underpinning reinforcement is well beyond the scope of this chapter. Suffice it to say that an impressive array of neurobiological systems are at play. When a thirsty person takes a drink of water, it is a powerful source of reinforcement, and our neurobiology guarantees that in a similar state of thirst, we will again seek a drink of water. Unfortunately, most drugs of abuse interact with the same neurobiological system that governs our reinforcing relationship to primary sources of reinforcement. As popularized by a past director of the National Institute on Drug Abuse, Dr. Alan Leshner, drugs of abuse hijack this neurobiological system and insidiously shift a user's motivation toward a compulsive focus on drug-derived reinforcement. The result is that an addicted person develops a compulsive motivation to seek drug-based reinforcement and that that reinforcement is of exceptional strength.

While daunting, this conceptualization does point toward an effective treatment mechanism. In order to help an individual enter into recovery from drug addiction, it is necessary to reduce the reinforcing efficacy of the drug. We would argue that this is the goal of all drug abuse treatment efforts at some level. The cognitive behavior

treatments seek to restructure thoughts about drugs or to reorganize a user's cognitions and skill set so that they conceptualize the negative aspects of drug use as being more salient than the positive aspects. Motivational therapies seek to alter the user's motivation to seek the drug reinforcement; pharmacologic and immunotherapeutic approaches seek to block the drug from ever interacting with the user's reward-related neurobiology. While some will surely disagree, we postulate that all successful treatment approaches can be couched in terms of lowering the abused drug's reinforcing efficacy. One approach that takes this as its stated goal is contingency management (CM). The remainder of this chapter will focus on this approach. We will briefly describe the basic science supporting the approach and discuss prototypic examples of how to use the approach, key factors to consider when using the approach, populations for which the approach has been used, barriers to implementation, technology supports for this approach, and finally potential limitations to the use of the approach. A series of meta-analyses supports the use of CM [1, 19, 39, 58]. The interested reader is encouraged to consult these publications as they are much more detailed than this chapter. There also exist a number of books on the topic of CM. This brief chapter can provide only a glimpse of the wealth of growing research on CM. Consulting these other texts is crucial prior to actual implementation of the procedure.

29.2 Underlying Logic of CM Approaches

One of the clearest demonstrations of the underlying principle of CM-based interventions is found in a study by Nader and Woolverton [45]. In this study, they allowed rhesus monkeys to make choices between intravenously delivered cocaine and food [45]. When the choice was between cocaine and one pellet of food, the monkeys showed a strong preference for self-administering the cocaine. However, when the dose of cocaine was held constant and the magnitude of the alternative source of reinforcement (food) was increased to four pellets per choice, the monkeys chose to self-administer cocaine on only about half of the choice opportunities. Finally, when the magnitude of the alternative reinforcer was increased to 16 food pellets per choice, the monkeys selected the alternative reinforcer, food, almost exclusively. As discussed in Roll [68], this well-designed experiment demonstrates the powerful impact of arranging an environment so that the organism needs to make choices between a drug and a salient, high-magnitude, alternative source of reinforcement. This finding has been demonstrated by many investigators working with different drugs, different alternative reinforcers, and different animal species (e.g., [14]). When the magnitude of the alternative source of reinforcement is low, the drug has a powerful reinforcing efficacy. However, simply by elevating the magnitude of the available alternative sources of reinforcement, the reinforcing efficacy of the drug can be reduced to such a low level that it is not self-administered. That is to say, it is no longer an effective reinforcer.

It is reasonable to question how applicable these findings are to humans. In order to address this question, Higgins and colleagues conducted a similar study with human volunteers in which they investigated the impact of manipulating the magnitude of alternative reinforcers on cocaine self-administration [24, 25]. In this study, recreational cocaine users were recruited to participate in an outpatient study. Participants came to the laboratory where they made ten repeated choices between cocaine and money on a given day. Cocaine dose was 10 mg per choice and was held constant throughout the study. Money was used as an alternative source of reinforcement and was provided at three different levels: $0.50, $1.00, and $2.00. During a given session, monetary value was always held constant. In each experimental session, a participant made ten exclusive choices between cocaine and money. When the money value was low, participants elected to self-administer cocaine exclusively. As the value of the alternative source of reinforcement increased to $1.00, participants elected to receive about half of the available cocaine doses, and when the

magnitude of the alternative was increased to $2.00, participants switched their preference—relative to that demonstrated with the low magnitudes of alternative reinforcement—and elected to decline cocaine and receive only money. This procedure has been replicated with other types of drugs besides cocaine (e.g., [74, 75]). Exactly as in the Nader and Woolverton study with monkeys, the penchant for humans to self-administer drugs typically decreases in an orderly and predictable fashion as the amount of the alternative source of reinforcement increases. These data demonstrate that providing a salient alternative source of reinforcement of sufficient magnitude reduces a drug's reinforcing efficacy. As noted, this is the hallmark of the successful treatment of drug addiction. Contingency-management approaches take advantage of this observation and seek to arrange a drug user's environment so that they can garner salient alternative sources of reinforcement when abstaining from drugs and forfeit that reinforcement when consuming drugs (Note: this section was adapted from [68]; also see [7]).

29.3 Prototypic Examples

Contingency management can take many forms, but in all cases, it is a technique that clinicians use to *engineer* a drug user's environment so that the drug user must choose between drug use (maintained by the drug's reinforcing efficacy) and other non-drug reinforcers. The salient non-drug reinforcers that have often been employed included access to housing [43]; access to employment [76]; provision of vouchers which can be exchanged for monetarily-based goods and services [24, 25]; access to prizes which are valued by the user (e.g., [55]); escape from judicial sanctions [57]; and access to one's monetary resources [66]. Several research groups have developed potential lists of other types of reinforcers that can be employed, and these include such things as reduced clinic fees, access to clinic-sponsored social events, reduced time in psychosocial counseling, fee rebates, and donated goods and services (e.g., [6, 70]).

While the CM class of interventions have been used for most types of drug abuse treatment [28], they have, in our opinion, been most successful for those types of addictions for which no viable pharmacotherapy exists. This largely excludes opioid addiction and nicotine addiction as both of these disorders are well-controlled with pharmacotherapy (e.g., opioids: [10]; nicotine: [8]). That is not to say that CM cannot be a useful adjunct for the management of opiate addiction or smoking cessation. For example, take-home doses of methadone delivered contingent on compliance with clinic regulations and the continued provision of drug-free urine tests is a relatively common practice (e.g., [84]). Contingency management may also have utility in treating nicotine addiction (e.g., [37]), but in our experience, CM is usually a secondary focus to the pharmacotherapy, which is the first-line treatment of these disorders. Please note that even when good pharmacotherapy is available, some populations such as pregnant women may not be able to use the pharmacotherapy. In cases such as this, CM may become a very important treatment modality (e.g., [29]). However, we still do not have accepted pharmacotherapies for psychostimulant addiction (excluding nicotine addiction), especially cocaine and methamphetamine. It is for these disorders that we believe CM is a useful first-line approach. There are two types of CM that are most commonly employed in the treatment of psychostimulant addiction. The first, popularized by Higgins (e.g., [24, 25]), is perhaps best described as voucher-based reinforcement therapy (VBRT), and the second, popularized by Petry (e.g., [55]), is variously referred to as the Fishbowl technique and prize-based CM but is more accurately known as Variable Magnitude of Reinforcement CM (e.g., [78]). Examples of each are provided below, and in the following section, the key factors related to the efficacy of the procedures are discussed.

Steve Higgins at the University of Vermont first demonstrated the efficacy of VBRT in a relatively large randomized clinical trial designed to assess the intervention's impact on cocaine using individuals [26]. The basic procedures for this type of intervention are as follows: Patients

receive vouchers for the provision of biological samples (urine or breath) that indicate no recent drug use. Participants receive a voucher each time they test negative for the target drug. These vouchers can then be exchanged for goods or services. The initial voucher value is set at a low value (e.g., $2.50 USD). Each consecutive instance of abstinence increases the magnitude of the voucher by a small amount (e.g., $1.50 USD). Three consecutive abstinences result in the delivery of an additional bonus (e.g., $10.00 USD). A drug-positive urine sample, or failure to test, results in a reset of the voucher magnitude back to its original level (i.e., $2.50), from which the escalation can begin again.

The late Nancy Petry at the University of Connecticut popularized the variable magnitude of reinforcement procedure [48, 56]. This procedure involves making "draws" from a bowl of chips representing different prize/reinforcer magnitudes. These chips can be exchanged for goods that are available on-site. Typically, about half of the chips say "good job" and do not result in the delivery of any tangible reinforcement. 41.8% of the chips result in a small reinforcer (worth about $1.00 USD), 8% result in a large reinforcer (worth about $20.00 USD), and 0.2% result in a jumbo reinforcer (worth about $80.00 USD). Participants earn at least one draw for each urine sample submitted that is drug negative. The number of draws awarded at each urine collection escalates by one chip with consecutive instances of drug-negative urine tests. Missing or drug-positive urine samples result in a reset to one draw available when the next negative sample is submitted.

Both of these (VBRT and Variable Magnitude of Reinforcement) procedures are quite effective at treating psychostimulant addiction. In fact, the United States of America Veteran's Administration has recently adopted CM as a treatment modality for psychostimulant addiction [64]. Often, people wonder about the relative efficacy of the two procedures. It is important to note that there is substantial evidence suggesting that they both work. We are aware of no evidence demonstrating the superiority of one over the other. Both procedures have the advantage that they allow clinicians and consumers of their services to celebrate success (e.g., drug abstinence) in a clinical session as opposed to focusing on failure (drug use). The Variable Magnitude of Reinforcement procedure has a potential advantage in that the prize drawing phase has an inherent excitement built into and an element of chance which many may find exciting. This may confer additional reinforcing efficacy to the prizes above and beyond that which can be accounted for via their monetary value via a process of conditioning (e.g., [4]). However, this suggestion is in need of empirical assessment. Some have suggested that on the face of it, this may resemble gambling and be a risk for pushing individuals who are seeking treatment for addiction to develop or exacerbate a pathological gambling problem. It is important to note that the Variable Magnitude of Reinforcement procedure is not gambling. The participant does not put up any of their own resources and does not have an opportunity for personal financial loss as is the case in gambling. In addition, we have studied those going through this type of CM procedure and found no evidence that they transition to or develop a gambling disorder [54].

A potential advantage of the VBRT procedure relative to the Variable Magnitude of Reinforcement procedure is that it allows a skillful clinician to engineer the voucher exchanges so that the consumer/patient comes into contact with powerful sources of non-drug reinforcement that exist in the consumer's natural environment. The goal is that these sources of reinforcement will come to exert control over the consumer's behavior as they initiate and maintain their recovery from their addiction. For example, exchanging vouchers for goods or services that allow the consumer to increase the reinforcement they get: from family interactions (e.g., exchanging a voucher so a mother can go roller skating with her daughter); from employment (e.g., exchanging a voucher for a set of clothes to wear at a job interview); or from engaging in a hobby (e.g., exchanging a voucher for a fishing license so that the consumer can engage in a hobby), all serve to increase the consumers contact with potentially powerful sources of non-drug reinforcement. In other words, the vouchers can act as behavioral

vectors to draw the consumer's behavior into contact with non-drug reinforcers. It should be noted that in the Variable Magnitude of Reinforcement procedure, this can also be accomplished by tailoring the prizes that are available to consumers.

In summary, both of these procedures work well and have improved the lives of many individuals who have benefited from treatment that utilized these approaches. There is no immediate reason to prefer one approach over the other. Both are effective if delivered with high degrees of fidelity [48]. There is good evidence that the procedures work for most types of addiction [19, 23, 27, 39, 48, 58] and for many populations including adolescents [13], polysubstance abusers [18], pregnant women [29], and those afflicted with both substance use disorders and serious and persistent mental health issues [40]. There is also evidence that the procedures work best for those who rapidly initiate abstinence during treatment [90] and for those who begin treatment in a drug-free state [85]. The utility of the CM procedures for treatment in the criminal justice system is less compelling (e.g., [22]; although see [17]). This is perhaps not surprising as most criminal justice systems are punishment based. While punishment is usually to be avoided in therapeutic contexts because of the proclivity of the person being punished to escape the punisher (e.g., terminate the treatment interaction), that is not an option in a criminal justice setting in which the person is compelled to engage in treatment. Given these circumstances, contingent punishment should be quite effective in controlling behavior. For example, if a cocaine user is clearly informed that if they use cocaine they will be incarcerated, it is a powerful contingency management protocol based on punishment. This is the norm in many criminal justice systems (punishments range from mild sanction in some countries to death in others!). In such a milieu, it is unlikely that a reinforcement-based CM procedure will garner much additional control over a user's behavior unless very high-magnitude reinforcers are employed. In criminal justice systems where behavior is less controlled, however, CM interventions should be effective.

29.4 Key Factors

In this section, we briefly describe what we believe are four key factors for the successful implementation of any variety of CM. For a detailed discussion of these factors and others, please consult [48, 52, 88].

The first factor to consider is the procedure by which vouchers or prizes (henceforth both referred to as reinforcers) are disbursed. This is known in parlance of operant psychology as the schedule of reinforcement. Schedules of reinforcement have been extensively studied, and it has been repeatedly demonstrated that schedule changes can have profound impacts on behavior [20, 72]. Higgins developed the basic schedule that is routinely employed in CM procedures. This has two key components. First, as outlined in the examples in the previous section, there is an escalation in reinforcement magnitude for consecutive instances of abstinence. Second, as described above, there is a reset in reinforcer magnitude (voucher value or number of prize draws) following a failure to abstain. The combination of these components seems to provide the greatest likelihood for achieving a successful treatment outcome [71, 72]. While we do not precisely know why these components are operative, it is likely that they function to integrate individual instances of abstinence into a consecutive period of abstinence. If each abstinence were reinforced independently of those that preceded or followed it, the behavioral target would be individual instances of abstinence. By linking consecutive instances of abstinence via the escalation and reset procedure, the target becomes consecutive instances of abstinence, which should be the goal of all treatment efforts. Whenever it is possible, CM procedures should try to incorporate both of these schedule components to have the greatest likelihood of success.

The second factor to consider is the magnitude, or value, of the reinforcers used. There exists an extensive body of literature from both laboratory and clinical trials and with different species including humans that unambiguously demonstrates that higher magnitudes of reinforcement are better at controlling behavior [45,

50, 89]. Clinically, this means that the higher the value of the reinforcer employed, the more effective it is likely to be. Use of reinforcer magnitudes that are too low to control behavior (e.g., [50]) will result in failure of the intervention. Unfortunately, this could be interpreted as a failure of the CM protocol, when in fact it is a lack of fidelity to the protocol that is responsible for the failure. One should not expect a low-magnitude reinforcer procedure to be very effective. This often poses a significant challenge to the implementation of CM [73]. Treatment centers are often under-resourced and do not have the means to employ high-magnitude monetary reinforcers such as vouchers and prizes. In this case, other non-cash-based reinforcers can be used (as described above), or community donations can be sought (e.g., [5]). It is our belief that funders are beginning to embrace CM interventions as many insurance companies employ CM-based efforts to control health behaviors and as the United States Veterans Administration has adopted CM as a primary treatment strategy [63]. Hopefully, this will reduce the difficulty surrounding the provision of reinforcement of sufficient magnitude.

It should be noted that what is reinforcing for one person may not be reinforcing for another. Thus, when using non-cash-based reinforcers, it is incumbent on the clinician to find reinforcers that are salient to individual consumers. This can be done by identifying a functional relationship between behavior and reinforcers as described in Johnston and Pennypacker [33]. Also of note is that reinforcement magnitude can be changed during treatment, if necessary, to garner more control over a user's behavior. In a study by Robles and colleagues [67], it was demonstrated that even treatment-resistant cocaine users would abstain if high-magnitude vouchers (e.g., $100.00 US) were used.

The third factor to consider when developing, or delivering, a CM protocol is delay [50, 53, 75]. There are two types of delay that are common in CM protocols. The first is the delay between earning a reinforcer (e.g., providing biological evidence of drug abstinence) and receiving the reinforcer. That is, how long after someone provides a drug-negative urine sample until they receive their prize or voucher. In order to be maximally effective, this delay should be minimized. Another type of delay encountered when using vouchers is an exchange delay [32]. That is the delay between telling the counselor what you want to exchange your voucher for and the actual receipt of the item. Again, in order to maximize protocol efficacy, this delay should be minimized.

The fourth and final factor we wish to mention is intervention duration. While it is quite understandable that clinicians, consumers, their families, and funders want short, effective, treatment, it is important to remember that drug users spend a lifetime developing an addiction; it may not be reasonable to think that the behavioral patterns established in order to support compulsive drug-taking behavior can be terminated quickly. For this reason, we recommend that the longest possible duration of treatment be employed. There is evidence to suggest that longer treatments are more effective than shorter ones [69] and that long-term treatment is acceptable to consumers [77]. Notably, dozens of studies have shown that CM continues to decrease substance use as long as it is in place and ceases to work once it is removed, e.g., A-B-A, or return to baseline studies have shown this multiple times across various substances of abuse. Many have questioned the utility of CM because once the contingency is taken away, drug use often returns soon after. However, we view this as a strength of the CM approach. This is not unlike an ideal medication that works when it is taken with almost no side effects and does not work relatively soon after not being taken. Still, some have documented that the effects of CM can remain for up to 18 months after treatment.

29.5 Barriers

Given the widely accepted efficacy and relative ease of implementation, one could reasonably ask why CM is not more widely employed. To begin with, it is often employed although perhaps not as frequently as one would expect. In our

experience, three common barriers are raised that hinder effective implementation of the procedure. These barriers have been discussed in detail, and interested readers should consult the literature for a thorough vetting (e.g., [64, 73]).

Primary among the barriers is the perceived cost of the CM interventions. We have touched on this in several of the above sections. Cost is an issue, but non-monetary reinforcers can be employed. Also, some of the most cited studies have shown that average cost can be between $100 and $200 in efficacious CM interventions [51, 56]. Some work has demonstrated unanticipated benefits such as decreased hospitalizations and improved comorbid psychiatric functioning [40] suggesting that potential cost offsets could be used to fund interventions. CM is cost-effective [44]; it is sometimes a matter of convincing payers of that efficacy.

An important issue to consider in this context as well is the cost of CM compared to other available treatments. Relative to most forms of psychosocial counseling that are available for psychostimulant use, for example, the cost should be evaluated carefully (e.g., societal costs, legal costs, emergency department costs) given the high costs associated with poorly performing treatments or a lack of available treatments as is the case for psychostimulants.

Another common concern is provider perceptions [11]. Providers sometimes argue that in order to be effective, treatment needs to engage a consumer's *intrinsic motivation* and not be based on a procedure that engineers the user's environment. The very existence of this construct (intrinsic motivation) is controversial. Moreover, when confronted with the efficacy of the CM interventions, most clinicians adopt a more conciliatory approach. Clinicians also have, on occasion, had personal experiences with substance use disorders and are themselves in recovery. In this case, they may believe that others need to follow the same strategies they used to obtain and maintain abstinence. Thankfully, this is an increasingly rare occurrence. It would be akin to a physician who suffered from bronchitis which was cured by antibiotic Z insisting that antibiotic Z is the only way to treat bronchitis based on her personal experience.

It has also been argued that CM protocols are too complex. Proponents of this argument claim that busy, poorly resourced clinicians do not have the time needed to calculate reinforcer value and carry out prize draws or voucher exchanges. While we certainly agree that clinicians are overworked and underpaid, we find this class of argument to be repugnant. It is akin to a surgeon declining to operate on someone because the surgical procedure was too complex, and they were too busy with other procedures. Again, it is important to consider the question of "too complex, compared to what?" Many psychosocial techniques are not easily deployed due to the intense training and fidelity needed. Even after being deployed after the therapist in question has achieved high enough fidelity, most clinicians agree that without consistent and ongoing trainings, there is a natural, therapeutic "drift" that occurs over time among many psychosocial treatments. Thus, the necessary training and monitoring is both costly and labor intensive and can also be magnitudes more complex than CM. Moreover, the advent of technology to aid clinicians with the delivery of CM (and the ability to conduct online voucher exchanges) [42] obviates most of these concerns. We discuss this in some detail below.

The final perception we wish to discuss is one of consumer resources. It has been suggested that CM-based interventions will only work for those who have limited financial resources. While it is undeniable that drug addiction eats away at a person's resources until they are depleted and that most abusers are financially deprived, we are aware of no data to suggest that CM efficacy is influenced by income level. In fact, research has shown the income level (both legal and illegal) does not impact CM efficacy [64]. That said, most treatment efforts and especially those involving clinical research protocols for substance abuse are populated by individuals of limited financial means. Further work is needed to assess the efficacy of the monetarily-based procedures in those with relative wealth.

29.6 Combining Experimental Technologies with Incentives for Behavior Change Remotely Monitoring Outcomes

As mentioned, one of the barriers to more widespread implementation and dissemination of CM has been the necessity of participants attending frequent clinic visits, driven mostly by the short half-life of point of care tests for drugs and alcohol. This is also driven by the need to deliver an immediate consequence consistent with evidence, or lack thereof, of a desired behavior. Notably, a strength of CM is that it can be administered by individuals with minimal training and no clinical credentials [38, 83]. This has led to new lines of research that seek to take advantage of novel, automated technologies that can streamline the delivery of incentives electronically and are paired with inexpensive biochemical monitoring [49]. As mobile phones are increasingly becoming a part of everyday life [81], this has generated much research activity focused on the virtual delivery of reinforcers to individuals that can be almost anywhere, including those dwelling in rural or otherwise remote locations that are essentially a "drug and alcohol use disorder treatment desert." Ironically, while CM has been criticized for years as being difficult to disseminate, as technology evolves, it appears that CM is becoming more portable than many other treatment modalities. Many of these technology-based CM strategies are in the feasibility stage, but significant progress has been made in remote monitoring of participants, intervention delivery, and delivery of reinforcers through technology.

In 2013, Alessi and colleagues published a randomized study that assessed the efficacy and feasibility of a CM intervention to reinforce alcohol abstinence using mobile technology [3]. This trial included 30 heavy drinking adults that were given a portable breathalyzer and a cell phone and were trained how to record a video of themselves provisioning breath samples prior to submitting the video in exchange for different incentives. Participants were randomized to two different groups: (1) a control group that received incentives for submitting breath samples, and payment was not contingent on the status of the sample, and (2) an active CM treatment group that received the same amount of incentives as the control group, but they also received escalating vouchers for the submission of alcohol-negative breath samples. Study staff communicated with participants through text messaging to send daily reminders for when the samples were due. This study demonstrated medium to large CM effects, showing that CM was significantly associated with (1) increased daily alcohol abstinence, (2) duration of abstinence from alcohol, and (3) decreases in self-reported drinking days and severity of drinking-associated problems during the intervention [3].

Another example from the smoking cessation literature is a trial that compared the effect of an online CM intervention to a non-CM, online monitoring, and goal-setting intervention [15]. The CM intervention significantly improved short-term smoking abstinence rates compared to the non-CM, online monitoring, and goal-setting intervention [15]. Similar to what Alessi and colleagues did in the above noted alcohol intervention, the distribution of incentives occurred virtually immediately after the submission of smoking-negative sample using carbon monoxide (CO; biochemical measure of recent smoking) as the biomarker [15]. A similar, "video-observed CO submission" online program was developed for adolescents dwelling in Appalachia. Adolescents in this area have smoking rates that are significantly elevated in comparison to the national average. Given that this population is harder to reach and is at higher risk, adapted CM interventions have the capacity to make a significant difference. In this study, 62 adolescents agreed to submit three videos each day showing the participants submitting the required breath samples using a portable CO breathalyzer. For adolescents in the CM group, provision of a smoking-negative sample would earn them virtual vouchers that could be exchanged for a variety of prizes. Those randomized to the monitoring and goal-setting condition received prizes for simply submitting the requi-

site video recordings. This trial was conducted almost entirely online, but it did require study staff to review the video to ensure that the appropriate person and sample had been collected before the vouchers were delivered [65].

Notably, a recent systematic review that examined 39 CM-based remote monitoring studies (18 targeted substance use; 11 targeted diet, exercise, or weight loss; 10 targeted medication adherence or in-home monitoring) found that 71% of the studies resulted in clinically and statistically significant treatment effects in favor of CM. These data support the benefits of adopting remote, technology-based CM interventions for both drug and alcohol use disorder but also for other health-impairing behaviors such as medication non-adherence [36]. In fact, the FDA has approved a mobile-based CM app for substance use disorders (SUDs) (Pear therapeutics, Inc. developed reSET) [59]. Other, related software applications are currently in development, some of which are supported through the National Institutes of Health's Small Business Innovation Research and Small Business Technology Transfer programs.

Beyond experimental software technologies that are under development, there are novel hardware technologies that could rapidly leverage the inherent strengths of CM, especially if paired with the optimal software applications that are simultaneously emerging. One example is BACTrack, a battery-operated breath alcohol capture analysis device that connects to a participants' cellphone through Bluetooth (KHN Solutions, San Francisco, CA, USA) [61]. This hardware has not been used in conjunction with CM yet in large demonstration project, but early pilot data indicate that it could be a valuable tool to monitor alcohol use similar to the portable CO breath analyzer noted in the studies above and utilized elsewhere for similar, remote monitoring studies of smoking cessation treatments. Another, more commonly researched tool for remotely monitoring alcohol use is a transdermal alcohol monitoring tool. This hardware eliminates any need for a clinician or staff member because it will passively collect patient samples. The Secure Continuous Remote Alcohol Monitoring (SCRAM) continuously collects and monitors participants' alcohol consumption through an ankle monitor that collects and analyzes perspiration [2, 9]. This device has been used with CM, but in a recent investigation, there were no statistically significant differences in the primary outcomes of treatment attendance and alcohol abstinence between the CM and control groups [2]. However, there is some additional, more promising data published supporting the utility and feasibility of transdermal monitoring of alcohol use [2, 3].

29.7 Attendance and Medication Adherence Technologies

In the area of utilizing CM for promoting increased attendance and increased treatment adherence, there are also new technologies being designed including biosensors and pill bottle electronic reminder systems and monitors [21, 60]. The progress being made in this area is encouraging because treatment attendance, adherence, and medication adherence all have remained major barriers to the large-scale and consistent delivery of evidence-based treatments across drug and alcohol use therapeutic areas, but also in several other therapeutic areas [35]. For example, a recently published study by Raiff and colleagues assessed the feasibility of combining CM with a remote medication adherence monitoring system ("Wisepill") to target medication adherence among three adults with type 2 diabetes. Adherence to each patient's diabetes medication was remotely recorded in real time using the Wisepill device [60], a portable and electronically monitored pill dispenser. Patients received monetary incentives in exchange for time-window compliant evidence of daily tallied medication adherence. The results indicated that adherence was increased for all participants who were exposed to the CM intervention [15]. While the evidence is more dated, CM has also shown promise for improving medication adherence among HIV-positive methadone patients [82]. A 2007 published trial randomized participants to one of two groups: (1) a group that received medication-adherence coaching sessions

on a biweekly basis or (2) a voucher group that received CM combined with the coaching sessions. The study found that the CM group experienced significantly higher medication adherence compared to the coaching session-only group [82].

A 2012 systematic review that focused on incentive-based interventions for targeting medication adherence concluded that while CM shows significant promise in the field and evidence is being accumulated that continues to support its use, it remains understudied [16]. A comparison between several studies demonstrated that CM adherence-based interventions increased medication adherence by 20% on average. However, the effect sizes varied greatly. This may have been the result of CM being applied non-uniformly and in some cases not as originally designed or intended in order to cause sustained behavior change [16]. While adherence to medications often diminished after the CM intervention was removed [16], this is not unlike most efficacious adherence interventions or treatments in the form of pharmacotherapies or other behavioral interventions. Further, it is important to note that a long-standing scientific principle for treatment development across therapeutic area is that a treatment works when it is in place and does not work when taken away. This is often associated with predictable and safe treatment effects that can be readily applied in the real world. However, long-term behavior change with CM and virtually all other SUD therapies with a comparable evidence base is an area that remains in need of investigation.

29.8 Limitations

While we are strong proponents for the use of CM-based interventions, we are also realistic. As of yet, there is no silver bullet for the treatment of psychostimulant addiction, including CM. In our experience however, CM is a great treatment modality for initiating abstinence. While some have demonstrated encouraging long-term maintenance of abstinence post-CM-based treatment (e.g., [30]), a perception lingers that long-term effects are difficult to demonstrate. As discussed above, we believe that VBRT provides a mechanism for bringing consumers in contact with non-drug sources of reinforcement than can serve to maintain abstinence, but in our experience, this is not an automatic occurrence. Once individuals are treated for their addiction, they often find themselves right back in the same environment that occasioned their drug use in the first place. In this environment, the same pressures began to re-exert their influence and a risk of relapse is high. This brings us to our second limitation. We do not believe that CM should be a standalone intervention in most instances. Instead, we recommend pairing it with other evidence-based treatment. Drug abusers have complicated chaotic lives. They need help navigating affective, legal, and cognitive aspects of their addiction. While CM initiates abstinence and provides a sober client for the clinician to work with, it does nothing to inherently address these other concerns. These need to be addressed in the therapeutic relationship in order to maximize the likelihood of maintaining the abstinence which CM is so effective at initiating.

29.9 Conclusion

An impressive array of basic science research supports the notion that drugs of abuse serve as potent reinforcers. Further, the hallmark of successful drug abuse treatment is the diminution of the drug's reinforcing efficacy. CM is a very effective means for accomplishing this, especially in the treatment of psychostimulant addictions. Different types of CM appear to be generally effective and when delivered with high fidelity offer the clinician and the consumer perhaps their best chance for breaking the pernicious cycle of addiction.

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Group Therapy for Substance Use Disorders

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R. Kathryn McHugh, Jungjin Kim,
Sara Park Perrins, and Roger D. Weiss

Contents

Abstract

Group therapy is the predominant type of behavioral therapy offered in substance use disorder treatment settings. This chapter provides an overview of the research literature on the efficacy of group therapy for substance use disorders and discusses research challenges and important future directions in the study of this topic. Research on the efficacy of group therapy for substance use disorders has generally found that group therapy is associated with superior outcomes compared to no treatment or treatment-as-usual. Studies examining the combination of group therapy with other forms of treatment, such as pharmacotherapy, have been mixed, with some studies finding additive benefits and others finding no benefit. However, group therapy appears to be

R. K. McHugh (✉) · J. Kim · R. D. Weiss
Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA

Department of Psychiatry, Harvard Medical School, Boston, MA, USA
e-mail: kmchugh@mclean.harvard.edu

S. P. Perrins
School of Environmental and Forest Sciences, University of Washington, Seattle, WA, USA

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equally as effective as individual therapy and may offer cost benefits relative to individual treatment. Group therapy for co-occurring substance use disorders and other psychiatric disorders, such as bipolar disorder and post-traumatic stress disorder, is associated with benefits for both disorders. Due to methodological and logistical challenges of conducting research on group therapy, this treatment modality remains understudied compared to individual therapy. Additional research is needed to identify the most effective types of group therapy and its optimal delivery method, either alone or in combination with other therapies.

Keywords

Group therapy · Substance use disorders · Co-occurring disorders · Cognitive-behavioral therapy

30.1 Introduction

Group therapy for substance use disorders (SUDs) is a treatment modality that entails the presence of at least two independent (i.e., not related) patients and a therapist who conducts meetings with the goal of eliminating or reducing substance use or SUD symptoms [1]. Group therapy formats can emphasize the interactions among members and the therapist (process or supportive therapy groups), the acquisition of information and skills (psychoeducational or behavioral therapy groups), or both. The content of group therapy also varies and might include components such as psychoeducation, cognitive-behavioral or motivational interventions, "check-ins" about substance use and other symptoms, encouragement to attend 12-step or other mutual-help groups, relational interventions, skills training, and contingency management, among others.

The majority of SUD treatment programs offer group therapy (more than 94%) [2] and for many programs group therapy is their predominant focus. The predominance of group therapy in these settings may be attributable—at least in part—to the potential cost savings of a group rather than an individual approach. Cost analyses have found that group therapy is associated with substantially less therapist time per patient compared to individual therapy [3] and that it has both the lowest cost and best cost-effectiveness ratio of psychosocial treatment approaches [4, 5]. In addition, patients are generally satisfied with group therapy as indicated by similar (if not superior) retention rates compared to individual therapy and strong self-ratings of treatment satisfaction [3]. Studies of patient preference for group versus individual therapy are few; however, group therapy has been shown to be preferred over individual therapy by patients [6] and clinicians alike [7]. Thus, group therapy appears to be a highly acceptable and cost-effective approach to treating SUDs.

Despite its widespread use in the treatment of SUDs, group therapy has been studied far less extensively than individual therapy. In this review, we characterize the research on group therapy for patients with SUDs, with a focus on randomized controlled trials. We will limit our definition of group therapy to treatments that focus on substance use or associated symptoms, and not on treatments targeted specifically to other symptoms or co-occurring disorders (e.g., group cognitive-behavioral therapy (CBT) for depression in patients with SUDs). Where possible, we attempt to characterize the nature of the group therapy approach from content (e.g., cognitive-behavioral, psychoeducational), composition (e.g., targeted substance, single or mixed gender, dual diagnosis), and timing (e.g., acute care, aftercare) perspectives. We conclude with a commentary on limitations and challenges of conducting research on group therapy and provide an integration of findings from the extant literature.

30.2 Is Group Therapy Effective for the Treatment of SUDs?

Several studies have attempted to answer the basic question of whether group therapy is effective for the treatment of SUDs. These studies

either compare treatment-as-usual (usual care at a facility) to treatment-as-usual plus group therapy, or group therapy to no group therapy.

30.2.1 Comparing Group Therapy to Treatment-As-Usual or No Group Therapy

Studies of the effect of group therapy on SUD outcomes, in general, have suggested that group therapy is effective in reducing substance use and associated impairment. Stephens and colleagues [8] randomly assigned 291 individuals seeking treatment for marijuana to 14 sessions of group cognitive-behavioral therapy (CBT), 2 sessions of individual motivational treatment, or a waitlist control. Participants in both active treatment groups reported significantly greater reductions in marijuana use and consequences of use throughout treatment and at the 16-month follow-up than the waitlist control group. Group therapy and brief individual therapy were not significantly different on any outcomes. In a similar study, two sessions of group therapy were significantly more effective for reducing nicotine use in undergraduate smokers compared to a waitlist control group [9].

However, not all studies have yielded positive results. In a study of interventions to prevent relapse among abstinent smokers following 3 months of treatment with group therapy and/or nicotine replacement therapy, participants were randomly assigned to receive one of two counseling groups or no group treatment [10]. Abstinence rates were not significantly different across conditions after 12 months (range from 50% to 58%), suggesting that adding group counseling as a relapse prevention strategy after acute treatment may not be beneficial for increasing abstinence rates. Shorey and colleagues [11] randomized 117 post-detoxification patients at a residential treatment facility to receive adjunctive 8-session mindfulness and acceptance group therapy or treatment-as-usual. Groups were compared on the primary outcomes of drug craving and mindfulness, and no significant benefits of the group therapy relative to treatment-as-usual were observed.

30.2.2 Adding Group Therapy to Pharmacotherapy

Because pharmacotherapy is the first-line treatment for certain SUDs (e.g., opioid and nicotine use disorders), several trials have tested whether adding group therapy to medication can enhance outcomes.

A trial of adding 12 sessions of group CBT to the opioid antagonist naltrexone for opioid-dependent individuals found no difference between those who received group therapy and those who received naltrexone alone [12]. However, it is important to note in this study that fewer than 10% of the group therapy condition participants attended all group sessions. Moreover, participants in both conditions were permitted to engage in additional psychotherapy (including individual), with more than 85% of participants electing to do so. Thus, it is unclear whether the results reflect a failure of group therapy, an under-dosing of group therapy, or an effect of adjunctive treatment that was received by both groups (e.g., individual therapy).

Luthar and colleagues [13, 14] conducted two studies examining a relational psychotherapy group for mothers dependent on heroin. This relational intervention used a supportive approach focused on enhancing women's functioning and parenting. A study comparing this approach to methadone maintenance treatment as usual (including group counseling and case management) in 61 women found modest benefits of relational therapy for some parenting measures (e.g., risk of child maltreatment, affective interactions), but not others (e.g., limit setting, instrumental behaviors) [13]. Modest benefits were seen for depressive symptoms at post-treatment; however, this was no longer significant at follow-up. The relational group was associated with greater opioid abstinence, but not cocaine abstinence. This treatment was then examined in a larger study of 127 women receiving methadone maintenance compared to methadone maintenance plus a recovery training group therapy focused on psychoeducation and skills training [14]. Although the relational therapy was associated with some benefits at post-treatment, many

of these benefits were reversed over a 6-month follow-up, with the comparison condition associated with better functional and child maltreatment outcomes.

Nyamathi et al. [15, 16] randomized 256 methadone-maintained adults who also used alcohol into (1) motivational interviewing (MI), delivered in group sessions, (2) motivational interviewing delivered individually, or (3) a nurse-led hepatitis health promotion group counseling. The nurse-led hepatitis health promotion counseling consisted of three 60-minute interactive psychoeducational groups focused on ways to promote liver health-promoting behaviors, including limiting alcohol and drug use. The motivational interviewing (MI) sessions were also three 60-minute sessions, delivered either individually or in a group format by MI-trained specialists. Self-reported alcohol use did not differ among the treatment groups, but the MI interventions—both group and individual—significantly reduced drug use, as measured by a 30-day recall, when compared to the nurse-led group counseling.

A qualitative literature review of studies of group therapy added to buprenorphine maintenance for opioid use disorder found that most studies in this area were not randomized trials (e.g., naturalistic studies), limiting the ability to draw conclusions about the efficacy of group therapy in this population [17]. Likewise, studies have often utilized very modest sample sizes (e.g., $N = 30$) [18], further complicating the ability to clearly interpret the effectiveness of group therapy for opioid use disorder.

Studies of the addition of group therapy to medication for nicotine dependence have also yielded mixed results. In a study of 154 nicotine-dependent women randomized to receive combinations of bupropion or placebo along with either cognitive-behavioral or supportive group therapy, a complex and mixed set of results emerged [19]. Specifically, CBT resulted in significantly higher abstinence rates than supportive therapy among those taking bupropion. However, supportive therapy was associated with superior outcomes among participants receiving placebo. Moreover, the combination of bupropion and CBT did not result in better abstinence rates compared to either placebo condition [19].

A study by Smith and colleagues [20] randomized 677 smokers following a brief initial treatment (nicotine replacement therapy and 1 session of individual counseling) to 6 sessions of cognitive-behavioral group therapy, a motivational enhancement/supportive group therapy, or no group therapy; all participants also continued to receive nicotine replacement therapy. There were no significant differences among the three treatment conditions in terms of self-reported cigarette use; however, smokers who had not achieved abstinence during the initial treatment period had better outcomes in the motivational/supportive treatment relative to the cognitive-behavioral or no group conditions.

Overall, group therapy for SUDs appears to be superior to either waitlist or no treatment. Studies examining group therapy as an aftercare strategy or as added to pharmacotherapy are more mixed. In these studies, results imply that the effects of treatment may vary based on the subgroups (e.g., adding group therapy as aftercare may be effective for initial treatment non-responders) [20]. Additionally, mixed patterns of results regarding combination group therapy with pharmacotherapy imply that certain therapies may better complement certain medications; however, more studies are needed to understand whether such interactions exist and can be used to maximize outcomes.

30.3 Is Group Therapy as Good as Individual Therapy?

Several studies have tested whether therapy is more effective when delivered in a group or individual format. The largest well-controlled study of this association was conducted by Sobell and colleagues [3] in a sample of 264 individuals with "non-severe" alcohol and drug use problems (those with a history of severe dependence were excluded). Participants were randomly assigned to four sessions of a cognitive-behavioral motivational intervention in a group or individual format. Participants experienced significant

reductions in self-reported alcohol and drug use and consequences of substance use. Results also indicated no differences in substance use outcomes for individual versus group administration for either alcohol or drug use and no differences in treatment retention.

In another study of group versus individual delivery of motivational therapy, John and colleagues [21] randomized 343 alcohol-dependent inpatients in German psychiatric hospitals to receive either 3 sessions of individual therapy or 9 sessions of group therapy for enhancing motivation for alcohol abstinence following detoxification. Those in the group therapy condition reported more self-help group attendance; however, there were no differences in other forms of treatment-seeking and overall service utilization between groups. There were also no differences in alcohol outcomes between these groups, with fewer than 30% in each group reporting abstinence at 6 months after detoxification.

Studies comparing individual and group cognitive-behavioral therapy have yielded similar results. A study of the use of 9 weeks (12 sessions) of cognitive-behavioral relapse prevention in group or individual format for 47 cocaine-dependent patients following inpatient treatment found similar outcomes for both groups over time on rates of abstinence as well as drug-related problems and measures of functioning [22]. By the end of treatment, fewer than 50% of both groups had remained abstinent, although gains in functioning and impairment were sustained over 24 weeks of follow-up; at the final assessment point, the average days of cocaine use in the previous month was low (2 days in the individual therapy condition; less than 1 day in the group therapy condition).

A similar study also compared individual to group relapse prevention as part of an aftercare program for 132 patients with alcohol and drug dependence [23]. Patients received 12 weekly sessions of either 45–60 minutes individual or 60–90 minutes group therapy. Group and individual therapies had similar outcomes for treatment adherence and retention and self-reported alcohol and drug use. However, group therapy was associated with better social support at 12-month follow-up. A study conducted in Brazil randomized 155 patients with alcohol and/or drug dependence to receive 17 sessions of cognitive-behavioral therapy in either group or individual format [24]. This study also found no significant differences in session attendance or in self-reported alcohol or drug use outcomes between groups when controlling for baseline levels of use.

A Norwegian study tested 12 weeks of 90-minute women-only group therapy or 7 hours of individual delivery of a short-term therapy focusing on skill acquisition toward individualized treatment goals (i.e., abstinence or harm reduction) [25]. Study participants who responded to advertisements and reported "alcohol problems" were randomized to one of these conditions and followed for 21 months. Although there was a higher rate of abstinence among women in individual therapy at the 3-month follow-up, there were no differences between groups at any subsequent time throughout the follow-up period. At the end of 21 months, almost 70% had reduced their alcohol consumption from pretreatment levels and half of the total sample reduced alcohol use by at least 50%.

In a more recent study [26], 155 women with alcohol use disorder were randomly assigned to 12 sessions of a manual-based women-only cognitive-behavioral-based group therapy or individual therapy. Both groups had a significant reduction in the percentage of drinking days and heavy drinking days, which was maintained at the 12-month follow-up. There were no significant differences in outcomes between the group and individual conditions. A subsequent cost-effectiveness analysis of this study showed greater cost-effectiveness for the group format [5].

Although relatively few studies have specifically tested individual versus group therapies using the same group content, the available research very clearly suggests that individual and group therapies are relatively equivalent in terms of both retention and clinical outcomes. Thus, it seems that high-quality treatment can be administered as effectively in group as in individually delivered formats.

30.4 What Types of Group Therapy Are Most Effective?

The majority of studies examining group therapy for SUDs have focused on comparing two or more types of group therapy that vary in terms of content or approach. For example, several studies have compared skills training to other group therapies and have yielded mixed results. Eriksen et al. [27] randomized 24 alcohol-dependent participants to 8 sessions of social skills training or counseling. The social skills training group reported fewer drinking days, drank less alcohol overall, and had better employment outcomes. A comparison of coping skills and interactional (interpersonal) groups for alcohol use disorder found no overall differences between the conditions in terms of alcohol use; however, individuals rating high on psychopathy had better outcomes with the coping skills group and those low on psychopathy had better outcomes in the interactional group, both following treatment [28] and a 2-year follow-up [29]. A later study by this group randomized 250 alcohol-dependent patients to either a random treatment assignment or matched treatment assignment based on the level of psychopathy [28]. Results of this study were mixed, with higher rates of abstinence in the randomized condition, but fewer alcohol-related consequences in the matched condition.

Several studies have compared cognitive-behavioral therapies to other therapies or control conditions. Kaminer et al. [30] randomized 88 adolescents presenting for outpatient substance abuse treatment to receive either cognitive-behavioral or psychoeducational group therapy. Results suggested an early benefit for cognitive-behavioral therapy; however, this was moderated by gender and age (with younger males responding better to cognitive-behavioral therapy) and the benefits were not maintained at 6-month follow-up. Both groups exhibited similar changes in substance use and functioning over time [30].

Similarly, mixed results were found by Pomerleau et al. [31] in a study of 32 alcohol-dependent men comparing behavioral therapy to psychodynamic group therapy. Results indicated better retention and less alcohol use in the behavioral therapy condition (consisting of several behavioral interventions, such as stimulus control and shaping), but higher rates of abstinence among completers of the psychodynamic therapy. A later study of male patients diagnosed with alcohol dependence in a Veterans Administration hospital found no differences between cognitive-behavioral and interpersonal therapies in alcohol use outcomes [32]. A study comparing 6 weeks of 12-step counseling (usual care) to behavioral skills training therapy, transactional analysis therapy, or their combination found that all conditions were associated with superior outcomes compared to transactional analysis alone [33].

A comparison of 6 sessions of cognitive-behavioral group therapy for smoking cessation compared to a health education control group plus nicotine replacement therapy in a sample of 154 African American smokers found greater rates of abstinence (past week) among those in the cognitive-behavioral therapy condition through 6 months of follow-up, with 31% versus 14% of participants abstinent at the end of follow-up [34].

Telch et al. [35] compared supportive therapy, behavioral therapy (covert sensitization), and a control therapy in 28 alcohol-dependent patients in an outpatient setting. Although those in the supportive therapy reported lower daily drinking, there were no differences among groups on alcohol craving or randomly collected blood-alcohol levels across the three conditions.

Mindfulness-based interventions are increasingly utilized in SUD treatment settings, and group therapy is no exception. Bowen and colleagues [36] randomized 286 patients who recently completed residential or intensive outpatient treatment for SUD into 8 weeks of a mindfulness-based relapse prevention group, a cognitive-behavioral relapse prevention group, or treatment-as-usual (involving psychoeducation and 12-step facilitation). Those assigned to mindfulness-based relapse prevention and cognitive-behavioral relapse prevention had significantly reduced risk of relapse to substance use or heavy drinking when compared to treatment-as-usual. The cognitive-behavioral group therapy

outperformed mindfulness-based group therapy with regard to time to first drug use, but the mindfulness-based group had significantly fewer days of substance use and heavy drinking compared to both cognitive-behavioral group and treatment-as-usual at the 12-month follow-up.

Little research has compared group therapy to family therapy; however, a comparison of a process group therapy, family therapy, and family education for adolescents with SUDs suggested that family therapy was most effective in achieving drug abstinence [37].

Couples therapy may be the only setting wherein a group format has been shown yield worse substance-related outcomes than individual (i.e., single-couple). O'Farrell et al. [38] randomized 101 patients with alcohol dependence and their partners (without SUD) to either group behavioral couples therapy or the standard conjoint behavioral couples therapy. Substance use and relational outcomes were significantly worse for the group therapy cohort, suggesting that the standard one-couple therapy is superior to a multi-couple group format.

Overall, results comparing types of group therapy have been mostly inconclusive. Moreover, given dramatic variability across studies, it is difficult to make any generalizations based on the existing literature. Several studies have suggested that more skills-based therapies (e.g., cognitive-behavioral therapy) outperform less structured therapies, although this has not been consistently replicated, with other studies suggesting similar outcomes for other group therapy types. Several studies have suggested that there may be key moderators of treatment response (e.g., psychopathy, age); however, more research is needed to better understand what works best for whom. Accordingly, at this time, more well-controlled studies are needed to determine what types of group therapy are most effective.

30.5 Comparing Group Therapies for Co-Occurring Disorders

Other psychiatric disorders commonly co-occur with SUDs [39, 40]. Accordingly, numerous studies of group therapy for SUDs have examined therapies targeted to both the SUD and co-occurring psychiatric disorders.

Weiss et al. [41] compared usual care to usual care plus 12–20 sessions of an integrated group therapy for SUDs and bipolar disorder in a sample of 45 participants. Results indicated that group therapy was associated with significantly lower SUD severity, more months abstinent, and longer duration of abstinence relative to usual care alone. In a subsequent study, 62 outpatients with co-occurring bipolar disorder and substance dependence were randomly assigned to 20 sessions of either the integrated treatment or group drug counseling [42]. Patients in the integrated group therapy had fewer days of substance use following treatment and throughout 3 months of follow-up; however, mood outcomes were similar between groups. Weiss and colleagues [42] then tested the implementation of a 12-session version of the treatment with drug counselors without previous training in cognitive-behavioral therapy. Sixty-one participants were randomized to the integrated treatment or group counseling and results indicated better outcomes for both substance (e.g., likelihood of abstinence) and mood symptoms (e.g., greater reduction in risk for a mood episode) in the integrated treatment group.

In a study comparing dialectical behavioral therapy (DBT), which included a group therapy component, to treatment-as-usual for 28 women with co-occurring borderline personality disorder and substance dependence, there was significantly greater treatment adherence, more days abstinent, and more negative urine screens in the DBT group [43]. These findings suggesting the benefits of DBT were replicated in women with heroin dependence when compared to individual therapy [44].

In a study conducted in Australia, James et al. [45] randomized 63 participants with co-occurring alcohol or drug use and a psychotic disorder to receive either usual care and 1 session of substance use education or 6 sessions of an integrated treatment for both disorders. The integrated dual disorder treatment group was associated with significantly greater improvement in psychiatric symptoms, substance use, and SUD severity. In a similar study, Bellack et al. [46] ran-

domized 129 outpatients with a diagnosis of drug dependence and serious mental illness (psychotic or major affective disorder) to receive an integrated behavioral treatment (Behavioral Treatment for Substance Abuse in Severe and Persistent Mental Illness) or supportive group discussion twice weekly for 6 months. Results indicated that the integrated treatment was associated with more negative urine screens as well as better treatment retention and functional outcomes (e.g., quality of life).

Results for co-occurring depression and anxiety disorders have been more mixed. Lydecker and colleagues [47] compared an integrated cognitive-behavioral therapy for co-occurring depression and SUDs to 12-step facilitation in a sample of 206 veterans with a current substance dependence diagnosis and a lifetime diagnosis of major depressive disorder. Both treatments were associated with significant improvements in both depression and substance use outcomes; however, there was evidence for better maintenance of substance use outcome gains in the integrated treatment group.

Studies comparing Seeking Safety, an integrated treatment for co-occurring SUDs and posttraumatic stress disorder, to usual care or alternative group treatments have found both positive results [48] and mixed results [49]. In a large trial of Seeking Safety, Hien et al. [50] randomized 353 women with posttraumatic stress disorder symptoms and a diagnosis of a drug or alcohol use disorder to receive either 12 sessions of Seeking Safety or a comparison health education treatment. Results indicated significant improvement in posttraumatic stress disorder symptoms in both groups with no differences between groups and no significant effects of treatment on either alcohol or drug use outcomes. A subsequent secondary analysis of this study showed that posttraumatic stress disorder symptoms in those in the Seeking Safety group displayed more rapid improvement than the comparison group, which was, in turn, associated with reduction in alcohol and cocaine use [51].

Intimate partner violence frequently co-occurs with SUDs. Easton et al. [52] examined whether group therapy could improve outcome in this population. They randomized 85 men with alcohol dependence and a history of domestic violence offense into either a 12-week CBT-based substance use and domestic violence group or a 12-step facilitation group. The substance use and domestic violence group outperformed the 12-step facilitation group on alcohol use outcomes, and this group trended toward less frequent physical violence over time in comparison to the 12-step group.

Group therapy targeting co-occurring SUDs and other disorders have been successful in some cases (e.g., bipolar disorder and psychotic disorders), with more mixed results for anxiety and depressive disorders. Nonetheless, integrated group therapies are promising for the reduction in symptoms of both SUDs and co-occurring disorders and are an important area for further study.

30.6 How Can We Maximize Outcomes in Group Therapy?

Because the evidence generally supports the effectiveness of group therapy for SUDs, recent research has begun to examine ways to maximize its effectiveness. Several studies have tested ways to enhance group therapy by adding adjunctive interventions or manipulating group factors.

30.6.1 Adjunctive Treatments

Contingency management involves providing patients with reinforcers (incentives such as money or vouchers) for engaging in beneficial behaviors, such as providing negative urine drug screens or attending treatment sessions. Several studies have examined the addition of contingency management to group therapy to enhance attendance. Petry et al. [53] examined the addition of a contingency management group to standard outpatient care (including group counseling and monitoring with urine toxicology screens) in community-based outpatient substance abuse treatment clinics. The addition of contingency management was associated with better program attendance (including more days of attendance

and longer duration in treatment) and longer duration of drug abstinence. Other studies have similarly found benefits of adding incentives for attending group sessions [54, 55], although one study found only modest effects for attendance incentives [56].

Santa Ana et al. [57] randomized 101 dually diagnosed individuals from a detoxification unit of psychiatric hospital to receive 2 sessions of either a motivational enhancement group therapy or a group therapy control condition in addition to standard care, to enhance adherence to aftercare. Results indicated that group motivational enhancement resulted in more aftercare sessions attended and fewer drinking days and heavy drinking days.

Studies examining the addition of adjunctive individual therapy to group therapy suggest that the benefits of this approach are modest, at best. In a large study of behavioral therapies for cocaine dependence, 487 individuals were randomized to 1 of 4 treatments, including 24 sessions of group counseling alone, or in combination with 36 sessions of 1 of 3 individual therapies: cognitive therapy, supportive-expressive psychodynamic therapy, or 12-step oriented drug counseling [58]. The best outcomes on substance use were seen for the group drug counseling plus individual drug counseling intervention, followed by group drug counseling alone [59]. However, there were no differences among conditions on other functional outcomes (e.g., interpersonal functioning). Thus, the addition of individual drug counseling, and not other individual therapies, was associated with the enhancement of some group therapy outcomes. Another study examined group counseling compared to group counseling plus individual relapse prevention therapy for cocaine dependence [60]. Results at a 6-month follow-up indicated greater likelihood of cocaine abstinence in group therapy alone, but fewer days of cocaine use among those who were not abstinent in the group plus individual therapy condition.

Technology-based interventions for substance use disorders is a topic of emerging interest [61]. In a large, multisite trial, 507 substance-dependent patients entering treatment were randomized into either 12 weeks of treatment-as-usual (composed of individual and group therapies) or treatment-as-usual with adjunctive internet-based contingency management and community reinforcement approach modules [62]. The group receiving adjunctive treatment had a lower dropout rate and a higher abstinence rate than the treatment-as-usual group.

30.6.2 Intensity and Group Composition

Coviello et al. [63] randomized 94 patients with cocaine use disorder to group therapy programs of varying intensities over a 4-week treatment program, including either 6 hours of treatment (4 of which were group) or 12 hours of treatment (7 of which were group) per week [63]. There were no significant differences between study cohorts in terms of severity of substance use problems or other functional outcomes; on average, patients in both conditions improved on these measures.

Several studies have examined gender-specific group therapy for SUDs [64–66]. Greenfield et al. [66] compared a women-only relapse prevention group therapy, the Women's Recovery Group (WRG), to mixed-gender Group Drug Counseling. Results demonstrated higher satisfaction among women in the Women's Recovery Group and similar drug use outcomes between groups. The WRG also appeared to have better alcohol use outcomes and better maintenance of gains 6 months following treatment. Women in the WRG provided more frequent affiliative statements [67] and women in groups with high levels of affiliative statements had better substance use outcomes, particularly in the WRG condition [68]. Moreover, the WRG seemed to have particularly beneficial effects on substance use outcomes for women with high psychiatric severity [69].

Several considerations may be valuable in attempting to enhance group therapy outcomes. First, adding incentives for attendance appears to enhance retention, thereby ensuring a higher "dose" of therapy. Technology-based interventions have the potential to improve access to

incentive-based treatments. Second, treatment targeted to a population of interest (e.g., women) may yield added benefits relative to more general group therapy. However, studies of the addition of individual to group therapy remain somewhat inconclusive and require more research. Results to date suggest that the type of individual therapy added to group therapy may be important to determining outcomes, and that those who are not able to achieve abstinence in group therapy alone may benefit from individual therapy. Nonetheless, additional research is needed to better understand the potential benefits of combining group and individual therapies.

30.7 Summary and Integration of the Literature

Although research on group therapy for SUDs varies widely in the types of group therapy, the substance of abuse, the population of interest, and timing and delivery of treatment, several trends emerge from the existing literature. In general, studies adding group treatment to minimal or no treatment suggest that group therapy is associated with improved substance use and often also functional outcomes [8, 41]. Although not all studies have found evidence for this effect [10], studies predominantly support group therapy as an effective intervention for SUDs. Results are mixed for adding group therapy to more powerful treatments (e.g., certain pharmacotherapies), with some evidence for no benefit of adding group therapy [12] and others finding benefits for some outcomes or in certain subgroups [13, 19]. However, many of these studies have been limited by either small sample sizes or uncontrolled designs (e.g., no limitations on additional adjunctive treatments); it thus remains unclear whether group therapy can achieve additive benefits when combined with pharmacotherapy.

Likewise, comparisons of different types of group therapy have generally yielded variable results. The relative effectiveness of different types of group treatment may depend on the fit of the intervention to the target population. For example, several integrated group therapies (such as those for SUD patients with co-occurring psychosis or bipolar disorder) have been associated with better outcomes than general alcohol and drug counseling therapies [42, 46]. Thus, the degree to which the treatment "fits" the population may be critical to understanding which treatment works best for whom.

Studies comparing individual to group-based delivery of substance abuse treatment (predominantly motivational enhancement or cognitive-behavioral therapy) have not found significant differences between individual and group therapies on substance use or other functional outcomes or differences in treatment retention. Although there is limited evidence for greater social functioning following group therapy [23] and greater patient preference for individual therapy [3], the evidence overall seems to support similar efficacy for group and individual therapies. Studies examining the mechanisms of these approaches may be of benefit to personalizing treatments for individuals. For example, group affiliation is a group-specific process that appears to confer outcome benefits [68].

Given the mixed findings on effectiveness, strategies to maximize outcomes are of particular importance. The addition of incentives for attending treatment appears to improve retention, maximizing the dose of therapy that patients receive. Because the findings examining the addition of individual therapy to group therapy have been mixed, contingency management (possibly using technology-based platforms) may be the best available strategy to enhance group therapy outcomes.

The mixed outcomes reported above are likely due in part to the heterogeneity of studies and populations, including the dosing (i.e., number of sessions) administered and the timing of when treatment occurs. In addition, many studies have used small sample sizes, which substantially limits the ability to identify differences in outcomes, particularly when comparing two active treatments, such as pharmacotherapy versus pharmacotherapy plus group therapy, or two types of group therapy. Thus, it is clear that more research is needed to understand what types of group therapy are most effective and under what conditions.

30.7.1 Why Is There So Little Research on Group Therapy for SUDs?

There are numerous study design considerations that are unique to conducting research on group therapy. Features such as open versus closed enrollment (i.e., whether all participants start treatment at the same time vs. "rolling" enrollment), group content/approach, and group composition (size and member characteristics) are all specific to group therapy research and are not relevant to studies of individual therapies. Additive designs may be of less concern than comparative designs for which conclusions about differential effects become more complicated. For example, comparing a single-gender group to a mixed-gender group might involve differences in both content (e.g., gender-specific group material) and composition (e.g., all women vs. men and women). Comparing individual to group therapy is even more challenging given the lack of clear guidance on equating the dosing of treatments. For example, if both group and individual sessions were 60 minutes, patients in individual therapy may gain a higher dose of therapy through more attention. However, if group sessions were longer, patients in group would be receiving more time in treatment. How to equivalently dose these types of therapy remains an open question (e.g., Is a 60-minute individual session equivalent to a 90-minute group session?).

The study of group therapy is also complicated by the number of potential variables that might contribute to the treatment's effectiveness. For example, active ingredients may include both the content of the group (e.g., the intervention components) and the format (i.e., group composition). Thus, studies can test one or both of these components, such as testing a group versus individual treatment or testing two types of group content or composition (e.g., single- vs. mixed-gender groups). Given the variability of studies conducted to date and—not surprisingly—variability in results, future well-designed research on group therapies will be important to improve treatments and to ultimately enhance outcomes for patients with SUDs.

30.7.2 Conclusion

Group therapy is the predominant method of delivery of psychosocial treatments for SUDs. This approach is associated with a lower cost than many other options as well as high satisfaction among patients. Evidence for the effectiveness of group therapy is mixed, and interpretation of the literature is limited by the heterogeneity of studies and the absence of many large, well-controlled studies. Nonetheless, as a whole, group therapy appears to be an effective treatment for a range of SUDs, particularly when the treatment is specific and well defined. Group treatment may be a particularly effective option for those with co-occurring psychiatric and substance use disorders. Studies suggest that group therapy is generally as effective as individual therapy, although the specific types of group therapy associated with the best outcomes remain unclear.

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31 Couple and Family Therapy in Treatment of Alcoholism and Drug Abuse

Keith Klostermann and Timothy J. O'Farrell

Contents

Abstract

Historically, the prevailing wisdom in treating substance abuse was that it was a personal problem, best treated on an individual basis. However, the near myopic focus on individual-based treatment has slowly given way to a greater acknowledgment of the family's role in the development and maintenance of drug and alcohol misuse problems. Over the past four decades, the results of numerous studies have concluded that partner- and family-involved treatments produce better outcomes across several domains of functioning (e.g., reduced substance use, improved marital and family functioning) compared to individual-based interventions. The purpose of this chapter is to (a) discuss the impact of substance

K. Klostermann
Medaille College, Buffalo, NY, USA

T. J. O'Farrell (✉)
Harvard Medical School, Brockton, NY, USA
e-mail: timothy_ofarrell@hms.harvard.edu

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abuse on the family; (b) present the models, techniques, and principles of couples and family therapy that have been used with substance-abusing clients, their partners, and extended family members; (c) discuss the potential barriers to implementing partner- and family-involved approaches for substance use; and (d) explore future directions with respect to partner- and family-involved therapies for substance-abusing clients.

Keywords

Family · Treatment · Alcoholism · Drug abuse · Substance abuse

Historically, the prevailing wisdom in treating substance abuse was that it was a personal problem, best treated on an individual basis. This viewpoint characterized the thinking about treatment for much of the twentieth century [44]. However, the near myopic focus on individual-based treatment has slowly given way to a greater acknowledgment of the family's role in the development and maintenance of drug and alcohol misuse problems. Having an intimate partner with a substance use disorder creates stress and tension in the relationship and chaos in the family [29, 45] that may contribute to separation or divorce [1]. In response to the systemic implications of substance abuse, an increasing number of treatment providers are focusing on the individual and family as a way to reduce or eliminate substance abuse by one or more of its members.

Over the past four decades, the results of numerous studies have concluded that partner- and family-involved treatments produce better outcomes across several domains of functioning (e.g., reduced substance use, improved marital and family functioning) compared to individual-based interventions [60, 61]. Consequently, the Joint Commission on Accreditation of Health Care Organizations (JCAHO) standards for accrediting substance abuse treatment programs in the United States requires that an adult family member be included, at minimum, in the initial assessment phase of the treatment process [3].

The purpose of this chapter is to (a) discuss the impact of substance abuse on the family and describe the systemic principles that may aid in improving interactions among family members; (b) present the models, techniques, and principles of couples and family therapy that have been used with substance-abusing clients, their partners, and extended family members; (c) discuss the potential barriers to implementing partner- and family-involved approaches for substance use; and (d) explore possible future directions with respect to partner- and family-involved therapies with substance-abusing clients.

31.1 The Concept of Family

Given that societal norms and attitudes influence definitions of cultural constructs such as "family," coupled with the fact that cultures and beliefs are very dynamic, the definition of marriage and family continues to evolve. Consequently, family units may include the following configurations: (a) a traditional nuclear family in which members are cohabiting in the household; (b) a single-parent household; (c) a "blended" family resulting from divorce, separation, or remarriage; (d) lesbian or gay couples with or without custodial children; (e) a multigenerational household including grandparents, parents, and children; or (e) long-term cohabiting partners who are not romantically linked, but define themselves as a family [48]. Depending on the individual's conceptualization of family, coupled with his or her treatment needs, any of these configurations may be involved in the treatment process.

31.2 Co-dependence and Enabling

Originally developed by Alcoholics Anonymous (AA; [2]), the term co-dependency refers to help from family members, which either directly or indirectly supports the substance-abusing family member's addictive behaviors. Despite the often overwhelming stress and numerous relational complications resulting from the addicted family

member's behavior, the co-dependent individual becomes intertwined with the individual's addiction and behaves in ways that contribute to sustaining the problematic behavioral patterns [59].

Enabling, a hallmark of co-dependency, is defined as behaviors that perpetuate the substance use [38] and may include activities and behaviors that make it easier for the individual to continue drinking or using or to protect him or her from the resulting negative consequences (e.g., personal, social, financial).

31.3 The Relationship Between Substance Use and Family Maladjustment

The relationship between substance use and relationship problems is not unidirectional with one causing the other. Rather, the link between problematic drinking or drug use and relationship distress appears to be bidirectional in nature, with each influencing the other. On one hand, families in which a member abuses substances may experience high levels of relationship dissatisfaction and be characterized by instability, conflict, sexual dissatisfaction, or psychological distress. On the other hand, several studies have also found relationship dysfunction to be strongly linked with substance use (e.g., [17, 20, 40]). Thus, the relationship between substance use and relationship problems is reciprocal with each serving as a precursor to the other; in other words, these couples end up stuck in a vicious cycle that can be difficult to break [62].

Although the misuse of alcohol and other psychoactive substances by adults has serious consequences (personal, financial, social), the secondary negative effects on children living in these homes are equally destructive [31]. Stress and the associated negative impacts on children and adolescents in these families have been associated with a greater likelihood of adolescent substance use [5].

The strong interrelationship between substance use and family interaction suggests that the role of family in developing and maintaining the issue should, at minimum, be considered as part of any intervention. Simply stated, couple- and family-therapy approaches share two primary objectives: (a) harness the power of the family and/or dyadic system to positively support the patient's recovery efforts, and (b) alter unhealthy interaction patterns to create a family environment more conducive to the individual's long-term recovery efforts, thus replacing the vicious cycle with a more virtuous one.

31.4 Foundational Frameworks

In general, three major approaches to family treatment of substance misuse have evolved: (1) family disease model, (2) family systems theory, and (3) behavioral family theory [49]. The family disease model proposes that both the individual and his or her family members have a disease. More specifically, substance misuse is considered a disease, and family members are believed to suffer from co-dependency. Family systems theory views substance misuse as a symptom of overall family dysfunction [70]. The presence or absence of alcohol or drugs becomes the organizing principle in family interactions. From the family systems perspective, substance use represents an unhealthy attempt to manage difficulties, which over time become homeostatic and regulates family transactions. Behavioral family therapy models are heavily influenced by operant and social learning theories in their conceptualization of the substance user within the family context. Simply stated, behavioral approaches assume that family interactions serve to reinforce alcohol- and drug-using behavior. From this vantage, substance-using behavior is learned in the context of social interactions (e.g., observing peers, parents, role models in the media) and reinforced by contingencies in the individual's environment.

31.5 Couples Therapy

A conjoint approach that has received extensive empirical support for the treatment of alcoholism and substance abuse is Behavioral Couples Therapy (BCT; [16]), which has also been

referred to as Behavioral Marital Therapy and Learning Sobriety Together. During the last four decades, couples therapy for substance abuse has received extensive empirical scrutiny, with most research focusing on BCT. In general, these studies have compared BCT to some form of traditional individual-based treatment for substance abuse (e.g., coping skills therapy, 12-step facilitation). Findings from these studies have consistently found that participants who received BCT (a) experienced higher rates of abstinence and fewer drug- or alcohol-related problems (e.g., [18, 77, 78]), (b) have happier relationships [16], and (c) experienced a lower risk of relationship dissolution (e.g., separation, divorce; see [64]) compared to those in the individual treatment condition.

BCT is based on the assumption that substance use occurs in an interactional context, is maintained in part by interactions between the client and partner, and is changed most effectively by teaching partners individual coping skills and also by helping the couple change unhealthy interactions that serve to maintain or reinforce the problematic substance use patterns. Clients learn skills to help support abstinence and develop plans to support and maintain abstinence (i.e., continuing recovery plans); partners learn skills to enhance relationship functioning around the following domains: (1) caring behaviors, (2) communication, and (3) conflict resolution. Sessions are focused on reinforcing positive changes in client's behavior and decreasing behaviors that may trigger or reinforce drinking or drug use, and teaching (and rehearsing) new skills. The focus in BCT is twofold: (1) eliminate or decrease substance use, and (2) enhance relationship functioning.

Since the 1970s, the results of numerous studies have consistently revealed that involving the partner in treatment resulted in better outcomes for substance-misusing individuals and their families. Although BCT is a manualized treatment and the therapist is active and directive during treatment, it is also important to note that the therapist respects the clients' autonomy and need for self-determination [48]. Given the existing knowledge about the importance of client factors in relation to outcome [79], the optimal stance is one of collaboration in exploring each partner goals and their thoughts about the means to achieve them.

Traditionally, the substance-abusing patient and his or her partner are seen together in BCT, typically for 12–20 sessions over 4–6 months. In those cases in which the identified patient is unwilling to engage in treatment, unilateral family therapy (UFT) may be an effective alternative. In UFT, the therapist works exclusively with the non-substance using partner in helping to engage the identified client into treatment [15]. This approach is described in detail later in this chapter.

31.6 Family Therapy Approaches

Some of the more common family therapy approaches utilized with substance-abusing patients are now described including family prevention models, community reinforcement and family training (CRAFT), Johnson intervention, unilateral family therapy, behavioral contracting, multisystemic family therapy (MFT), network therapy, solution-focused therapy (SFT), Stanton's therapeutic techniques, and Wegscheider-Cruse's approach. Although many of these approaches share similarities, they differ in terms of emphasis on the specific level of recovery (i.e., attainment of abstinence, adjustment to abstinence, and long-term maintenance; [22]) and areas of emphasis.

In general, the goal of most family-focused prevention-interventions is to strengthen the family's role in the positive development of children in the hope of decreasing future substance misuse problems within these children as they grow into adulthood [9]. The emphasis on family prevention programs may include parent-child interactions, communication skill training, child management principles, and parent training. Effective parenting skills are essential in preventing the development of child substance abuse and may be enhanced with additional training on topics such as setting limits, praising appropriate behavior, using clear expectations, and adminis-

tering consistent (and appropriate) discipline [37]. Previous studies (e.g., [10, 11]) reveal parent training approaches are viable methods of preventing premature drug use among children.

Examples of successful family prevention/intervention models include the Focus on Families Project [4], Preparing for the Drug Free Years [21], Family Effectiveness Training [73], the Strengthening Families Program [39], and a universal prevention-intervention combining family and school programs [69]. The targeted children for these models range in age from 3 to 14 years.

In Community Reinforcement Training (CRT), changes in social reinforcement and contingencies are used to shape clients' behavior (e.g., [66]) in more positive ways with the goal of shifting the client's thinking to recognize abstinence as more rewarding than further substance misuse [54]. An offshoot of CRT, *Community Reinforcement and Family Training* (CRAFT; [67]) is an approach in which family members (e.g., spouses of substance abusers) are engaged in the individual's treatment process with the hope of increasing treatment compliance. As part of this process, family members are taught skills to use with the client including increasing motivation for change, improving communication, and safety skills. A more direct approach, the *Johnson Institute Intervention*, commonly referred to as the "intervention," involves training family members and significant others to confront the substance abuser, request that he or she seek treatment, and impose consequences for not seeking help [28]. The goal of this program is treatment engagement by the substance abuser. However, this approach has been widely debated and is controversial (on practical and ethical bases); moreover, there is limited evidence of effectiveness in engaging substance abusers into treatment [6]. Given the confrontational nature of this approach, coupled with the heterogeneity of substance abusers, this approach may not be a good fit for everyone.

In *Unilateral Family Therapy* (UFT; [74]), the therapist helps family members strengthen coping skills, improve family functioning, and create a family environment conducive to abstinence. Family members engage in a series of formal steps before considering the possibility of confronting the substance abuser about his or her drinking or drug use and seeking formal treatment. Thomas et al. [75] found that participation in UFT was associated with increased likelihood that substance-misusing individuals would enter treatment or reduce their drinking. Rather than trying to motivate the substance-abusing partner to seek help, Dittrich [12] developed a group treatment program for wives of treatment-resistant substance abusers aimed at helping partners deal with the emotional distress resulting from client's problematic substance misuse. Similar to the principles of Al-Anon, this approach suggests family members should detach from the substance abuser in a gentle and caring way, accept they are powerless to control the substance abuser, and seek support from the Al-Anon community.

Similar to other behavioral approaches, *Behavioral Contracting* [71] involves the use of a collaboratively developed contract between the therapist and the client in which the client agrees to engage in recovery-related activities and behaviors as part of the treatment process. The contract may be helpful in developing clear, behaviorally specific, positive, and achievable goals and include rewards for goal attainment and consequences for non-compliance with agreed-upon activities. The key to successful behavioral contracts is to make sure the goals are small and achievable; given the instability among substance-abusing clients and challenges to remaining abstinent, goals must be small enough to be felt "do-able" otherwise, clients can become easily overwhelmed with the recovery process [57].

Based on social–ecological theory, *Multisystemic Family Therapy* (MFT; [27]) aims to alter the client's environment in ways that are more conducive to prosocial behaviors by focusing on multiple systems including family and peer domains. Families learn skills to increase cohesion and improve structure within the system. The role of the therapist is to identify family strengths and highlight competence while collaboratively developing feasible and achievable

interventions. MFT is among the most heavily investigated family interventions [27].

Recognizing that the majority of change occurs in-between sessions and not within, *Network Therapy* [19] enlists the support of important family members and friends in the treatment process—not as clients, but as a support network capable of assisting the client during difficult times. The primary foci of treatment are twofold: attaining abstinence and relapse prevention. The client's network can serve as an important adjunct to office-based services and become an important resource and support during the recovery process.

Solution-Focused Therapy (SFT; [8]) is a strength-based approach in which clients are considered experts on their lives and are believed to possess the resources necessary for change. The role of the therapist is to identify and highlight client's strengths and resources and consider how they may be used in developing solutions to the presenting problem. Techniques such as identifying exceptions and the strategic use of compliments can be helpful in highlighting client's competence in similar areas. The therapist helps clients develop positive, small, concrete, and behaviorally descriptive goals and may use scaling questions as a way to identify next steps, assess progress, or measure a family member's level of commitment to the treatment process. The use of the miracle question is a creative way of identifying goals by asking clients to think about a future in which the presenting issue is less severe or non-existent. There is much debate about the usefulness of this approach with some believing the nearly exclusive focus on solutions rather than problems is too simplistic, while others believe the simplicity of the approach is what makes it so appealing to therapists and clients. Unfortunately, the empirical literature supporting the efficacy of this approach is less developed than some of the other models [65].

According to *Stanton's Therapeutic Techniques* [70], substance misuse is believed to result from a failed attempt at resolving a developmental milestone. The family tries to maintain homeostasis by indirectly reinforcing the substance-abusing behavior. According to Stanton, the primary goals for clients are (1) abstinence, (2) employment or attending school or a training program, and (3) independence. The therapist actively directs the course of treatment with the primary objective of altering problematic behavioral sequences and helping family members develop healthier boundaries. Thus, the therapist seeks to identify and disrupt the family's dysfunctional patterns in an effort to promote growth and behavioral change.

Wegscheider-Cruse's Theory [80] of family alcoholism proposes that family members take on various roles to maintain family balance and cope with the substance abuser's behavior. The *enabler* is the person emotionally closest to the client and may make excuses, protect the client from negative consequences, or take over the client's responsibilities. The enabler's behavior reinforces the client's problematic use. The *hero* is usually the oldest child in the family and outwardly appears to be well adjusted and successful, usually an overachiever. The *scapegoat* becomes the focal point for the family's problems and deflects attention away from the substance abuser. The lost child typically seeks to avoid trouble and blend into the background. This child's needs are often not met and his or her accomplishments typically go unnoticed. The *mascot* recognizes that something is wrong; however, it is convinced by other members within the system that things are fine. Thus, the role of the therapist is to create awareness of family roles and their impact on the substance-misusing patterns within the system. Similar to other approaches, treatment involves educating the family about substance misuses, challenging denial, and providing suggestions for help, which often includes self-help activities.

31.7 Family Treatments for Adolescent Substance Use Disorders

The bulk of clinical trials examining family treatments for substance abuse primarily examined

adult clients and the impact of children growing up in these homes. However, it is also important to discuss available family treatments for adolescents who struggle with alcohol or drug problems. Two specific family therapy approaches have been developed for use with substance-abusing adolescents: (a) Brief Strategic Family Therapy (BSFT), and (b) Multidimensional Family Therapy (MDFT).

Brief Strategic Family Therapy (BSFT; [72]) integrates elements of structural and strategic family therapy to treat adolescent substance abuse in a systemic context [26]. More specifically, BSFT focuses on the here-and-now, and is problem focused with the goal of creating awareness of unhealthy relational patterns that contribute to adolescent substance use. The BSFT therapist is active and directive and strives to replace unhealthy interaction patterns with healthier ways of relating as a family unit. There are three underlying assumptions of BSFT: (1) family members are interrelated with one's behavior impacting the entire system; (2) families engage in unhealthy interactional patterns that become part of the family routine, despite not working or being unhealthy; and (3) the therapy process is problem focused, structured, and goal driven [25].

Similar to BSFT, *Multidimensional Family Therapy* (MDFT; [42]) combines elements of strategic and structural family therapy to treat adolescent problem behavior and emotional concerns. MDFT focuses on enhancing adolescent and family motivation for treatment, strengthening relationships and improving communication within the family, and developing conflict-resolution skills for managing interparental conflict or parent-child conflicts [24]. Adolescents are taught to recognize unhealthy people/situations, which may contribute to lapse or relapse and how to avoid slipping into other unhealthy behaviors. The goal of MDFT is to strengthen important social systems within the adolescent's life that may serve as protective factors against substance abuse and other problematic behaviors [41].

31.8 Barriers to Couple and Family Therapy

There are several clinically significant barriers unique to family interventions with substance-abusing patients and their families. One common and important impediment to couples and family treatment with a substance-abusing member is partner violence. O'Farrell and Murphy [63] report approximately 40% of men admitted into substance abuse treatment have perpetrated some form of violence toward their partner in the year preceding treatment. In cases where there is a risk of severe violence (i.e., aggression that has the potential to result in serious injury or is life threatening), the immediate intervention goal is safety; in these situations, partner and family therapy is contra-indicated (e.g., [35]). For some families, there may be also legal restrictions (i.e., restraining orders, no contact orders) that preclude conjoint family sessions.

Another barrier involves the presence of more than one active substance-misusing family member within the family, particularly if these individuals have formed a drinking or drug use partnership of some type [33]. These dual-using family systems may support continued use versus abstinence since shared recreational activities typically involve substance use. Research on family-based approaches for these family configurations is lacking and it is often recommended that individual therapy be used prior to engaging family members in treatment, especially when there are discrepant levels of commitment between partners toward recovery. Another demonstrated barrier to family interventions to treat substance abuse is the existence of high levels of blame and rumination from family members (usually the partner) toward the client [36]. Interestingly, there are also important practical and logistical barriers to partner or family intervention; these include (a) geographical distances among family members or among family members and the treatment provider; (b) family members who are divorced, incarcerated, or otherwise separated; (c) coordination of family members' and treatment providers' schedules; and (d)

securing reimbursement for services delivered to multiple individuals in the context of formal treatment [32].

The simple fact is that couple and family approaches add a level of complexity to therapy—for clients, clinicians, and agencies [48]. Not only does the client have to agree to treatment, but also their partner must agree to attend and support their partner's recovery attempts, which for some may be difficult—especially when the partner does not see the systemic nature of the problem ("It's his problem—why do I have to go to therapy?"). Engaging and retaining clients in outpatient substance abuse treatment is challenging [14, 56, 68]. Although partner-involved substance abuse treatments are often shown to be more efficacious than individual treatments (e.g., [36]), they rely on the willingness of both partners to participate in treatment [30].

McCrady [46, 47] contends that a therapist's clinical experiences influence his or her beliefs about treatment and best practices. Couple and family treatment is more difficult than individual psychotherapy, which may explain why so many clinicians avoid involving significant others and family members in the treatment process. While the majority of clinicians (98%) conduct individual psychotherapy, only 49% work with couples and only 34% see families [58].

31.9 Future Directions

Despite recent advances in partner- and family-involved approaches for the treatment of alcoholism and drug abuse, there are several important gaps in both the research literature and clinical practice that reflect the next generation of research in this area. More specifically, the following four areas seem most pressing: (a) dissemination of evidence-based marital and family treatments to community-based treatment programs; (b) application of these approaches on specific populations; (c) examination of the mechanisms of action underlying the positive effects observed; and (d) exploring the use of partner- and family-involved models as part of a stepped care approach.

31.9.1 Dissemination

Despite often volumes of data supporting the effectiveness and efficacy of certain treatments or modalities, there is a discrepancy between the most commonly provided treatments in clinical practice and those with the strongest evidence for effectiveness [23, 53]. Although a number of couple and family approaches have demonstrated research support for their efficacy, very few have been widely adopted in community-based treatment. McGovern et al. [51] examined community addiction providers' (i.e., directors [n = 21] and clinicians [n = 89]) experiences, beliefs, and readiness to implement a variety of evidence-based practices. Results were mixed; providers reported more readiness to adopt 12-step facilitation, cognitive behavioral therapy, motivational interviewing, and relapse prevention, while less ready to implement contingency management, BCT, and pharmacotherapies. The investigators concluded that successful dissemination requires a clear rationale for the new service and leadership must demonstrate the relevance of the treatment to clinicians and staff, even if empirical support is already established. Other factors to consider include degree of difficulty in implementation, how closely (or not) the treatment is aligned with the therapist's preferred theoretical orientation or agency counseling approach, cost of providing treatment, and whether or not the treatment fills a perceived area of need for the clinic [34]. Each of these areas may serve as a potential barrier to successful dissemination of the treatment.

31.9.2 Specific Populations

Although the body of empirical literature supporting the use of couple and family therapy for substance abuse is substantial, it is critical to also recognize its limitations. Among these are the types of families that are typically the subject of such studies, which usually include largely White, male substance-abusing patients. Studies on the efficacy of marital and family therapy approaches for women with substance use disorders are far less common, although available evi-

dence does suggest that they are efficacious [50]. Even fewer studies have examined partner- and family-involved interventions with same-sex couples [35]. Future studies are needed to examine gender orientation–specific factors as well as non-gender orientation–specific factors that may increase substance misuse among gay and lesbian individuals.

Furthermore, a great deal of research has been conducted related to both family therapy and culture and ethnicity, but very little of this has appeared in the family therapy literature on substance abuse. This represents what is likely the most important gap in the extant empirical literature to date. Among major life experiences that must be accounted for when treating families in which a member has a problem with drinking or drug use is how factors such as acculturation and ethnic identity influence the treatment process.

31.9.3 Mechanisms of Action

We now have confidence that many treatments are effective [55], but despite the successful efforts of substance abuse treatment researchers to conduct rigorous clinical trials and spell out in treatment manuals what the treatments consist of, little research has actually investigated what the active ingredients of these treatments are [43]. In other words, what are the mechanisms of action that make certain partner- and family-involved approaches curative? If these factors are identified, then these approaches can be modified to optimize their efficiency to create enhanced interventions.

31.9.4 Partner- and Family-Involved Treatment in the Context of Stepped Care

Despite the demonstrated efficacy of manualized marital and family approaches, there are large individual differences in patient response to treatment. As noted by McKay [52], even for the most efficacious treatments, there are a certain number of people who do not respond to treatment; yet in an effort to tightly control the intervention, non-responding patients receive the same amount of manualized treatment as those who respond well. Research on standardized interventions to treat substance abuse disorders is beginning to shift away from a "one-size-fits-all" perspective and move toward adaptive interventions. Adaptive interventions, although standardized, call for different dosages of treatment to be employed strategically with patients and families across time. Given the heterogeneity in familial characteristics and response to treatment, future studies are needed to develop tailored interventions based on treatment algorithms that dictate treatment modifications triggered by the patient's initial response and changes in symptom severity. Thus, more flexible versions of marital and family treatments may be more easily disseminated to community providers and more palatable to patients receiving the intervention.

31.10 Conclusion

As has been well documented in scholarly journals and popular media, the emotional, economic, and societal toll of alcoholism and drug abuse is incalculable. The effects of substance use disorders affect not only the clients, but also those around them; in fact, those emotionally closest to the substance-abusing client often suffer the most. Over the past 40 years, the results of numerous studies have consistently supported the positive impact of involving supportive others and family in the client's treatment [7, 13, 76]. Therapists that do not include partners or family in the treatment process run the risk of not being helpful.

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Network Therapy

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Marc Galanter

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M. Galanter (✉)
Division of Alcoholism and Drug Abuse, Department of Psychiatry, NYU School of Medicine, New York, NY, USA
e-mail: marcgalanter@nyu.edu

Abstract

Office-based practice for the treatment of patients with substance use disorders is limited in important information obscured by a

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patient's denial of illness and lack of support for the patient in the face of potential relapse. This chapter provides a description of the rationale and technique for employing the support of family and close friends for the treatment of addictive disorders. This chapter provides clinical examples of how network therapy is applied, and research for validation of this approach, as well as a role for the use of Twelve-Step facilitation in conjunction with this approach.

Keywords

Addiction · Family therapy · Medication · Social support

32.1 Introduction

Psychotherapy for people dependent on alcohol and other drugs presents unique problems for the office-based practitioner. Among these are the ever-present vulnerability to relapse to substance use and high dropout rates. In order to address this problem, we can consider how engaging the input of people close to an addicted person can help in achieving a stable abstinence and deal with the vulnerability to dropout from treatment. To understand this option, it is first important to understand that certain conditioned drug-seeking behaviors may be extinguished if appropriate aversive stimuli are interposed after triggers to drug use are presented.

A drug user can become entangled in an interlocking web of self-perpetuating reinforcers that contribute to the persistence of drug abuse, despite compromising consequences, and the user's imperviousness to a traditional, psychodynamic psychotherapeutic approach does not necessarily take such conditioning factors into account. This is because neither the user nor the therapist is typically aware of their existence due to the unconscious nature of the conditioned response of drug-seeking. The therapist's attempt to alter the course of the stimulus–response sequence is therefore often not viable, even with the aid of a willing patient, as neither party is necessarily aware that a conditioned sequence is taking place.

Sufficient exploration, however, can reveal the relevant stimuli and their effect through conditioned sequences of drug-seeking behavior. An earlier publication described a technique for guided recall of relevant conditioned stimuli in a psychotherapeutic context, whereby the person with alcohol or substance use disorder may become aware of the sequence of circumstances that can precipitate relapse [16]. Once this is done, the patient's own distress at the course of the addictive process, generated by the patient's own motivation for escaping the addictive pattern, may be mobilized. This motivational distress then serves as an aversive stimulus. The implicit assumption behind this therapeutic approach is that the patient in question wants to alter his or her pattern of drug use and that the recognition of a particular stimulus as a conditioned component of addiction will then allow the patient, in effect, to initiate the extinction process. If a patient is committed to achieving abstinence from an addictive drug such as alcohol or cocaine but is in jeopardy of occasional slips, this cognitive labeling can facilitate consolidation of an abstinent adaptation.

As we shall see, the input of people close to the patient can help to reveal triggers to drugs use that may not be apparent to the patient. Such an approach is less valuable in the context of (a) a lack of motivation for abstinence, (b) fragile social supports, or (c) compulsive substance abuse unmanageable by the patient in the patient's usual social settings. Hospitalization or replacement therapy (e.g., methadone or buprenorphine) may be necessary in such cases, because ambulatory stabilization through psychotherapeutic support is often not feasible, even with the support of family and close peers. On the other hand, for willing patients, or ones whom family and friends have convinced to cooperate, the Network approach can be most valuable.

32.2 The Network Therapy Technique

This approach can be useful in addressing a broad range of addicted patients characterized by the following clinical hallmarks of addictive illness. When they initiate consumption of their addictive agent, be it alcohol, cocaine, opioids, or depressant drugs, they frequently cannot limit that consumption to a reasonable and predictable level; this phenomenon has been termed *loss of control* by clinicians who treat persons dependent on alcohol or drugs [26]. Second, they have consistently demonstrated relapse to the agent of abuse; that is, they have attempted to stop using the drug for varying periods of time but have returned to it, despite a specific intent to avoid it.

This treatment approach is not necessary for those with substance use disorder who can learn to set limits on their use of alcohol or drugs; their substance use may be treated as a behavioral symptom in a more traditional psychotherapeutic fashion. Nor is it directed at those patients for whom the addictive pattern is most unmanageable, such as addicted people with unusual destabilizing circumstances such as homelessness, severe character pathology, or psychosis. These patients may need special supportive care such as inpatient detoxification or long-term residential treatment.

32.2.1 Key Elements

Three key elements are integrated in the network therapy (NT) technique. The first is a cognitive–behavioral approach to relapse prevention, which has been considered valuable in addiction treatment [37]. Emphasis in this approach is placed on triggers to relapse and behavioral techniques for avoiding them, in preference to exploring underlying psychodynamic issues.

Second, support of the patient's natural social network is engaged in treatment. Peer support in AA has long been shown to be an effective vehicle for promoting abstinence, and the idea of the therapist's intervening with family and friends in starting treatment was employed in one of the early ambulatory techniques specific to addiction [27]. The involvement of spouses [33] has since been shown to be effective in enhancing the outcome of professional therapy.

Third, the orchestration of resources to provide community reinforcement suggests a more robust treatment intervention by providing a support for drug-free rehabilitation [4]. In this relation, Khantzian pointed to the "primary care therapist" as one who functions in direct coordinating and monitoring roles in order to combine psychotherapeutic and self-help elements [30]. It is this overall management role over circumstances outside as well as inside the office session that is presented to trainees, in order to maximize the effectiveness of the intervention.

32.3 CBT and Social Support

Cognitive–Behavioral Therapy This format for treatment has been shown to be effective for a wide variety of substance use disorders, including alcohol [38], marijuana [44], and cocaine dependence [7]. It is premised on the original findings by Wikler [48] on conditioning models of drug-seeking in heroin-addicted subjects.

The *cognitive–behavioral therapy* (CBT) approach is goal oriented and focuses on current circumstances in the patient's life. In network therapy, reference in both individual and conjoint sessions can be made to salient past experiences. CBT sessions are typically structured, so, for example, patients begin each Network session with a recounting of recent events directly relevant to their addiction and recovery. This is followed by active participation and interaction of therapist, patient, and Network members in response to the patient's report. CBT emphasizes psychoeducation in the context of relapse prevention, so that circumstances, thoughts, and interpersonal situations that have historically precipitated substance use are identified, and the patient (and Network members as well) are taught to anticipate where such triggers can precipitate substance use.

The process of guided recall, noted previously, is particularly important because it allows the therapist both individual sessions with the patient alone—and network sessions—in conjunction with Network members along with the patient—to guide the patient to recognize a sequence of conditioned stimuli (triggers) that play a role in drug-seeking. Such triggers may not initially be apparent to the patient or Network members, but with encouragement and prompting, can emerge over the course of an exploration of the circumstances that have led, either in the past, or in a recent "slip," to substance use.

Social Support This issue has been studied in a variety of data sets in relation to the recovery from substance use disorders. For example, in the federal Project MATCH, three modalities, Twelve-Step facilitation (TSF), motivational enhancement, and cognitive–behavioral approaches, were compared. In a secondary analysis of findings from this multisite study, it was found [50] that certain aspects of social support were most predictive of abstinence outcomes. Two social network characteristics that had a positive effect on outcome were the size of the supportive social network in the person's life, and the number of members who were abstainers (or recovering from alcohol use disorder). I have found that nonproblem drinking participants are important to a long-term clinical outcome. In a matter of fact, a large number of Network members, when their participation is effectively maintained over time, can counter a variety of circumstances that may undermine a patient's abstinence. In addition, they can provide varied aspects of support relative to the patient's experience in recovery. And indeed, they should be free of substance-related problems. Of interest in this context, it has been reported that men are more typically encouraged by their wives to seek help, whereas women are more often encouraged by mothers, siblings, and children [6].

Community Reinforcement Family involvement in substance abuse treatment has long been shown to be effective in improving outcome, and there are numerous approaches that make use of social network involvement in treatment, including Behavioral Couples Therapy [14], Marital Therapy [39], and the Community Reinforcement Approach [5, 36].

More specifically, the Community Reinforcement and Family Training (CRAFT) Program includes many aspects of treatment that are also employed in Network Therapy. The CRAFT approach was developed to encourage drinkers to enter therapy and reduce drinking, in part by eliciting support of concerned others as well as to enhance satisfaction with life among members of the patient's social network who were concerned about his or her drinking. As in Network Therapy, the CRAFT program includes a functional analysis of the patient's substance use, that is to say, understanding the substance use with respect to its antecedents and consequences. Like Network Therapy, it also serves to minimize reciprocal blaming and defensiveness among the concerned significant others, and to promote a patient's sobriety-oriented activities.

In one large trial in which concerned significant others were randomized to one of three conditions, a comparison was made between Al-Anon-facilitated therapy, an approach similar to the Johnson Institute interventions, and the CRAFT model [15]. The CRAFT intervention was more effective in engaging treatment-refusing people with alcohol use disorder as compared to the other two approaches. Similar positive findings were obtained in studies on CRAFT with illicit drug users [31, 35]. In another study, concerned significant others were successfully trained to apply a modified Johnson Intervention technique in the absence of a therapist, and this approach was found to be successful [32].

32.3.1 Initial Encounter: Starting a Social Network

The following approach is applicable, as appropriate, to patients with moderate to severe substance alcohol use disorder (F10.20) or similar severity of other substance use disorders [2]. It

can be applied in ASAM levels of care 1–4, as appropriate [34].

How does one go about developing NT? The patient should be asked to bring his or her spouse or a close friend to the first session. Patients with alcohol use disorder often dislike certain things they hear when they first come for treatment and may deny or rationalize, even if they have voluntarily sought help. Because of their denial of the problem, a significant other is essential to both history taking and implementing a viable treatment plan. A close relative or spouse can often cut through the denial in a way that an unfamiliar therapist cannot and can therefore be invaluable in setting a standard of realism in dealing with the addiction.

Some patients make clear that they wish to come to the initial session on their own. This is often associated with their desire to preserve the option of continued substance abuse and is born out of the fear that an alliance will be established independent of them to prevent this. Although a delay may be tolerated for a session or two, it should be stated unambiguously at the outset that effective treatment can be undertaken only on the basis of a therapeutic alliance built around the addiction issue that includes the support of significant others and that it is expected that a network of close friends and/or relatives will be brought in within a session or two at the most.

The weight of clinical experience supports the view that abstinence is the most practical goal to propose to the addicted person for his or her rehabilitation [23, 24]. For abstinence to be expected, however, the therapist should ensure the provision of necessary social supports for the patient. Let us consider how a long-term support network is initiated for this purpose, beginning with availability of the therapist, significant others, and a self-help group.

In the first place, the therapist should be available for consultation on the phone and should indicate to the patient that he or she wants to be called if problems arise. This makes the therapist's commitment clear and sets the tone for a "team effort." It begins to undercut one reason for relapse, the patient's sense of being on the patient's own if unable to manage the situation. The astute therapist, however, will assure that he or she does not spend excessive time on the telephone or in emergency sessions. The patient will therefore develop a support network that can handle the majority of problems involved in day-to-day assistance. This generally will leave the therapist to respond only to occasional questions of interpreting the terms of the understanding among himself or herself, the patient, and support network members. If there is a question about the ability of the patient and network to manage the period between the initial sessions, the first few scheduled sessions may be arranged at intervals of only 1–3 days. In any case, frequent appointments should be scheduled at the outset if a pharmacologic detoxification with benzodiazepines is indicated, so that the patient need never manage more than a few days' medication at a time.

What is most essential, however, is that the network be forged into a working group to provide necessary support for the patient between the initial sessions. Membership ranges from one to several persons close to the patient. Larger networks have been used by Speck [43] in treating schizophrenic patients. Contacts between network members at this stage typically include telephone calls (at the therapist's or patient's initiative), dinner arrangements, and social encounters and should be preplanned to a fair extent during the joint session. These encounters are most often undertaken at the time when alcohol or drug use is likely to occur. In planning together, however, it should be made clear to network members that relatively little unusual effort will be required for the long term, and that after the patient is stabilized, their participation will amount to little more than attendance at infrequent meetings with the patient and the therapist. This is reassuring to those network members who are unable to make a major time commitment to the patient as well as to those patients who do not want to be placed in a dependent position.

32.3.2 Defining the Network's Membership

Once the patient has come for an appointment, establishing a network is a task undertaken

with active collaboration of the patient and the therapist. The two, aided by those parties who join the network initially, must search for the right balance of members. The therapist must carefully promote the choice of appropriate network members, however, just as the platoon leader selects those who will go into combat. The network will be crucial in determining the balance of the therapy. This process is not without problems, and the therapist must think in a strategic fashion of the interactions that may take place among network members.

32.3.3 Defining the Network's Task

As conceived here, the therapist's relationship to the network is like that of a task-oriented team leader, rather than that of a family therapist oriented toward insight. The network is established to implement a straightforward task, that of aiding the therapist in sustaining the patient's abstinence. It must be directed with the same clarity of purpose that a task force is directed in any effective organization. Competing and alternative goals must be suppressed, or at least prevented from interfering with the primary task.

Unlike family members involved in traditional family therapy, network members are not led to expect symptom relief for themselves or self-realization. This prevents the development of competing goals for the network's meetings. It also assures the members protection from having their own motives scrutinized and thereby supports their continuing involvement without the threat of an assault on their psychological defenses. Because network members have—kindly—volunteered to participate, their motives must not be impugned. Their constructive behavior should be commended. It is useful to acknowledge appreciation for the contribution they are making to the therapy. There is always a counterproductive tendency on their part to minimize the value of their contribution. The network must, therefore, be structured as an effective working group with high morale.

32.3.4 Use of Pharmacotherapy in the Network Format

For the person with alcohol use disorder, disulfiram may be of marginal use in assuring abstinence when used in a traditional counseling context [15], but becomes much more valuable when carefully integrated into work with the patient and network, particularly when the drug is taken under observation. A similar circumstance applies to the use of oral naltrexone for stabilizing abstinence in an opioid-dependent person. In the case of alcohol, it is a good idea to use the initial telephone contact to engage the patient's agreement to abstain from alcohol for the day immediately prior to the first session. The therapist then has the option of prescribing or administering disulfiram at that time. For a patient who is earnest about seeking assistance for alcoholism, this is often not difficult, if some time is spent on the phone-making plans to avoid a drinking context during that period. If it is not feasible to undertake this on the phone, it may be addressed in the first session. Such planning with the patient almost always involves organizing time with significant others and therefore serves as a basis for developing the patient's support network.

The administration of disulfiram under observation is a treatment option that is easily adapted to work with social networks. A patient who takes disulfiram cannot drink; a patient who agrees to be observed by a responsible party while taking disulfiram will not miss his or her dose without the observer's knowing. This may take a measure of persuasion and, above all, the therapist's commitment that such an approach can be reasonable and helpful.

As noted previously, individual therapists traditionally have seen the addicted person as a patient with poor prognosis. This is largely because in the context of traditional psychotherapy, there are no behavioral controls to prevent the recurrence of drug use, and resources are not available for behavioral intervention if a recurrence takes place—which it usually does. A system of impediments to the emergence of relapse, resting heavily on the actual

or symbolic role of the network, must therefore be established. The therapist must have assistance in addressing any minor episode of drinking so that this ever-present problem does not lead to an unmanageable relapse or an unsuccessful termination of therapy.

32.3.5 Format for Medication Observation by the Network

1. Take the medication every morning in front of a network member.
2. Take the pill so that person can observe you swallowing them.
3. Have the observer write down the time of day the pills were taken on a list prepared by the therapist.
4. The observer brings the list in to the therapist's office at each network session.
5. The observer leaves a message on the therapist's answering machine on any day in which the patient had not taken the pills in a way that ingestion was not clearly observed.

32.3.6 Meeting Arrangements

At the outset of therapy, it is important to see the patient with the group on a weekly basis for at least the first month. Unstable circumstances demand more frequent contacts with the network. Sessions can be tapered off to biweekly and then to monthly intervals after a time.

To sustain the continuing commitment of the group, particularly that between the therapist and the network members, network sessions should be held every 3 months or so for the duration of the individual therapy. Once the patient has stabilized, the meetings tend less to address day-to-day issues. They may begin with the patient's recounting of the drug situation. Reflections on the patient's progress and goals, or sometimes on relations among the network members, then may be discussed. In any case, it is essential that network members contact the therapist if they are concerned about the patient's possible use of alcohol or drugs, and that the therapist contacts the network members if the therapist becomes concerned about a potential relapse.

32.3.7 Adapting Individual Therapy to the Network Treatment

As noted previously, network sessions are scheduled on a weekly basis at the outset of treatment. This is likely to compromise the number of individual contacts. Indeed, if sessions are held once a week, the patient may not be seen individually for a period of time. The patient may perceive this as a deprivation unless the individual therapy is presented as an opportunity for further growth predicated on achieving stable abstinence assured through work with the network.

When the individual therapy does begin, the traditional objectives of therapy must be arranged so as to accommodate the goals of the substance abuse treatment. For insight-oriented therapy, clarification of unconscious motivations is a primary objective; for supportive therapy, the bolstering of established constructive defenses is primary. In the therapeutic context that is described here, however, the following objectives are given precedence.

Of first importance is the need to address exposure to substances of abuse or exposure to cues that might precipitate alcohol or drug use [17]. Both patient and therapist should be sensitive to this matter and explore these situations as they arise. Second, a stable social context in an appropriate social environment—one conducive to abstinence with minimal disruption of life circumstances—should be supported. Considerations of minor disruptions in place of residence, friends, or job need not be a primary issue for the patient with character disorder or neurosis, but they cannot go untended here. For a considerable period of time, the person with substance use disorder is highly vulnerable to exacerbations of the disorder, and, in some respects, must be viewed with the considerable caution with which one treats the recently compensated person with psychosis.

Finally, after these priorities have been attended to, psychological conflicts that the

patient must resolve, relative to his or her own growth, are considered. As the therapy continues, these come to assume a more prominent role. In the earlier phases, they are likely to reflect directly issues associated with the previous drug use. Later, however, as the issue of addiction becomes less compelling from day to day, the context of the treatment increasingly will come to resemble the traditional psychotherapeutic context. Given the optimism generated by an initial victory over the addictive process, the patient will be in an excellent position to move forward in therapy with a positive view of his or her future.

32.4 Twelve-Step Facilitation (TSF)

In addition to the NT approach described here, TSF can be employed by the treating clinician. TSF is designed to promote involvement in AA by engaging a patient in participating in the fellowship's first three steps. It was developed for alcohol use disorder, but it can be employed for other substances, as well. (A full description of TSF is available at https://pubs.niaaa.nih.gov.) It can be combined in practice with group therapeutic approaches [13].

Over the course of treatment, which can supplement Network sessions, the patient is encouraged to participate in AA, and his or her progress can be shared with Network members. The patient is expected to attend AA meetings weekly and discuss his or her experience with the treating clinician.

Step 1 of Alcoholics Anonymous reads as follows:

> We Admitted We Were Powerless Over Alcohol—That Our Lives Had Become Unmanageable

This entails the acceptance of personal limitation, in this case, involving the loss of control over drinking. Although some individuals apparently achieve this acceptance via a single leap of faith, it is also possible to think of acceptance as a process involving a series of stages. This can begin with "I have a problem with alcohol," followed by "Alcohol (drinking) is gradually making my life more difficult and is causing problems for me," and "I have lost my ability to effectively control (limit) my use of alcohol."

This represents a statement of personal *limitation.* Accepting powerlessness over alcohol is much like having to accept any other personal limitation or handicap. Some people have a hard time relating to Step 1 as it is written. They can relate to it better if it is framed in terms of limitation.

Steps 2 and 3 are framed as such:

> Came to Believe That a Power Greater Than Ourselves Could Restore Us to Sanity.
>
> Made a Decision to Turn Our Will and Our Lives Over to the Care of God as We Understood Him.

Discussion with the patient focuses on issues like this: What does he or she believe in? Who are his or her heroes? What are his or her most cherished values? Of what religious background is the patient? Does he or she still practice? If not, when and why did he or she stop? What does the idea of "turning over" your will mean to patients? Has the patient ever followed someone else's advice, simply on the basis of trust and faith? If so, who and when? What about trusting the wisdom of AA based on faith? What resistance does the patient have to Turning It Over as opposed to "going it alone"?

32.4.1 General Approach

The clinician reviews with the patient on a weekly basis: What meetings were attended, and what were the patient's reactions to them? Reading: What did the patient read in the book, *Alcoholics Anonymous*, and what was his or her reaction?

Urges to drink are reviewed weekly: When and where? What did the patient do? How could the patient use AA to help with urges in the future?

It is emphasized that recovery comes only through active involvement in the 12-Step program as opposed to trying not to drink through solitary, white-knuckle determination or by simply attending but not participating in meetings. Attending meetings marks the start of establishing a new network of friends that will be critical to recovery. Patients are encouraged to get phone

numbers of people whom they can call. Merely going to meetings without participating in them is not the same thing as working the 12-Step program and is not likely to be helpful to recovering patients when they have strong urges to drink or when they have a slip.

32.5 Research on Network Therapy

Network therapy is included under the American Psychiatric Association (APA) Practice Guidelines [3] for substance use disorders as an approach to facilitating adherence to a treatment plan. The Substance Abuse and Mental Health Services Administration (SAMHSA) includes a description of NT in its National Registry of Evidence-based Program and Practices [42] and NT is listed as one of its Treatment Improvement Protocol TIP 39 Substance Abuse Treatment and Family Therapy approaches [9]. To date, five studies have demonstrated their effectiveness in treatment and training. Each addressed the technique's validation from a different perspective: a trial in office management; studies of its effectiveness in the training of psychiatric residents and of counselors who work with people with cocaine use disorder; an evaluation of acceptance of the network approach in an Internet technology transfer course and a trial evaluating the impact of NT relative to medication management in heroin-addicted persons inducted on to buprenorphine. In addition, NT components that have been adapted and combined with other psychosocial treatments to treat patients with opioid or alcohol dependence are described later.

32.5.1 An Office-Based Clinical Trial

A chart review was conducted on a series of 60 substance-dependent patients, with follow-up appointments scheduled through the period of treatment and up to 1 year thereafter [18]. For 27 patients, the primary drug of dependence was alcohol; for 23, it was cocaine; for 6, it was opioids; for 3, it was marijuana; and for 1, it was nicotine. In all but eight of the patients, networks were fully established. Of the 60 patients, 46 experienced full improvement (i.e., abstinence for at least 6 months) or major improvement (i.e., a marked decline in drug use to nonproblematic levels). The study demonstrated the viability of establishing networks and applying them in the practitioner's treatment setting. It also served as a basis for the ensuing developmental research supported by the National Institute on Drug Abuse.

32.5.2 Treatment by Psychiatry Residents

We developed and implemented a network therapy training sequence in the New York University psychiatric residency program and then evaluated the clinical outcome of a group of cocaine-dependent patients treated by the residents. The psychiatric residency was chosen because of the growing importance of clinical training in the management of addiction in outpatient care in residency programs, in line with the standards set for specialty certification.

A training manual was prepared on the network technique, defining the specifics of the treatment in a manner allowing for uniformity in practice. It was developed for use as a training tool and then as a guide for the residents during the treatment phase. Network therapy tape segments drawn from a library of 130 videotaped sessions were used to illustrate typical therapy situations. A network therapy rating scale was developed to assess the technique's application, with items emphasizing key aspects of treatment [29]. The scale was evaluated for its reliability in distinguishing between two contrasting addiction therapies, network therapy and systemic family therapy, both presented to faculty and residents on videotape. The internal consistency of responses for each of the techniques was high for both the faculty and the resident samples, and both groups consistently distinguished the two modalities. The scale was then used by clinical supervisors as a didactic aid for training and to monitor therapist adherence to the study treatment manual.

We trained third-year psychiatry residents to apply the network therapy approach, with an emphasis placed on distinctions in technique between the treatment of addiction and of other major mental illness or personality disorder. The residents then worked with a sample of 47 patients with cocaine use disorder. Once treatment was initiated, 77% of the subjects established a network, that is, brought in at least one member for a network session. In fact, 1.47 collaterals on average attended any given network session, across all the subjects and sessions. This is notable, because compliance after initial screening was not necessarily assured. Almost all of those who completed a 24-week regimen (15 of 17) produced urines negative for cocaine in their last three toxicologies. On the other hand, only a minority of those who attended the first week but who did not complete the sequence (4 of 18) met this outcome criterion [20]. The residents, inexperienced in drug treatment, achieved results similar to those reported for experienced professionals [8, 25]. These comparisons supported the feasibility of successful training of psychiatry residents naive to addiction treatment and the efficacy of the treatment in their hands.

To better understand the role of therapeutic alliance in NT, Glazer et al. [22] reviewed videotaped network sessions on 21 out of the 47 patients with cocaine use disorder and rated them on level of patient–therapist alliance using the PENN Helping Alliance Rating Scale and the Working Alliance Inventory. The tapes that were selected to be rated were those that represented the participants' first videotaped NT session. Results showed a significant positive correlation between therapeutic alliance and outcomes as measured by the percentage of cocaine-free urine toxicology screens and by eight consecutive cocaine-free urines.

32.5.3 Treatment by Addiction Counselors

This study was conducted in a community-based addictions treatment clinic, and the network therapy training sequence was essentially the same as the one applied to the psychiatry residents [28]. A cohort of 10 cocaine-dependent patients received treatment at the community program with a format that included network therapy, along with the clinic's usual package of modalities, and an additional 20 cocaine-dependent patients received treatment as usual and served as control subjects. The network therapy was found to enhance the outcome of the experimental patients. Of 107 urinalyses conducted on the network therapy patients, 88% were negative, but only 66% of the 82 urine samples from the control subjects were negative, a significantly lower proportion. The mean retention in treatment was 13.9 weeks for the network patients, reflecting a trend toward greater retention than the 10.7 weeks for control subjects.

The results of this study supported the feasibility of transferring the network technology into community-based settings with the potential for enhancing outcomes. Addiction counselors working in a typical outpatient rehabilitation setting were able to learn and then incorporate network therapy into their largely Twelve-Step-oriented treatment regimens without undue difficulty and with improved outcome.

32.5.4 Use of the Internet

We studied ways in which psychiatrists and other professionals could be offered training by a distance-learning method using the Internet, a medium that offers the advantage of not being fixed in either time or location. An advertisement was placed in *Psychiatric News*, the newspaper of the American Psychiatric Association, offering an Internet course combining network therapy with the use of naltrexone for the treatment of alcoholism.

The sequence of material presented on the Internet was divided into three didactic "sessions," followed by a set of questions, with a hypertext link to download relevant references and a certificate of completion. The course took about 2 hours for the student to complete. Our assessment was based on 679 sequential counts, representing 240 unique respondents who went

beyond the introductory web page [21]. Of these respondents, 154 were psychiatrists, who responded positively to the course. A majority responded "a good deal" or "very much" (a score of 3 or 4 on a 4-point scale) to the following statements: "It helped me understand the management of alcoholism treatment" (56%); "It helped me learn to use family or friends in network treatment for alcoholism" (75%); and "It improved my ability to use naltrexone in treating alcoholism" (64%). The four studies described in this section support the use of network therapy as an effective treatment for addictive disorders. They are especially encouraging given the relative ease with which different types of clinicians were engaged and trained in the network approach. Because the approach combines a number of well-established clinical techniques that can be adapted to delivery in typical clinical settings, it is apparently suitable for use by general clinicians and addiction specialists.

32.5.5 Network Therapy in Buprenorphine Maintenance

Galanter et al. [19] evaluated the impact of NT relative to a control condition (medical management, MM) among 66 patients who were inducted on to buprenorphine for 16 weeks and then tapered to zero dose. Network Therapy resulted in a greater percentage of opioid-free urines than did MM (65% vs. 45%). By the end of treatment, NT patients were more likely to experience a positive outcome relative to secondary heroin use (50% vs. 23%). The use of NT in office practice may enhance the effectiveness of eliminating secondary heroin use during buprenorphine maintenance.

32.5.6 Use of Alcoholics Anonymous and Other Self-Help Groups

This approach involves the option for use of Twelve Step facilitation concomitant with Network Therapy. TS involves the following points:

1. Patients should be expected to go to meetings of AA or related groups at least two to three times, with follow-up discussion in therapy.
2. If patients have reservations about these meetings, the therapist should try to help them understand how to deal with those reservations. Issues such as social anxiety should be explored if they make a patient reluctant to participate. Generally, resistance to AA can be related to other areas of inhibition in a person's life, as well as to the denial of addiction.
3. As with other spiritually oriented involvements, it is important to explore the patient's orientation toward this issue.
4. Be prepared to listen.

32.6 Adaptations of Network Therapy Treatment

Rothenberg et al. [41] adapted NT and combined it with relapse prevention and a voucher reinforcement system in the treatment of opioid-dependent patients who were enrolled in a 6-month course of treatment with naltrexone referred to as behavioral naltrexone therapy (BNT). The NT component involved one significant other who could monitor adherence to naltrexone. In addition to the patient receiving vouchers for each day of abstinence and each pill taken, the network member was reinforced with a voucher for each pill recorded as monitored. The primary treatment outcome was retention in treatment. Patients who used methadone at baseline did more poorly than those using only heroin as demonstrated in the retention rates: 39% vs. 65%, and 0% vs. 31%, respectively, at 1 month and 6 months.

Copello et al. [10] combined elements of NT with social aspects of the community reinforcement approach and relapse prevention referred to as social behavior and network therapy (SBNT) in the treatment of persons with alcohol drinking problems. A number of social skills training strategies are incorporated into the treatment especially those involving social competence in relation to the development of positive social

support for change in alcohol use. Every individual involved in treatment is considered a client in his or her own right and the person with alcohol problems is referred to as the focal client. The core element of the approach is mobilizing the support of the network even though this may involve network sessions that are conducted in the absence of the focal client. In their initial feasibility study with 33 clients, there were two cases in which sessions were held with network members in the absence of the focal client and in both cases reengagement of the focal client in treatment was achieved. Out of the 33 clients enrolled in the study, 23 formed a network with the mean number of network members = 1.82 and the mean number of network sessions = 5.24. In a multisite, randomized, controlled trial of 742 clients with alcohol problems, the UKATT Research Team [45] compared SBNT to motivational enhancement therapy (MET). Both treatment groups exhibited similar reductions in alcohol consumption and alcohol-related problems and improvement in mental functioning over a 12-month period. Attending more sessions was associated with a better outcome, and SBNT patients with greater motivation to change and those with more negative short-term expectancies were more likely to attend [12].

Additional studies involving the UKATT study sample were conducted assessing (1) cost-effectiveness [46], (2) client-treatment matching effects [47], (3) clients' perceptions of change in alcohol drinking behaviors [40], and drinking goal preference [1]. The UKATT team evaluated the cost-effectiveness of SBNT relative to motivational enhancement therapy. SBNT resulted in a fivefold cost savings in health, social, and criminal justice service expenditures and was similar to cost-effectiveness estimates obtained for motivational enhancement therapy. The UKATT Research Team [47] tested a priori hypotheses concerning client-treatment matching effects similar to those tested in Project MATCH. The findings were consistent with Project MATCH in that no hypothesized matching effects were significant. Orford et al. [40] interviewed a subset of clients (n = 397) who participated in this trial to assess their views concerning whether any positive changes in drinking behavior had occurred and to what they attributed those changes. At 3 months after randomization to treatment, SBNT clients made more social attributions (e.g., involvement of others in supporting behavioral change) and MET clients made more motivational attributions (e.g., awareness of the consequences of drinking). Patients who initially stated a preference for abstinence showed a better outcome than those stating a preference for nonabstinence. This was true at both 3-month and 12-month follow-ups [1].

Copello et al. [11] adapted SBNT for persons presenting with drug problems. Of 31 clients enrolled in the study, 23 received SBNT and had outcomes data available at 3-month follow-up. Reductions in the amount of heroin used per day and increases in family cohesion and family satisfaction were documented. Open-ended interviews with clients, network members, and therapists were conducted in a qualitative investigation of respondents' perceptions of SBNT [49]. Major themes that emerged from analysis of the interview responses included the value of SBNT in (1) increasing network support for reducing drug use, (2) promoting open and honest communication between clients and network members about drug use, and (3) increasing network members' understanding of drugs and the focal person's behavior. Williamson et al. [49] suggest that these features of SBNT may be more prominent when the problem is one of illicit drug use than when the problem involves the alcohol use.

32.7 Principles of Network Treatment

32.7.1 Start a Network as Soon as Possible

1. It is important to see the alcohol or drug abuser promptly, because the window of opportunity for openness to treatment is generally brief. A week's delay can result in a person's reverting back to drunkenness or losing motivation.
2. If the person is married, engage the spouse early on, preferably at the time of the first

phone call. Point out that substance use disorder is a family problem. For most drugs, you can enlist the spouse in assuring that the patient arrives at your office with a day's sobriety.

3. In the initial interview, frame the exchange so that a good case is built for the grave consequences of the patient's substance use disorder, and do this before the patient can introduce his or her system of denial. That way you are not putting the spouse or other network members in the awkward position of having to contradict a close relation.
4. Then make clear that the patient needs to be abstinent, starting now. (A tapered detoxification may be necessary sometimes, as with depressant pills.)
5. When seeing a patient with alcohol use disorder for the first time, start the patient on disulfiram treatment as soon as possible, in the office if you can. Have the patient continue taking disulfiram under observation of a network member.
6. Start arranging for a network to be assembled at the first session, generally involving a number of the patient's family or close friends.
7. From the very first meeting you should consider how to ensure sobriety till the next meeting, and plan that with the network. Initially, their immediate company, a plan for daily AA attendance, and planned activities may all be necessary.

32.7.2 Manage the Network With Care

1. Include people who are close to the patient, have a long-standing relationship with the patient, and are trusted. Avoid members with substance problems, because they will let you down when you need their unbiased support. Avoid superiors and subordinates at work, because they have an overriding relationship with the patient independent of friendship.
2. Get a balanced group. Avoid a network composed solely of the parental generation, or of younger people, or of people of the opposite sex. Sometimes a nascent network selects itself for a consultation if the patient is reluctant to address his or her own problem. Such a group will later supportively engage the patient in the network, with your careful guidance.
3. Make sure that the mood of meetings is trusting and free of recrimination. Avoid letting the patient or the network members feel guilty or angry in meetings. Explain issues of conflict in terms of the problems presented by substance use disorder; do not get into personality conflicts.
4. The tone should be directive. That is to say, give explicit instructions to support and ensure abstinence. A feeling of teamwork should be promoted, with no psychologizing or impugning members' motives.
5. Meet as frequently as necessary to ensure abstinence, perhaps once a week for a month, every other week for the next few months, and every month or two by the end of a year.
6. The network should have no agenda other than to support the patient's abstinence. But as abstinence is stabilized, the network can help the patient plan for a new drug-free adaptation. It is not there to work on family relations or help other members with their problems, although it may do this indirectly.

32.7.3 Keep the Network's Agenda Focused

1. Maintaining abstinence. The patient and the network members should report at the outset of each session any exposure of the patient to alcohol and drugs. The patient and network members should be instructed on the nature of relapse and plan with the therapist how to sustain abstinence. Cues to conditioned drug-seeking should be examined.
2. Supporting the network's integrity. Everyone has a role in this. The patient is expected to make sure that network members keep their meeting appointments and stay involved with the treatment. The therapist sets meeting times and summons the network for any emergency,

such as relapse; the therapist does whatever is necessary to secure stability of the membership if the patient is having trouble doing so. Network members' responsibility is to attend network sessions, although they may be asked to undertake other supportive activity with the patient.

3. Securing future behavior. The therapist should combine any and all modalities necessary to ensure the patient's stability, such as a stable, drug-free residence; the avoidance of substance-abusing friends; attendance at Twelve-Step meetings; medications such as disulfiram or blocking agents; observed urinalysis; and ancillary psychiatric care. Written agreements may be handy, such as a mutually acceptable contingency contract with penalties for violation of understandings.

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33 CRA and CRAFT: Behavioral Treatments for Both Motivated and Unmotivated Substance-Abusing Individuals and Their Family Members

Hendrik G. Roozen and Jane Ellen Smith

Contents

Abstract

The Community Reinforcement Approach (CRA) is a behavioral treatment for individuals with substance-use problems. It is predicated upon the belief that a non-drinking/non-using lifestyle must be experienced by individuals as rewarding in order for them to choose it consistently over substance use. As part of CRA, the client's "community" (e.g., family, friends, colleagues, organizations, work) is explored to find new areas of potential reinforcement that can compete with substance use. CRA therapists work with clients to decide on which goals they want to pursue in life, and they then teach these clients the skills required to achieve these goals. An adaptation of CRA is the Adolescent Community Reinforcement Approach (A-CRA), which is geared specifically toward the treatment of adolescents, young adults, and their parents or caregivers. Community Reinforcement and Family Training (CRAFT) is a treatment for the family members or close friends (Concerned Significant Others, CSOs) of unmotivated, treatment-refusing substance abusers (Identified Patients, IPs). CRAFT therapists work with CSOs in an attempt to change the home environment of the unmotivated IPs such that a healthy and enjoyable lifestyle is supported over one dominated by substance use. CRAFT goals include getting IPs to seek treatment and reducing IP substance use, and also having CSOs increase

H. G. Roozen
University of New Mexico, Albuquerque, NM, USA

J. E. Smith (✉)
Department of Psychology, University of New Mexico, Albuquerque, NM, USA
e-mail: janellen@unm.edu

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their own happiness regardless. CRA, A-CRA, and CRAFT have solid empirical support, and each has been used successfully with diverse populations and various drugs of choice.

33.1 Introduction

The Community Reinforcement Approach (CRA) is built upon the Skinnerian principles of behavioral modification. The rationale is that desired behaviors are considered malleable by their consequences and will most likely occur when they are systematically reinforced. Skinner's colleague, Nathan Azrin, tested and applied this perspective in clinical practice to treat various mental health problems, including addictions [7, 11, 44]. Given the scientific, theoretically driven background of operant conditioning, it is not surprising that CRA has proven to be efficacious in routine clinical practice. This same operant behavioral foundation has been considered the lynchpin of the Token Economy [5] and Contingency Management (CM) [42].

Azrin believed that individuals' physical environment (their "community"), including their family, work, recreational activities, and social life, could be rearranged such that they received more powerful reinforcement from the community for sober behavior versus substance-using behavior. As part of this strategy, CRA assists clients to sample enjoyable pro-social activities that are unrelated to alcohol and/or drugs. Importantly, experimental research on instrumental learning has shown that new learning is context dependent [16, 17]. Thus, behavioral modifications to prevent relapse should eventually take place in clients' own communities. Furthermore, an important aspect of CRA is that it teaches clients new skills to make their reinforcers more accessible, and to help them to cope with obstacles and potential high-risk situations. As such, CRA involves a variety of techniques, including the training of communication skills, alcohol and/or drugs refusal skills, problem solving, behavioral partner relationship therapy, procedures to support medication compliance, and career counseling for the unemployed. CRA makes extensive use of modeling, role-playing, and shaping.

Two offshoots of CRA, the Adolescent Community Reinforcement Approach (A-CRA) and Community Reinforcement and Family Training (CRAFT) were created to prioritize family members or even target them directly by unilateral therapy (i.e., CRAFT). These will be discussed in this chapter as well.

33.2 Understanding and Using CRA, A-CRA, and CRAFT

33.2.1 CRA Procedures

33.2.1.1 CRA Functional Analyses

One of the first CRA procedures conducted by a clinician is the functional analysis (FA) of substance-using behavior. This semi-structured interview (see [58]) allows the clinician *and* the client to clearly see the events that set the stage for a common substance-use episode, as well as the positive and negative consequences that follow. The clinician first works with the client to identify external (people, places, times) and internal (thoughts, feelings) triggers. This information is later used to determine how to alter or effectively cope with triggers that have led to substance use in the past. The second part of the FA involves the clinician gathering more information about how the substance of choice is used, such as how much is consumed and over what period of time. These details can be useful in quantitatively gauging progress as therapy proceeds.

Finally, the clinician uses the FA to explore both the positive and negative consequences associated with substance use. Discussing the positive consequences is critical, because they represent the motives that sustain the substance use. For example, a client may state that he enjoys drinking because it allows him to avoid dealing with all his negative thoughts about work and finances. Once these drinking-related "rewards" (positive consequences) are identified, the clinician can help the client generate non-drinking alternatives either for avoiding the negative

thoughts, or for solving the work and finance problems themselves. The negative consequences of substance use are broken down into multiple domains, such as interpersonal, physical, emotional, legal, job, and financial.

The CRA program's second type of FA is for healthy, pro-social behaviors (e.g., going for a walk with a friend). The objective is to work with the client to *increase* these behaviors so that they can compete with substance use. A better understanding of the antecedents and consequences surrounding these behaviors helps the clinician see why a pro-social behavior is sometimes chosen over a substance-using one (and vice versa) and identify possible mechanisms for getting the client to select the healthy alternative more often.

33.2.1.2 Sobriety Sampling

Sobriety sampling is a method for encouraging clients to "sample" a time-limited period of sobriety. A "trial period" of sobriety is experienced by clients as more attainable than a demand for a life-long commitment to abstinence. Sobriety sampling is used regardless of whether the final treatment goal is abstinence, moderation, or even harm reduction. If the goal is abstinence, small, manageable periods of sobriety are linked together over time. If the client hopes to become a moderate drinker/substance user, the clinician still asks for the client to start treatment by sampling a period of sobriety. Some of the benefits of sobriety sampling, which are discussed with the client, include providing an opportunity to experiment with new coping strategies, and increasing self-efficacy through goal attainment.

Once the client has agreed to sample sobriety, the length of the trial period must be negotiated. The client's motivators for abstinence are linked to the goal. For example, a clinician might state, "You said that your next review at your job is 6 weeks away, and that your boss has already expressed some concern about your work performance. I bet if you were totally sober for the next 6 weeks your behavior at work would improve, and it would be obvious to your boss. That might be a good reason to shoot for 6 weeks of sobriety. What do you think?" If the client is unwilling or feels unable to agree to the suggested period of sobriety, the clinician will negotiate with the client to reach a mutually agreed-upon goal.

The final part of sobriety sampling entails setting up a plan such that the client can actively work to achieve the goal. Using information collected during the FA for substance use, the client is encouraged to identify alternatives to substance use and to develop plans for handling common triggers. It is often helpful to identify and problem solve any upcoming high-risk situation and to develop specific backup plans.

33.2.1.3 CRA Treatment Plan: Happiness Scale and Goals of Counseling

The CRA treatment plan is built around the Happiness Scale and the Goals of Counseling forms. The Happiness Scale is a multi-item questionnaire that asks clients to rate their happiness on a 10-point scale (where 10 indicates "completely happy") in each of the following areas: substance use, job or educational progress, money management, social life, personal habits, marriage/family relationships, legal issues, emotional life, communication, spirituality, and general happiness (see [58]). Information regarding the client's happiness in each of these categories helps set the stage for developing the goals of treatment. For example, the clinician might say, "I see that you've rated your 'personal habits' a '4.' What would have to change in order for you to be able to rate 'personal habits' a '5' or '6'?" The Happiness Scale also can be readministered throughout therapy to track progress in specific domains.

The same domains from the Happiness Scale are listed on the Goals of Counseling form, where the clinician works with the client to set goals that are positive (what the client *wants* as opposed to what he/she does not want anymore), specific, measurable, realistic, and under the client's control. In addition to setting specific goals, the clinician and client work together to identify the necessary steps needed to accomplish each goal. A representative goal in the personal habits area might be to eat at least two fruits and vegetables every day. The initial steps toward attaining that

goal might be to identify a conveniently located store that carries good fruits/vegetables, and to sample a new fruit and vegetable in the upcoming week. These weekly steps toward a goal are essentially the homework assignment. Importantly, the clinician checks on progress toward completing the homework weekly and discusses any barriers that have appeared.

Establishing and working on goals to improve various areas of the client's life is fundamental to the CRA approach, given that the overall objective is to increase sources of substance-free reinforcement for the client. Many of these goals, and the strategies (steps) for attaining them, require specific behavioral skills training. The CRA program offers skills training in such areas as communication, problem solving, and drink/drug refusal.

33.2.1.4 Positive Communication Skills

CRA emphasizes the importance of positive communication training, in part because many individuals who abuse substances report that problematic interactions serve as relapse triggers. Furthermore, effective communication paves the way for the successful implementation of goal-related tasks, such as interviewing for jobs, asking teachers for extra help, and talking with a partner about relationship struggles. CRA clinicians present the rationale for focusing on communication training, and then offer several communication guidelines for starting a difficult conversation (see full list in [58]): (1) label your feeling: "I feel ___"?, (2) give an understanding statement, (3) take partial responsibility, and (4) offer to help. Assume, for example, that an adolescent male who has been grounded for 4 weeks would like to attend a school social event. The clinician would work with the client to develop the beginning of a conversation with his mother that sounded somewhat similar to: "Mom, I feel a bit disappointed (*label your feeling*), but can totally see why you'd want me to finish out this last week of being grounded (*understanding statement*). I know I screwed up, and that's what got me grounded in the first place (*partial responsibility statement*). But I haven't gotten into any trouble the last 3 weeks. Is there anything else I could do to make up for cutting the full 4 weeks a few days short in order to attend the school event?" (*offer to help*).

Clients report that when they start a conversation with these communication components, they typically are met with less defensiveness from the listener. The message being conveyed is that more than one person contributes to interpersonal problems, and the communicator is willing to take an active role in improving the situation. Clinicians teach these skills by providing relevant examples and engaging the client in role-plays.

33.2.1.5 Problem-Solving Skills

Many individuals who abuse substances report that they resort to alcohol or drugs as their strategy for dealing with problems that seem unsolvable (or that at least generate considerable stress). CRA's problem-solving skills training module, which is based on the work by D'Zurilla and Goldfried [20], outlines seven main steps: (1) narrowly define the problem, (2) generate potential solutions (brainstorm), (3) eliminate undesired suggestions, (4) select one potential solution, (5) generate possible obstacles, (6) address these obstacles, and (7) assign the specific task (i.e., the homework). As with all homework assignments, the clinician carefully evaluates the outcome of the task at the start of the next therapy session.

This problem-solving procedure allows clients to break down problems into manageable steps, to think creatively about possible solutions, and to realistically assess the likelihood that the proposed solution will work. Once clients have put their proposed solution into action, they are taught to critically evaluate the outcome. If the proposed solution did not meet their needs, they are encouraged either to modify the attempted solution or to select a different solution generated during step #2. Some of the common types of problems for which this exercise is conducted include finding new non-drinking friends, developing healthy sleep routines, dealing with cravings, and managing stress.

33.2.1.6 Drink and Drug Refusal Skills

CRA encourages clients to create social environments that are supportive of sobriety, and nonetheless clients will find themselves periodically in situations that require them to assertively refuse offers of alcohol or drugs. CRA's drink/drug refusal skills training starts with helping clients anticipate and prepare for high-risk situations, and identifying supportive individuals who can be available in the event that a client is struggling in one of these situations. Information gathered during the FA can be extremely useful when helping the client identify personally relevant high-risk situations. Assertive communication skills are then taught and practiced with the client in role-plays.

Oftentimes clients are overly confident that they will be able to walk into these situations and "simply not drink" (and not use other substances). Despite this confidence, refusal is often much more difficult than anticipated, and thus clients are encouraged to practice refusing offers assertively. Clients first are asked to identify verbal responses or behaviors that have helped them successfully reject offers of substances in the past. These suggestions are supplemented with additional ideas, such as: (1) simply saying "no, thanks" without feeling guilty, (2) using appropriate body language (good eye contact, a firm stance, etc.), (3) suggesting alternatives ("No, thanks, but I'll take a coffee"), (4) changing the subject ("Did you see that game last night? Unbelievable!"), (5) directly addressing the aggressor about the issue if needed ("I'm definitely not interested in smoking. Why is it important to *you* that I smoke?"), and (6) leaving the situation. Clients are asked to generate their own assertive response style and are coached in its implementation.

33.2.1.7 Job-Finding Skills

An important component of reinforcement for many individuals is a job that they value. Meaningful employment can compete with time otherwise left idle for substance use, and can provide a boost to self-esteem, enjoyable social relationships, and of course—money. Relying on the work outlined by Azrin and Besalel in their Job Club Counselor's Manual [8], CRA offers a step-by-step approach to obtaining a satisfying job and keeping it. The procedure begins by asking clients to carefully consider the types of jobs for which they are best suited, such as ones that are unlikely to contribute to relapse. A system is established for tracking contacts with potential employers, and clients are assisted with developing resumes and completing job applications in a manner that highlights their strengths. Role-plays are conducted to provide practice in calling potential employers and going on job interviews. With respect to keeping a job, clinicians help clients anticipate difficult work situations based on previous job problems, and problem-solving skills are used to generate potential solutions.

33.2.1.8 Social/Recreational Counseling

Prior to treatment, clients' social and recreational environments are strongly associated with substance use, and consequently identifying enjoyable substance-free social activities often is a difficult task. Clinicians ideally should attempt to identify at least some activities that occur during high-risk times (e.g., weekends, evenings) and thereby directly compete with substance use. CRA offers several methods for developing ideas and specific plans for increasing healthy social activities, including the use of problem solving, or setting goals and strategies as part of the Goals of Counseling procedure. Additionally, the FA for pro-social, healthy behaviors (see Sect. 33.2.1.1) can be conducted. Instruments such as the Pleasant Activities List (PAL; [72]) or Social Circle [93] can be employed as well. Once an activity is identified, a homework assignment is made to sample the activity, and, as usual, potential barriers (e.g., transportation, money, fear of rejection) are discussed.

Periodically clinicians are skeptical about a client following through and sampling a new activity despite being motivated to do so. In these cases, clinicians utilize Systematic Encouragement to increase the likelihood that the client will successfully complete that homework assignment in the upcoming week. Systematic Encouragement involves helping the client take

the first step toward engaging in the new activity before leaving the session. For example, assume a client is interested in learning how to do woodworking, but appears unlikely to make any progress toward pursuing that goal without assistance. The clinician would help the client search for relevant information about woodworking courses or workshops online, and then would ask the client to register right in the session. Potential obstacles would be addressed in the process, such as whether the client had sufficient money for the course, and if transportation was available. The clinician would start the next session by reviewing the client's woodworking assignment, primarily to determine whether the experience had been enjoyable.

33.2.1.9 Relapse Prevention

CRA has multiple procedures that can be used to address relapses. For example, the FA can be readministered, but with a focus on the specific relapse episode. The clinician takes a solution-oriented approach to highlighting what triggered the relapse and to identifying alternatives to substance use in that particular situation. CRA clinicians also can borrow from the relapse literature more generally by drawing and labeling a behavioral "chain" to illustrate the events that led to the relapse. Clients are shown how a number of small and seemingly unrelated decisions throughout the day led them down the path to a relapse. Clinicians work with the clients to help them generate different decisions at multiple points along the chain—decisions that ultimately would not result in a relapse. Finally, CRA relapse prevention may include the Early Warning System, which entails clients setting up a plan for enlisting the support of a concerned family member or friend in the event that a relapse appears imminent.

33.2.1.10 Medication Monitoring

CRA's medication monitoring procedure is used with clients who have difficulty taking their prescribed medication. The procedure originally was developed for clients who were taking disulfiram (Antabuse), a medication that causes individuals to become very ill if they ingest alcohol. This "deterrent" to drinking is sometimes introduced to clients who repeatedly are unsuccessful at achieving even short periods of abstinence or who face serious consequences if they drink. But in order for disulfiram to be effective, it must be taken several days per week, and therefore, it is important to incorporate a medication monitoring component. The "monitor," a concerned individual who has daily contact with the client, attends a session with the client in order to learn positive communication skills for administering the disulfiram. For example, the monitor rehearses a conversation such as, "I appreciate you taking your pill today. This shows how hard you're trying, and how much you care about our family." In addition to teaching the monitor to express support and appreciation for the client's efforts, a plan is developed (with the client's consent) regarding the steps to take if the client refuses to take his or her medication (e.g., call the therapist). Although initially introduced to monitor disulfiram administration, more recently the medication monitoring procedure has been used to monitor a variety of other kinds of medication, such as for attention deficit hyperactivity disorder (ADHD), bipolar disorder, and depression.

33.2.1.11 Relationship Therapy

Improving interactions with a romantic partner can be another powerful source of reinforcement. CRA's relationship therapy highlights the importance of having communication and problem-solving skills, and teaches couples how to request and negotiate reasonable goals. The couple begins by completing the Relationship Happiness Scale, a tool similar to the original Happiness Scale. However, each individual rates his/her happiness with the *partner* on a 10-point scale across ten domains: household responsibilities, raising the children, social activities, money management, communication, sex and affection, job or school, emotional support, partner's independence, and general happiness. Each partner is asked to write down what he/she would like the partner to do in several of the ten domains while utilizing the guidelines for specifying goals and strategies (see Sect. 33.2.1.3), including being positive, specific, and using measurable terms.

They then are taught to use positive communication skills to make the request verbally. Homework assignments are made to tackle the negotiated goals. As part of the "Daily Reminder to be Nice" exercise, each partner commits to increasing at least one of seven partner-pleasing behaviors (e.g., expressing appreciation, giving a pleasant surprise) on a daily basis in an effort to reinstate positive behaviors that were more frequent at the beginning of the relationship. In subsequent sessions, the partners report on any barriers to completing their goals for the week and identify future goals.

33.2.2 CRA Scientific Support

For almost half a century, CRA has been accruing evidence of its efficacy and effectiveness in treating alcohol and drug problems. It is even viewed as one of the earliest evidence-based treatment methods [64]. The seminal CRA studies were conducted with inpatients on alcohol wards [7, 44]. In both studies, CRA did significantly better than standard treatment, which at the time was participation in a hospital's Alcoholics Anonymous program. Specifically, at 6-month follow-up, CRA participants had less drinking days and institutionalization and more days working compared to those in standard treatment. The second of these studies introduced several new procedures to the original CRA protocol, most notably a disulfiram (Antabuse) compliance monitoring program [7].

The third CRA study was the first one to use an outpatient population of problem drinkers [9]. The researchers contrasted three treatments: traditional (12-step) treatment with a disulfiram prescription, traditional treatment with the disulfiram compliance program, and CRA with the disulfiram compliance program. The compliance program included not only monitoring of the daily disulfiram use by a significant other (e.g., a spouse), but also training in positive communication skills. As expected, the conditions that included the disulfiram compliance component had the highest abstinence rates, with the CRA program outperforming the traditional program overall at 6 months.

A much larger study ($N = 237$) with an ethnically diverse population was conducted, which extended the design of the first outpatient study by examining whether one's willingness to take disulfiram affected the findings [62]. Although the study revealed less robust results, CRA still showed an advantage over traditional treatment on several outcome measures. The CRA program was modified in another study to make it applicable to a day treatment program for homeless alcohol-dependent individuals [87]. As predicted, CRA (conducted in groups) was proven to be more effective than the standard treatment offered at that particular homeless shelter in terms of drinking outcomes.

Although originally developed as a treatment for individuals with alcohol problems, CRA has proven to be promising for other types of substance use, including cocaine [6], tobacco [71], and opioids (e.g., [1, 12, 70]). Bickel and colleagues determined that a computerized version of CRA for opioid-dependent individuals that were on buprenorphine maintenance did as well as a therapist-delivered version of CRA, both of which did significantly better than standard treatment [13].

One hallmark of CRA is the clinical application of the CRA Happiness Scale (CRA-HS; [44, 58]). As noted, it serves as a compass for tracking satisfaction with life across multiple domains, and can be used to evaluate treatment outcome by repeatedly assessing changes that occur during treatment. It also is used as the basis for setting treatment goals. The shared decision-making involved in this process was already launched in the seminal studies and nowadays is considered critical in the recovery movement [4]. In a recent Dutch CRA study [73], it was shown that patients with high baseline levels of psychiatric symptoms reported relatively lower baseline and follow-up scores on the CRA-HS than patients with low initial levels of psychiatric symptoms. Interestingly, although patients with high levels of psychiatric symptoms on admission were relatively disadvantaged in terms of CRA-HS outcomes both at pre- and post-measurement, they showed a stronger and more remarkable improvement on this measure during the course of treatment [73].

Originally, the CRA-HS was based on the 10-item Marital Happiness Scale [10]. This scale was modified by Azrin [7] in order to be applicable to individual clients, and was coined the CRA-HS. About 20 years later, Meyers and Smith [58] published a version that contained a few modified life domains (see, [60], p 383). This scale was further expanded in the Netherlands by including several new items (see [77]), yet recent psychometric work in the Netherlands reduced the measure to 12 "core" items (with 6 additional optional items and 1 open-ended item; [15]). The newest studies also have confirmed the strong psychometric properties of the CRA-HS, and have focused on measurement invariance in cross-cultural non-clinical populations [75] and external validity in a clinical population [46].

33.2.2.1 CRA and Contingency Management

Contingency Management (CM), a behavioral program for substance-abusing individuals, has been among the highest-ranked treatments in several meta-analyses [25, 52, 68]. To date, almost 500 empirical CM studies have been conducted, with a large majority of them demonstrating the efficacy of CM [21]. CM has been extensively applied in concert with CRA [22]. For cocaine-dependent clients treated with CRA, the addition of CM was found to yield better results in Spain [26, 42, 81, 82, 83] . Even the efficacy of CRA and CM was shown in pregnant women or women with young children [80]. Over the years a series of studies that have examined cocaine-dependent individuals treated with a combination of CRA and CM (vouchers) for clean urines has found highly favorable results when contrasted with standard treatment (e.g., [27]; see [40]).

In an effort to identify patterns among CRA study results, Roozen and colleagues conducted a systematic review of 11 randomized controlled trials. They discovered strong evidence that CRA with vouchers was more effective than usual care in achieving cocaine abstinence and more effective than CRA alone. However, there was evidence that the effect of the vouchers dissipated over time after their discontinuation [69]. Interestingly, one study clearly determined that the addition of CRA to CM improved alcohol and employment outcomes compared to vouchers alone in cocaine-addicted individuals [41].

33.2.2.2 International Considerations

CRA has gained international recognition in more recent years. Besides the USA, the Netherlands, and Spain, a pilot study of CRA with substance-abusing individuals in Mexico detected highly promising findings [92]. Furthermore, the National Drugs Strategy of Ireland has acknowledged CRA as an effective evidence-based approach that can be used as an adjunct to services delivered within the rehabilitation pillar, and Germany has already sponsored a CRA conference. In Australia, an Aboriginal version of CRA has been created [78]. The CRA trainers' manual, "Clinical Guide to Alcohol Treatment: The Community Reinforcement Approach" [58], has been translated into German, Japanese, and Dutch. Based on its strong scientific support, CRA has been increasingly spread in Europe during the last decade. Groups have been trained in Ireland, Wales, Scotland, Sweden, Japan, Germany, and the Netherlands.

In the Netherlands, CRA is established as a mainstream treatment delivery system, whereby more than 2000 health professionals in addiction care and (forensic) psychiatry have been trained in CRA. Both outpatient and inpatient teams have successfully implemented CRA within the forensic psychiatry system [38]. Furthermore, several Dutch addiction treatment institutes are actively participating in trajectories to improve CRA treatment fidelity by having their clinicians' CRA sessions digitally recorded and then rated by CRA supervisors using a CRA coding system. Thus far at least 100 therapists have been successfully certified using this process. To further ensure treatment fidelity, a Dutch CRA therapist manual was developed, which describes the clinical CRA procedures in detail [77]. This manual has been translated into Japanese recently (2019). In summary, although the dissemination of CRA is moving forward rapidly in several countries, the number of European studies that report on outcomes of CRA-based treatment programs fall

short and efforts are needed to increase future research output.

33.2.3 A-CRA Procedures

33.2.3.1 Additional or Modified Procedures

When the substance-using client is an adolescent, the adolescent version of CRA (A-CRA) can be used (see [31, 36]). A-CRA comprises both an extension and adaption of CRA. For the most part this entails relying on age-modified questionnaires, and additional procedures such as anger management and the inclusion of sessions for the caregivers (e.g., parents, grandparents), both alone and with the adolescent client.

The sessions with just the caregiver(s) focus on discussing basic parenting practices that support the adolescent's sobriety, and teaching CRA communication and problem-solving skills. The "family" sessions that include the adolescent are similar in structure to the relationship therapy sessions, in that they emphasize the negotiation of goals and the establishment of clear strategies for obtaining the goals.

33.2.4 A-CRA Scientific Support

Multiple randomized clinical trials of A-CRA have been published in the past two decades. A-CRA was one of the treatments in the national Cannabis Youth Treatment Study. Similar to other treatments, A-CRA demonstrated significant pre–post improvements in days of abstinence and days in recovery (i.e., no substance-use problems and not institutionalized) *and* was the most cost-effective treatment [23]. Slesnick et al. [85] showed that A-CRA was more effective than usual care for homeless adolescents who used drugs. Specifically, the Community Reinforcement program resulted in less substance abuse (37% vs. 17% decrease), less depression (40% vs. 23%), and more increased social reliance (58% vs. 13%) than usual care. Moreover, early results from a multi-site study with over 2000 adolescents showed that A-CRA was equally effective across ethnic groups [30].

Additional randomized clinical trials have shown A-CRA to be effective for youth with juvenile justice involvement [39] and as a continuing care approach for adolescents after residential treatment [32, 33]. Secondary evaluation studies suggest that A-CRA shows potential to be an effective transdiagnostic treatment for adolescents with co-occurring psychiatric disorders [35], adolescents with forensic problems [45], and youth with opioid use problems [37].

Similar to adult CRA, clinicians decide which A-CRA procedures to use on the basis of individual client needs. Consequently, some clients may receive certain procedures multiple times (e.g., problem solving or communication skills) but never receive other procedures (e.g., anger management; [28]). Importantly, receiving ten or more unique procedures during a treatment episode has been found to maximize client outcomes [29]. The ratings of therapist fidelity have been based on an A-CRA coding manual [89] that used specific, behaviorally anchored items [88]. Using this rating system it was determined that the more competent the therapist was in delivering A-CRA, the better the adolescent did in treatment [18]. Also, a paper is available that addresses successful A-CRA dissemination and implementation in a national study [34].

33.2.4.1 International Considerations

In the USA, the practice of A-CRA has become mainstream, as it is offered in almost 100 different locations throughout the USA. Several A-CRA books [36] and manuals [31] have become available, and they have been translated into Portuguese and Dutch.

33.2.5 CRAFT Procedures

33.2.5.1 Enhancement of the Concerned Significant Other's Motivation

CRAFT does not work directly with the individual with the substance-use problem (Identified

Patient; IP), but with a concerned significant other (CSO). CRAFT teaches the CSO new behaviors and strategies to try out at home with the IP, with the overall goal of getting this treatment-refusing individual to seek treatment. CSOs' motivation to fully engage in CRAFT is enhanced when they are told that their wealth of knowledge about the IP's substance use, and their degree of contact with the IP, allows CSOs to make powerful changes in their IP's environment. The initial part of this foundational session begins by asking CSOs to describe the negative consequences they and their IP have experienced as a result of the substance use. Any past successful attempts to influence the IP's behavior are reviewed. Clinicians establish positive expectancies by reporting that CRAFT is highly effective in helping IPs engage in treatment (nearly seven out of ten times) and in decreasing the distress experienced by the CSO regardless of whether the IP enters treatment. Additionally, clinicians emphasize that CRAFT is effective across a wide variety of CSO–IP relationships (e.g., spouse, friend, parent), ethnicities, and substances. The clinician then outlines CRAFT's three main goals: (1) decrease the IP's substance use, (2) get the IP to enter treatment, and (3) increase the CSO's happiness (see [86]).

33.2.5.2 Functional Analysis of IP's Substance-Using Behavior

A functional analysis (FA) quite similar to the one completed with the substance-using individual during CRA is completed as part of CRAFT as well, but with the *CSO* providing the information about the IP. A common using episode is identified, and both the triggers and consequences (positive and negative) of the use are delineated. The CSO's challenge is to influence/change the IP's environment so that the IP responds in a healthier manner to triggers. Importantly, this new IP behavior must allow the IP to experience some of the positive consequences (and none of the negative consequences) that have been associated with substance use, or it will not be maintained over time. For example, assume the IP has gotten into a routine of starting to drink as soon as she arrives home from work, and then continuing this throughout the dinner preparation and well into the evening. Her partner (CSO) believes that the IP has resorted to alcohol as a way to alleviate stress. The CSO could develop a plan to help the IP deal with her stress in healthier ways, such as by hooking up a sound system in the kitchen for her so that she can listen to soothing music (a reinforcer for the IP) while cooking. Another option would be for the CSO to urge the IP to meet with her friend for a walk right after work, and then for the CSO to join the IP in the kitchen to prepare dinner together (like they used to enjoy doing). Ideally, the exercise and the conversation during the walk would alleviate some of the IP's stress, and would help the IP reestablish connections with non-drinking friends. As far as the CSO joining the IP in the kitchen, it would be necessary to establish that this still would be viewed by the IP as a rewarding activity.

As CSOs start attempting these "homework" assignments, it is worthwhile for CRAFT clinicians to help CSOs understand that simply making one change in behavior will not suddenly solve the IP's substance-use problem. Instead, CSOs typically need to introduce a number of changes (as outlined in the remaining CRAFT procedures below) before their IP decides to seek treatment.

33.2.5.3 Domestic Violence Precautions

CRAFT teaches CSOs how to modify their own behavior such that only substance-free IP behaviors are "rewarded," and how to allow IPs to experience the natural negative consequences of their substance use (see Sect. 33.2.5.6). However, before CSOs attempt to modify any behavior at home, domestic violence precautions must be discussed. IPs routinely are *not* pleased with these CSO behavior changes, and a high correlation already exists between domestic violence and substance use [2]. Thus, CRAFT clinicians always assess the risk for domestic violence, either through standard assessment instruments, or through a functional analysis for domestic violence (see [86]). If any doubt remains regarding whether a CSO will be safe while participating in CRAFT, the CSO will be referred to another program.

33.2.5.4 Communication Skills

Positive communication skills are essential for several CRAFT procedures, including the ultimate invitation for the IP to enter treatment. In the earlier stages of treatment, CSOs' reliance upon positive communication can help minimize IP defensiveness and anger when explaining the rationale behind the CSO's own behavior change, and when requesting changes in the IP's behavior. The basic components of positive communication for CRAFT essentially are the same as those introduced for CRA: offer an understanding statement, accept partial responsibility, and offer to help. Assume that a mother (CSO) is trying to get her 17-year-old daughter (IP), who recently was caught with marijuana at school, to check out a new substance-free music establishment with a non-using friend on a Saturday night. The CSO might be encouraged to say, "I'm guessing you might be reluctant to try out this new place. After all, we haven't heard much about it yet, and maybe you're worried that some of your friends won't think it's 'cool' (*understanding statement*). And maybe I shouldn't have dumped the idea on you so 'enthusiastically' yesterday when I first brought it up (*partial responsibility statement*). But I know you love getting out and listening to music with people your age. What about giving it a try? I'll even pay for a ride for you if you want to go (*offer to help*)." As noted previously, communication skills are taught through repeated practice in the context of role-plays.

33.2.5.5 Positive Reinforcement for Clean and Sober IP Behavior

CRAFT helps CSOs understand that individuals are more likely to repeat behaviors that are reinforced (rewarded), and so when CSOs actively reward *sober* behaviors, they increase the likelihood that those sober behaviors will be repeated. CSOs also are taught the distinction between CRAFT's positive reinforcement (which increases the likelihood of clean/sober behaviors) and "enabling," which unintentionally increases the likelihood of substance use. Once the idea of rewarding sober behavior is explained, clinicians assist CSOs in developing a plan for administering reasonable rewards for the most appropriate times and occasions. The rewards themselves should be inexpensive, but the type of reward varies based on the CSO–IP relationship, the personal preferences of the IP (i.e., what the IP really enjoys), and what the CSO feels comfortable offering. Common examples include CSOs doing a favor for the IP, offering a compliment, giving a hug, or spending pleasant time with the IP.

Since it is imperative that the rewards follow sober behavior, CSOs sometimes require training in discerning whether or not the IP has engaged in substance use recently. Also, if CSOs are interested in explaining *why* they are giving a reward to their IP, positive communication skills (noted above) are rehearsed. For example, a CSO might say to the IP, "I know you really like it when I go antiquing with you on Saturdays (*understanding statement*), and I haven't been making the time to do that lately (*partial responsibility statement*). I'll happily go with you tomorrow, and I'll even pack a lunch like I used to (*offer to help*), but only if you don't get high. You're really a lot of fun to be with when you're not using." The importance of the CSO leaving the situation (but without any "drama") if the IP ended up smoking would be stressed.

33.2.5.6 Negative Consequences for Substance-Using Behavior

Just as a behavior is likely to be repeated if it is rewarded, a behavior is less likely to be repeated if it is followed by a decrease in rewards or an increase in negative consequences. Oftentimes CSOs can play an active role in reducing the IP's substance use by withdrawing the same rewards mentioned above (or additional ones) when the IP has been using substances. CSOs typically feel more comfortable removing rewards if they have discussed the rationale for needing to do so with the IP in advance. Again, positive communication is essential, and the risk for a violent IP reaction is discussed.

Since CSOs tend to care deeply about the well-being of their IP, they find themselves engaging in certain behaviors that inadvertently

interfere with the natural, negative consequences of their IP's substance use. For example, by preparing something for the IP to eat when he comes home late and has missed dinner due to drinking, the CSO is preventing the IP from experiencing the full natural (negative) consequences of the decision to use substances. Clinicians discuss the potential ramifications of CSOs changing their own behavior (i.e., not getting the IP something to eat), including whether it would create more problems than it would solve. For example, an IP might lose a job and thus financially damage the entire family if the CSO did not call in sick for a hungover IP. But if deemed an appropriate behavior to target, a specific plan for changing the CSO's behavior would be developed. If the CSO wanted to explain the plan to the IP, the conversation would be rehearsed.

33.2.5.7 Helping CSOs Improve Their Own Lives

Most CSOs present to treatment in a state of distress, often in the form of anxiety, depression, or physical symptoms [67]. One of the primary goals of CRAFT is to help CSOs improve their own lives, regardless of whether the IP enters treatment. CSOs complete the Happiness Scale (from the CRA protocol) so that their degree of satisfaction across a variety of life domains can be assessed and goals can be set. For example, assume a CSO has elected not to pursue additional schooling, due to concerns about needing to be home to address any IP-related problem that arises. If this CSO rated "Job/Education" a "4," the clinician would work with the CSO to create a plan that would result in a higher rating in a few weeks. For instance, the CSO might decide to investigate online coursework, or to make an appointment with a college advisor about degree requirements and paths. As always, potential obstacles would be anticipated and addressed, including a possible negative reaction from the IP.

33.2.5.8 Inviting the IP to Sample Treatment

CRAFT clinicians urge CSOs to spend time learning the necessary skills prior to inviting their IP to enter treatment. This includes practicing and implementing the CRAFT procedures just outlined, such as rewarding non-using IP behavior, introducing negative consequences for IP substance use, and relying on positive communication skills throughout. Not surprisingly, CSOs often report that their IP's substance use has decreased somewhat prior to the IP agreeing to seek treatment. In addition to allowing time for the CRAFT procedures to have an effect on the IP, CSOs need to learn the communication skills required for extending the invitation, and to identify the ideal time to have that conversation. Regarding the latter, CSOs are taught to extend the invitation at a time when the IP is most likely to be willing to sample treatment. These "windows of opportunity" may occur when the IP is inquiring about what the CSO is addressing in treatment, is questioning why the CSO's behavior has changed (in reference to rewarding and withdrawing rewards for different behaviors), or is remorseful about a salient substance-related negative consequence.

"Motivational hooks" are incorporated into the treatment invitation, such as pointing out that IPs can have their own therapist (separate from the CSO's clinician), highlighting that therapy can help the IP in non-substance use domains as well (e.g., finding a job, decreasing anxiety or depression), and suggesting that the IP sample a session or two without making a full commitment to therapy. CSOs are taught that if their IP initially declines the invitation, they should continue engaging in their new CRAFT-consistent behaviors in order to increase the likelihood of treatment engagement in the near future. Importantly, clinicians need to do preparatory work to ensure that a therapist is available to see the IP without delay as soon as the IP agrees to sample treatment. Furthermore, the IP's therapist should have a theoretical approach consistent with CRAFT, such as a behavioral or cognitive behavioral orientation.

33.2.6 CRAFT Scientific Support

Data show that many individuals with substance-use disorders (SUDs) are treatment resistant [19].

For individuals with alcohol-use disorders, evidence suggests a large treatment gap, which is defined as the difference between the number of people who need care and those who actually receive it [51]. Although a relatively smaller treatment gap than previously reported has been observed recently, it still has been estimated that one-quarter of the people with alcohol-use disorders do not receive treatment [94].

Prior to the development of CRAFT, only a limited number of traditional programs were available for CSOs of treatment-refusing individuals (Identified Patients; IPs) with substance-use problems: Al-Anon/Nar-Anon [3] and the Johnson Institute Intervention (JII; [47]). Unilateral Family Therapy (UFT) was introduced as a format for involving individuals other than the IP. Thomas and colleagues conducted several studies with UFT and found promising results, but the studies tended to be small and lacked controls (e.g., [90, 91]).

In the tradition of UFT, CRAFT was created. Originally called CRT—Community Reinforcement Training—the first small study was conducted by Sisson and Azrin [84]. Twelve female CSOs were randomly assigned into either CRT ($n = 7$) or individual counseling + Al-Anon referrals ($n = 5$). Six of the seven women in the CRT group (86%) were able to get their problem-drinking IPs into treatment compared to none of the IPs in the comparison group.

The second CRAFT study that focused on IPs with alcohol problems was a large NIAAA-funded project that randomly assigned 130 CSOs into one of the three treatment groups: CRAFT, Al-Anon Facilitation Therapy (an individual therapy version of Al-Anon; [66]), or the JII. Results indicated that CRAFT-trained CSOs were significantly more effective in engaging unmotivated problem drinkers in treatment (64%) as compared with the CSOs in Al-Anon (13%) and JII (30%, [61]). Interestingly, CSOs improved in their own functioning independent of treatment condition and whether their IP entered treatment. For those IPs who entered treatment, they did so with their CSOs receiving an average of only 4.7 CRAFT or Al-Anon sessions and 5.7 Johnson Institute sessions.

The success of CRAFT also has been established for treatment-refusing IPs with illicit drug problems. In a pilot project, 62 CSOs from diverse ethnic backgrounds received CRAFT. As expected, these CSOs were able to get a high percentage of IPs (74%) into treatment very quickly (less than five CSO sessions) while also reducing the CSOs' own levels of depression, anxiety, and anger [56].

Kirby and colleagues conducted a CRAFT study in which 32 CSOs were randomly assigned to either CRAFT or 12-step meetings. Engagement rates were 64% for the CRAFT-trained CSOs and 17% for CSOs in the 12-step condition [48]. A large NIDA-funded study was conducted next in which 90 CSOs of illicit drug-using IPs were randomly assigned to CRAFT, CRAFT + Aftercare, or Al-Anon/Nar-Anon Facilitation Therapy. An aftercare component was added to one of the CRAFT conditions to mimic the availability of ongoing aftercare groups within the 12-step model. The results demonstrated that the combined CRAFT conditions' engagement rates (67%) were significantly higher than the Al-Anon/Nar-Anon rates (29%), but there were no significant engagement differences between the two CRAFT conditions [57]. More recently, an effectiveness study demonstrated that CRAFT could be successfully transferred from a controlled research setting to a community treatment agency, while maintaining levels of engagement quite similar to previous controlled studies [24]. CRAFT's success with adults was tested with adolescents in an uncontrolled trial that recruited the parents of 42 drug-abusing, treatment-refusing adolescents [95]. A total of 71 of the parents engaged their adolescents into treatment using CRAFT, and the parents overall experienced a significant reduction in negative symptoms. A recent project has focused on training parents in CRAFT in order to facilitate their treatment-resistant adolescent's treatment entry, and to manage their child after entry into community-based treatment [50].

A meta-analysis has confirmed the effectiveness of CRAFT [76]. It was demonstrated that CRAFT produced three times more IP engagement than Al-Anon/Nar-Anon and twice the

engagement of the Johnson Institute intervention. Furthermore, CSOs' mental health and family function improved, irrespective of IPs' successful treatment engagement.

A unique application of the CRAFT protocol was a study that delivered CRAFT in a group treatment format [54]. Participants were randomly assigned to a CRAFT group or to self-directed CRAFT, with the latter receiving the CRAFT self-help book [59]. The intent-to-treat analysis contrasted the CRAFT group engagement rate (60%) with the self-directed CRAFT rate (40%) and detected no statistically significant difference. However, for those CSOs assigned to the CRAFT group condition who attended at least one session, 71% engaged their IP into treatment. The implication is that CRAFT delivered in groups can be a cost-effective method of getting treatment-refusing IPs into treatment.

In summary, CRAFT has been found superior in engaging treatment-refusing substance-abusing individuals compared with traditional programs. CRAFT has been shown effective across ethnicities, different types of CSO–IP relationships, and various kinds of drugs of abuse. Furthermore, CRAFT works in less than five CSO sessions on average, and CSOs report psychological improvement regardless of the outcome of their engagement efforts.

33.2.6.1 International Considerations

Outside the USA, favorable results for CRAFT have been observed when compared to a waiting list [14]. The use of CRAFT recently has been expanded to target new populations, such as family members of already treatment-engaged substance-abusing individuals [55], parents of individuals with autism-spectrum disorders [96, 97], and family members of hikikomori individuals [79]. CRAFT has shown potential in forensic settings as well [63, 74]. Furthermore, CRAFT component analyses have been conducted to identify main components that facilitate treatment entry [49]. Three studies have now investigated using CRAFT with the CSOs of problem gamblers [43, 53, 65].

The CRAFT training manual, "Motivating Substance Abusers to Enter Treatment: Working with Family Members" [86], has been translated into German, Korean, Finnish, and Japanese to date. The self-help version [59] is available in Dutch, Finnish, Japanese, and Spanish. Therapists have been trained in CRAFT across the world, including the USA, Australia, Ireland, Wales, Scotland, the Netherlands, Sweden, Finland, Germany, Japan, and Canada.

33.2.7 Conclusion

The CRA/CRAFT "family" comprises a comprehensive and complementary treatment modality aimed at both individuals with substance-use problems and their family members. As noted, evidence has supported the efficacy and effectiveness of CRA/CRAFT in a wide variety of diagnostic and ethnic populations, as well as different age groups. Since the treatment does not exclusively reduce substance abuse but also addresses psychiatric and forensic problems, it has transdiagnostic potential. Furthermore, it has shown efficacy in both in- and outpatient facilities and outreach teams. Fortunately, the dissemination of these treatment packages is moving forward in many places throughout the world.

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Exercise for Substance Use Disorders

34

Larissa J. Mooney and Richard A. Rawson

Contents

Abstract

This chapter provides an overview of the rationale and evidence for exercise as a treatment intervention for substance use disorders.

L. J. Mooney (✉)
Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles (UCLA), Los Angeles, CA, USA

VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA
e-mail: lmooney@mednet.ucla.edu

R. A. Rawson
Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles (UCLA), Los Angeles, CA, USA

Vermont Center for Behavior and Health, University of Vermont, Burlington, VT, USA

The benefits of exercise on physical health, including weight management and cardiovascular outcomes, are well documented. Research has also demonstrated positive effects of exercise in reducing depression and anxiety and improving sleep and cognitive function. Negative affect states, such as depression and anxiety, are commonly associated with substance use and are risk factors for relapse. Exercise may facilitate abstinence by ameliorating negative affect via effects on the endogenous opioid system and potentiation of dopaminergic transmission. Recent clinical trials have demonstrated benefits of exercise as a treatment intervention for methamphetamine, alcohol, and other substance use disorders. Engagement in activities such as exercise

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may provide a reinforcing alternative behavior that is complementary to other treatment interventions while promoting health and facilitating treatment goals.

Keywords

Exercise · Substance use disorders · Treatment · Methamphetamine · Depression · Anxiety

34.1 Exercise Is Effective for Medical Conditions and Symptoms

The U.S. Department of Health and Human Services' updated *Physical Activity Guidelines for Americans* [91] provide a comprehensive review of the literature and document strong evidence for the general health benefits of physical activity. For adults, improvements ensuing from regular exercise at moderate levels include lower risk of early death, heart disease, stroke, diabetes, high blood pressure, adverse blood lipid profile, metabolic syndrome, and colon and breast cancers. Exercise is helpful for the prevention of weight gain and weight loss, particularly when combined with a lower caloric diet, and is also associated with improved cardiorespiratory and muscular fitness, reduced depression and anxiety risk, and better sleep and cognitive function.

Exercise has been shown to reduce fatigue in individuals with multiple medical conditions, including fibromyalgia [36] and ankylosing spondylitis [25]. The benefits of exercise in reducing chronic pain have also been extensively documented in the literature [29], including reductions in lower back pain and functional improvements from prescribed aerobic [55] and resistance [81] exercise programs. Although the overall quality of evidence is low due to sample sizes and issues with study design, improvements have been demonstrated in chronic pain severity, physical function, and quality of life [29].

34.2 Exercise Is Effective for Psychiatric Conditions and Symptoms

Substance use disorders (SUDs) are associated with elevated rates of comorbid psychiatric disorders, particularly depressive and anxiety disorders (e.g., [31, 40]). Severity of psychiatric symptoms has been associated with poorer treatment outcomes in multiple prior studies (e.g., [15, 30]). Upon cessation of substance use, withdrawal and abstinence syndromes comprising prominent psychiatric features may emerge (e.g., [56]). Syndromes may be characterized by drug cravings, coupled with marked depressive symptoms, including anhedonia, dysphoria, irritability, poor concentration, hypersomnia, low energy, and even suicidality [60]. The contribution of emotional stress to drug use and relapse has been well documented (e.g., [27, 83, 87]), and considerable evidence is accumulating to suggest that substance users exhibit deficits in their ability to process and regulate such stress.

Aerobic and resistance exercise interventions are useful for a wide range of psychiatric conditions, including anxiety and depression [79, 93]. The majority of studies have demonstrated efficacy of exercise in reducing symptoms of depression in both inpatient [54] and outpatient (e.g., [58]) settings; favorable results have been highlighted in several review articles (e.g., [6, 53]) and meta-analyses [20, 65]. Exercise has been shown to reduce depressive symptoms in medically compromised populations, including cardiac [69] and cancer [57] patients. The benefits of exercise relative to psychotropic medication [8] and psychotherapy [28, 33, 42] have also been investigated; equivalent benefits have been found comparing exercise with medication, time-limited or time-unlimited psychotherapy, group therapy, and cognitive–behavioral therapy.

State anxiety has been shown to acutely diminish after individual episodes of exercise [73], and aerobic exercise may confer significant benefit in the treatment of adults with moderate to severe panic disorder [12, 85] and obsessive–compulsive disorder [1]. The major-

ity of studies have suggested efficacy of exercise in mitigating stress-related symptoms across a variety of study populations, including nonclinical [5, 9, 47], clinical [1], and medically compromised [72] adults. In a study of adults with significant anxiety sensitivity, a 2-week exercise intervention significantly reduced anxiety sensitivity relative to a no-treatment control [84], an effect that mediated the benefits of exercise on negative affect states, including anxious and depressed mood.

34.3 Exercise Improves Cognition

Cognitive deficits have been observed in long-term users of various substances. Chronic opioid use, for example, is associated with deficits in attention, processing speed, working memory, and executive functions [61], which can negatively impact methadone treatment response [21]. Methamphetamine users suffer from cognitive impairments during initial months of abstinence, including working memory, selective attention [82], learning [32], and decision making (e.g., [7, 68]). Deficits in multiple cognitive domains have been observed in alcohol-dependent individuals, including impairment in visuospatial and perceptuomotor functions, executive functions, and short-term memory, in addition to dementia and Korsakoff syndrome [43].

Meta-analyses of randomized, controlled trials confirm that normal and cognitively impaired adults derive cognitive benefits from physical exercise [4, 17, 26, 38]. Improvements are the greatest for executive control processes (e.g., planning, scheduling, working memory, dealing with distraction, multitasking), for participants in combined strength and aerobic training regimens, and when exercise duration is greater than 30 minutes [17]. Angevaren et al. [4] found the largest effects of aerobic exercise on motor and auditory function, and moderate effects on cognitive speed and visual attention. Executive and other cognitive functions have been shown to improve after acute bouts of resistance exercise in middle-aged adults [16].

34.4 Exercise and Substance Use Disorders

34.4.1 Neurobiology of Exercise and Substance Use Disorders

Exercise may hasten or improve recovery from SUDs by modifying underlying neurobiological processes, such as dopamine activity [77]. A study demonstrated reversal of methamphetamine-induced striatal dopamine transporter and tyrosine hydroxylase damage after exercise in rodents [67]. In addition, neurotrophic proteins may be regulated in part by exercise and play an important role in regulating neuronal function in the brain and help to sustain normal cognitive, emotional, and behavioral functioning. Brain-derived neurotrophic factor (BDNF), the most widely expressed neurotrophin in the brain, supports synaptic plasticity, facilitates neurogenesis, and modulates neurotransmission [22].

An emerging literature suggests that BDNF may have a role in the pathogenesis of addictive disorders [37]. Treatment interventions that affect BDNF production may mediate synaptic plasticity and neuroprotection, which could, in turn, ameliorate negative affective symptoms, impulsivity, and other cognitive deficits associated with ongoing drug use and relapse risk. Exercise, for example, has been shown in preclinical [78, 80] and human [70] studies to enhance the BDNF release in the brain. This is potentially significant because of the purported benefits of exercise on cognitive functioning [64]; cognitive deficits have been observed in chronic substance users as evidenced by poor performance on memory, attention tasks, and learning deficits [74]. Substance use disorders are also associated with poor impulse control and selective processing [49]. In addition, exercise has been shown to ameliorate negative mood states that may contribute to substance relapse, and prior literature has suggested that low BDNF levels in individuals with SUDs may predispose individuals to higher rates of psychiatric comorbidity [3].

34.4.2 Exercise for Reducing Substance Use and Preventing Relapse

An emerging literature on exercise-based interventions for SUDs provides preliminary evidence in support of this approach. In a study of cocaine-addicted rodents, rats given access to aerobic activity demonstrated reduction in cocaine-seeking, relative to those that did not have access to such activity [50]. The majority of clinical research has focused on aerobic exercise as a potential intervention to aid smoking cessation and has shown mixed effects of exercise on smoking abstinence [90]; more consistent positive effects on cigarette cravings, withdrawal symptoms, and smoking-related behaviors after exercise sessions have been demonstrated [88]. In an investigation of women enrolled in a 12-week cognitive–behavioral smoking-cessation program, subjects were randomized to receive either vigorous aerobic exercise or health education three times a week [10]. Those who participated in the exercise group evidenced significant reductions in cigarette craving, negative affect, and nicotine withdrawal during most weeks of the program.

More recent studies have suggested a preliminary positive effect of exercise in facilitating alcohol use reduction in individuals with alcohol use disorder [51] and in reducing substance use in both treatment-engaged substance users [13] and in non-treatment-seeking cannabis users [14]. In the treatment-engaged population, it was noted that substance use outcomes were significantly better among substance users who attended at least 75% of exercise sessions [13]. An 8- to 9-week structured exercise program has also demonstrated efficacy in adolescents enrolled in drug-treatment programs; adolescents who improved in self-concept, anxiety, and depression risk factors reported reduced substance use relative to those who did not improve on similar measures [18]. Similarly, a prospective investigation of more than 4000 twins revealed lower rates of illicit drug use and alcohol-use consequences in adulthood among physically active adolescents, supporting prior work suggesting a relationship between low physical activity in adolescents and drug use [44].

There have been a number of recent reviews and meta-analyses on the role of exercise in treating patients with SUDs. Hallgren et al. [35] reviewed 22 studies on the efficacy of exercise to reduce alcohol use. Although the evidence did not support the efficacy of exercise to directly reduce alcohol use, exercise did provide benefits in reducing symptoms of depression and improving physical fitness. These conclusions were supported by Stoutenberg et al. [86], who emphasized that while exercise appeared to produce significant positive benefits to individuals in treatment for alcohol use disorders (e.g., reduced anxiety, depression, and impulsivity, and improved self-efficacy), the evidence for exercise in reducing alcohol use was very limited. Linke and colleagues [46] reviewed the impact of exercise on a heterogeneous set of patients with SUDs. Although they concluded that exercise might be a potentially useful intervention that warranted further research, they noted that in many trials, adherence to exercise protocols is poor and, therefore, results are difficult to interpret. Finally, Morris et al. [62] reviewed the literature on the role of exercise in improving outcomes and quality of life for individuals who had been previous users of methamphetamine. The results from this literature review support other findings that exercise can reduce anxiety and depression and improve numerous medical measures and quality of life in this population of former drug users.

34.5 Study of Exercise as an Intervention for Methamphetamine Use Disorder

A multisite study was conducted in the United States by the Clinical Trials Network (CTN), funded by the National Institute on Drug Abuse (NIDA), investigating the benefits of an exercise component added to residential programs addressing stimulant use disorders. The Stimulant Reduction Intervention using Dosed Exercise (STRIDE) study was a randomized controlled

trial that tested the effectiveness of the addition of exercise versus the addition of health education to treatment as usual in improving drug treatment outcomes in 302 participants with diagnostic and statistical manual of mental disorders, fourth edition (*DSM-IV*)-diagnosed stimulant abuse or dependence (e.g., cocaine, methamphetamine, and amphetamine) and receiving treatment initially in residential settings and then transitioning to outpatient settings; participants were randomized to receive either a dosed exercise intervention plus usual care or a health education intervention control plus usual care. Although the primary outcome of percentage of abstinent days did not show a significant treatment effect between groups, post hoc analyses controlling for treatment adherence and baseline stimulant use demonstrated greater stimulant abstinence rates among exercise-adherent participants [89].

From 2010 to 2015, the chapter authors (Mooney and Rawson) led a research team in conducting a NIDA-funded evaluation of exercise as a therapeutic intervention for methamphetamine users in early abstinence. The study examined the utility and efficacy of an 8-week, evidence-based aerobic and resistance exercise intervention to promote improved treatment outcomes for a sample of 150 individuals in residential treatment for methamphetamine use disorder. The study examined medical, psychiatric, neurocognitive, and behavioral benefits that may accrue during participation in an 8-week exercise intervention, as well as possible sustained beneficial impacts on drug use following completion of the exercise protocol and discharge from the residential treatment program. The project also included a brain imaging component to collect data leading to an improved understanding of the mechanisms that may underlie observed effects on treatment outcomes and symptom remediation associated with the exercise intervention.

DSM-IV-diagnosed methamphetamine-dependent individuals were screened to determine eligibility, and those randomized to the exercise intervention participated in supervised progressive endurance and resistance training three times per week for 8 weeks (24 sessions), consistent with current guidelines for comprehensive exercise programs (American College of Sports Medicine [ACSM], [2]). Each session consisted of a 5-minute warm-up, 30 minutes of aerobic activity on a treadmill, 15 minutes of resistance training, and a 5-minute cool-down with stretching and light calisthenics. The goal of the aerobic training was to accumulate at least 30 minutes of continuous aerobic exercise at a target intensity set by data derived from maximal incremental exercise testing (XT), as described later. Information derived from the incremental testing was also used to define a safe ceiling for exercise intensity for each participant. The goal of the resistance training was to develop adaptations in muscle strength and body composition to complement the aerobic training program. A total of nine exercises involving the major muscle groups were performed each day.

Participants randomized to the control condition participated in a health and wellness education session three times a week for 45 minutes. A counselor provided informational materials, facilitated discussion of educational content, monitored attendance, and documented participants' involvement. Sessions consisted of an integrated multimedia educational program addressing a variety of health, wellness, and lifestyle topics such as nutrition, dental care, acupressure, sleep hygiene, and health screening, adapted from a previously implemented wellness manual used by Kinnunen et al. [41].

All study participants completed a maximal incremental exercise test (XT) on a treadmill ergometer using a symptom-limited incremental protocol with linear increases in the work rate with respect to time [19]. This test occurred three times during participation—at baseline, study week 5, and immediately following the intervention phase or upon intervention termination. Aerobic capacity ($\dot{V}O_2$ max), and the metabolic or lactate threshold ($\dot{V}O_2\theta$), which is the level of oxygen uptake that defines one's ability to perform prolonged work, were measured using indirect calorimetry with an automated metabolic measurement system. The $\dot{V}O_2$ max and $\dot{V}O_2\theta$ were used as baseline markers of aerobic fitness

as well as for objective indices of each individual's tailored aerobic exercise intervention.

Participants underwent further fitness assessments to determine baseline body composition (skinfolds), muscle strength by 1-repetition maximum (1-RM) for leg press and chest press, and muscle endurance (repetitions to failure using 85% of their leg press and chest press 1-RM values). The 1-RM represents the maximum weight that can be lifted only once through a complete range of motion. The 1-RM and muscle endurance test data were used to establish baseline values of muscle strength and endurance in the study population and to help guide the development of the individually tailored resistance training exercise program (National Strength and Conditioning Association [NSCA], [63]). This test was administered at baseline, week 5, and upon intervention termination. Data obtained from the body composition analysis enabled tracking of changes in fat mass and, importantly, changes in the fat-free mass and skeletal muscle mass. These data were obtained using standard skinfold and girth measurement techniques [48] and calculated using the Jackson and Pollack equation [39] and magnetic resonance imaging (MRI)-validated equations, respectively [45].

A subset of consenting participants (15 from each condition) underwent two positron emission tomography (PET) sessions and two magnetic resonance imaging (MRI) sessions before commencement of the experimental condition and again after the 8 weeks of intervention. Brain region volumes were determined for subcortical regions, including the caudate, putamen, and nucleus accumbens. Dopamine D_2/D_3 receptor availability was calculated as binding potential (BP_{ND}) using the D2/D3 ligand [(18)F] fallypride. The MRI scan was used to confirm the absence of structural brain lesions and to aid in localization of volumes of interest.

34.5.1 Results from the Exercise Study

Methamphetamine users over the course of the 8-week trial were able to safely engage in exercise and derived significant health benefits over a short period. Data from the first 29 study completers, randomized to either exercise (EX, $n = 15$) or health education (ED, $n = 14$), were analyzed to evaluate exercise-related physical outcomes, including aerobic fitness, body composition, and muscle strength. EX subjects significantly improved maximum oxygen uptake by 0.63 ± 0.22 L/min (21%), leg press (LP) strength improved by 24.4 ± 5.6 kg (40%), and chest press (CP) strength by 20.6 ± 5.7 kg (49%). For EX subjects, LP and CP endurance improved by ten repetitions (120%) and seven repetitions (96%), respectively, and these changes were significantly greater than those seen in the ED group. Changes in body composition for EX subjects included significant reductions in body weight (average 1.7 ± 2.4 kg, 2%), percentage of relative body fat (2.8 ± 1.3%, 15%), and fat weight (2.8 ± 1.8 kg, 18%). None of these variables changed significantly in participants receiving ED [24].

Preliminary data collected from 50 study participants revealed diminished heart-rate variability (HRV) relative to age-matched, drug-free controls. HRV reflects the ability of the autonomic nervous system (ANS) to adapt quickly to stress and changes in the environment [23]. At the end of the 8-week study, HRV increased in individuals who participated in the exercise program, but no significant change was observed relative to baseline in individuals randomized to the health education control group, suggesting that physical activity improved balance in autonomic tone in MA users. In addition, results from the PET and MRI neuroimaging examination of a subset of participants suggest improvement in striatal dopamine receptor binding after participation in the exercise program. Study participants in the EX condition ($n = 10$) demonstrated improvement in striatal D2/D3 binding after 8 weeks of exercise according to analysis of PET (using ^{18}F-fallypride), whereas those in the ED condition ($n = 9$) did not [77], suggesting that exercise is an intervention that may ameliorate dopaminergic deficits in individuals with methamphetamine use disorder.

Although differences in relapse rates post discharge from residential treatment did not differ between 135 individuals randomized to the 8-week EX condition versus ED at 1, 3, and

6 months, when groups were analyzed based on the severity of methamphetamine use at baseline, a significant difference in relapse rates was observed in the lower severity users (as defined by use up to 18 days in the month prior to admission). Lower severity users (45.2% of the sample) were less likely to relapse to methamphetamine use at all three time points than higher severity users (54.8% of the sample), as measured by self-report and urine drug screen results [76]. Participants randomized to the EX intervention were more likely to experience reduction in depression and anxiety symptom severity than those in the ED group, and a dose effect was observed whereby attending more EX sessions was associated with greater reduction in symptoms [75]; furthermore, those with more severe medical, psychiatric, and SUDs were most likely to derive benefit in reduction of depressive symptoms from the EX intervention [34].

34.6 Summary/Conclusion

Exercise may be a useful approach to aiding individuals with SUDs in their efforts to avoid relapse after they have achieved abstinence via treatment. The addition of a new, non-drug-related activity could provide a reinforcing alternative behavior that may be effective in facilitating abstinence by enhancing positive mood states via the effects of exercise on the endogenous opioid system and potentiation of dopaminergic transmission [59]. Prior literature demonstrates that exercise can improve anxiety and depression, symptoms that are often associated with initial phases of abstinence after cessation of drug use. Such conditions predispose individuals to relapse and predict poorer treatment outcomes (e.g., [66, 71]). Exercise also improves sleep [92] and performance on cognitive tasks, which may be impaired in chronic substance users. In light of the documented associations between stress, negative affect, and substance relapse in addicted populations [11, 52], together with evidence demonstrating stress regulation deficits in substance users, the development of interventions to ameliorate symptoms of depression and anxiety and improve affect regulation may help to reduce relapse risk in this population. Relief of distressing psychological symptoms may serve to complement relapse prevention skills taught in common therapy approaches for substance users and to promote health and positive behavioral changes consistent with treatment goals.

Key Points

- Exercise is associated with numerous physical health benefits, including improved strength, cardiovascular fitness, weight management, and cognitive function.
- Emerging evidence demonstrates improvements in mental health symptoms associated with exercise, including reduction in depression and anxiety and improved sleep.
- Emerging evidence suggests beneficial effects of exercise as a treatment intervention for substance use disorders.
- Negative affects states, such as anxiety and depression, are common effects of substance use and are risk factors for relapse.
- Exercise may facilitate abstinence from substances by ameliorating negative affect via effects on the endogenous opioid system and dopaminergic transmission.

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Towards Addiction Treatment: Technological Advances & Applying Technology

35

Shea M. Lemley and Lisa A. Marsch

Contents

Abstract

Digital health, broadly defined as applying technology to better understand health behavior and offer healthcare resources, has shown promise in improving the treatment of substance use disorders (SUDs) worldwide. Relatively few individuals seek and receive SUD treatment due to factors such as lack of access and stigma; however, digital health interventions may help address these limitations. Digital health treatments have been shown to be effective when integrated into traditional care, as well as offered as standalone interventions outside of traditional care settings. Future efforts in the field of digital health for SUD treatment will need to address barriers such as consumer engagement and privacy issues.

Keywords

Addiction treatment · Digital technology · Substance use disorder · Digital health · Digital therapeutics

S. M. Lemley · L. A. Marsch (✉)
Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
e-mail: lisa.a.marsch@dartmouth.edu

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35.1 Introduction

In this chapter, we review applications of digital technology to substance use disorder (SUD) treatment. We provide an overview of the clinical utility of digital therapeutics for patients and providers and a review of technology-based treatments that are integrated within traditional care models and others that are standalone. We also discuss various limitations and constraints on the use of digital health in the treatment of substance use disorders. The goal of this chapter is to introduce clinicians to recent advances in the application of digital technology to substance use disorder care.

35.2 How Is Technology Relevant for Substance Use Disorder Treatment?

Digital technology has become increasingly pervasive in modern life, and access continues to spread across both geographic and demographic boundaries. From 2008 to 2018, the percentage of the world's population with internet access more than doubled, from an estimated 23.1–51.7% [1]. Much of this growth comes from less-developed countries, with internet use rates among the least developed countries more than tripling in this 10-year span, growth that was more than nine times that of developed countries [1]. And, within developed countries, underserved populations increasingly have access to the internet. In the United States, for example, internet access rates among those with low incomes increased from 54% to 81% during the period from 2008 to 2018 [2]. Not only is technology reaching more people, but novel applications of technology in everyday life have fundamentally changed areas as diverse as commerce, education, and communication. Although some of the most profound changes have been seen in these areas, digital technology also shows promise for improving health care [3].

Applications of digital technology to health care, broadly called digital health, have created new opportunities across the healthcare sector, changing how providers communicate with patients; create, maintain, and share medical records; and even receive training [4]. Advances in telehealth, for example, permit providers to work with patients remotely or receive training from experts in other locations [4]. Implementing electronic health and medical records (EHR/EMR) increases standardization, improves accuracy, and permits easier sharing of information across providers [5].

Growing numbers of digital health applications have been paralleled by increasing research that systematically seeks to evaluate the effectiveness and utility of digital health tools and interventions. There has been dramatic growth in recent decades in the number of publications on applications of digital technology to healthcare. Figure 35.1 illustrates the marked growth in published research containing the terms eHealth, digital health, mHealth, and digital therapeutics between 1995 and 2018.

In addition to research on digital health more broadly, researchers have examined applications of technology to substance use disorder (SUD) care. Because a thorough discussion of all areas of digital health for SUD is beyond the scope of this chapter, the chapter focuses on digital interventions to improve patient outcomes for substance use treatment. And, specifically, the chapter provides an overview of treatments for SUDs with empirical support from randomized controlled trials (RCTs), even though other promising technology-based treatments for SUD may be in earlier stages of research and development.

Moreover, various other stakeholders are interested in the potential applications of digital technology to health, including providers, countries, and international organizations [6, 7]. For example, the World Health Organization (WHO) and European Parliament have directed resources toward examining and addressing the use of digital health [6, 7]. Recognizing the growing prevalence and potential of digital health to address treatment needs, groups such as the WHO have also prepared and published plans and guidance on using and implementing digital health [7]. In addition to this national and international inter-

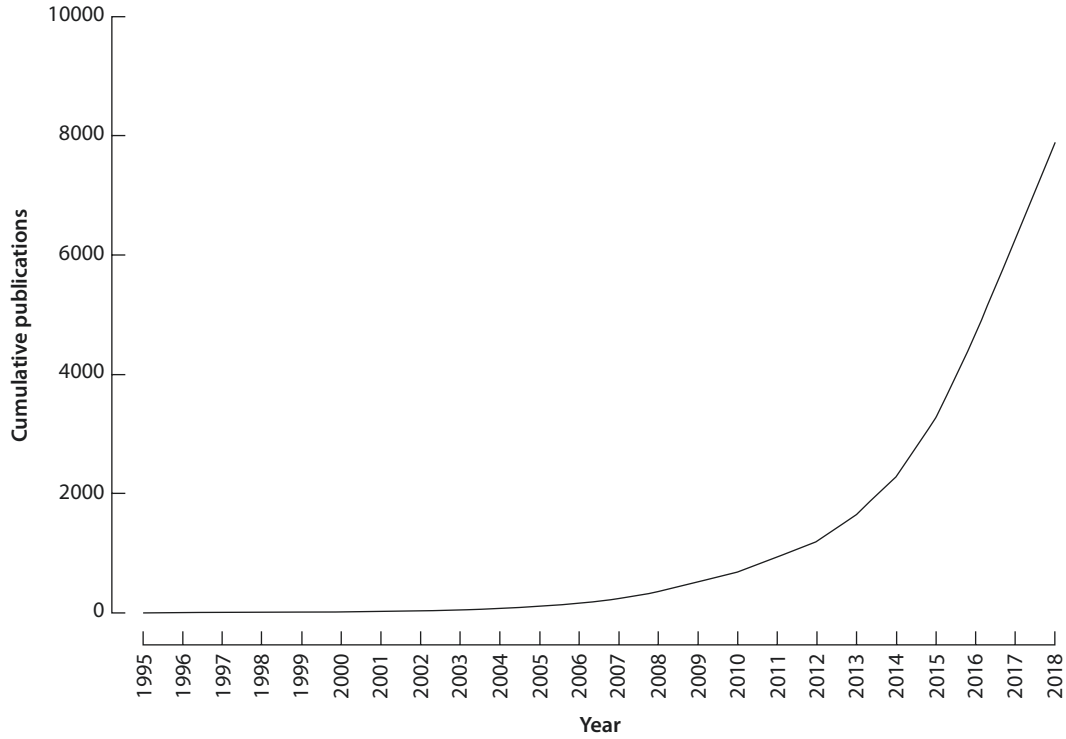

Fig. 35.1 Cumulative publications by year in eHealth, mHealth, "digital health," or "digital therapeutics" from Web of Science search for these terms spanning the years 1995–2018

est, digital health offers several advantages for providers and their patients.

35.3 Why Should SUD Providers Care?

Even the most effective healthcare providers can only help those who are receiving treatment. Unfortunately, only 7% of individuals with SUD seek and receive minimally adequate treatment [8]. Such low rates of seeking and receiving treatment are influenced by myriad patient-centered barriers, such as a lack of financial resources, few available providers, or a perception that treatment is unnecessary or will not be effective [8]. Two of the most common barriers that can prevent individuals from accessing needed services, however, are geographic isolation and stigma surrounding SUD and SUD treatment [9]. Importantly, digital interventions can extend access to care to reduce the impact of geographic and stigmatization barriers on treatment utilization. For example, individuals in rural and underserved settings may need to travel to see treatment providers, but digital interventions can reduce the burden of a provider visit by offering treatment in the patient's home. Similarly, individuals whose work schedules or other commitments prevent visiting a clinic during normal hours may benefit from the increased convenience of interventions that can be accessed remotely. When it comes to sensitive issues such as substance use, individuals—including those with SUD—are often more comfortable disclosing to a computer than to another person [10].

Not only do digital therapeutics demonstrate potential to reach individuals who would not otherwise receive care, they also have the advantage of providing more treatment to those already receiving services. Even when engaged in care, individuals typically receive relatively limited

therapy time; the vast majority of a person's life—approximately 5000 hours per year—is spent outside of treatment [11]. Thus, most of a person's experiences and decisions are occurring outside of the care setting. When it comes to this 5000-hour problem, digital treatments can help address this barrier by increasing time in treatment. For example, web-delivered treatment can effectively replace more than 80% of in-person therapy, such that a patient may only see a clinician twice a month [12]. Other exciting developments in digital health may also help extend treatment into individual's daily lives. One such development, ecological momentary interventions (EMI) use mobile digital technology to provide an intervention in "real time" and in real-world settings, increasing its temporal proximity to behaviors as they occur. For example, text messages have been used to deliver in-the-moment implementation intentions, which help patients link common substance use situations with alternative, non-substance-use behaviors [13]. Further, advances in mobile technology and passive sensing may provide promising extensions of SUD treatment into daily life. Such technology harnesses recent advances in GPS and biometric sensing to determine an individual's location and context using smartphones and wearable devices. Such tools can facilitate delivery of an intervention at the times and locations where it may be most likely to have an effect for that individual. These just-in-time adaptive interventions (JITAIs) are currently being developed to passively monitor an individual's context and behavior and then deliver appropriate interventions at precisely the time they are most needed [14].

Individuals with SUD are a heterogeneous population with varied demographic characteristics, in addition to various personal factors that may influence response to treatment. This heterogeneity may limit the effectiveness of standardized or "one-size-fits-all" treatments. Fortunately, many digital interventions provide individualized feedback based on a patient's current substance use or treatment progress. Others incorporate self-pacing of psychoeducational content and mastery-based progression through skill acquisition-based intervention components [12]. Such individualization allows for treatment success with varied substances of abuse and individuals from various walks of life, including youths and adults, individuals from lower socioeconomic status backgrounds, those with lower cognitive functioning, comorbid mental health and SUD, and polysubstance use [15–17].

Although a primary advantage of digital treatments is how they improve patient care, other advantages more directly benefit providers. Although a shortage of trained mental health providers is a global issue, this shortfall is worse in low- and middle-income countries [18]. Adding digital interventions as a supplement to in-person therapy can reduce the amount of time the provider spends with each patient, increasing the number of patients the provider can treat [19], as well as potentially improving cost-effectiveness [20]. Because providers can access more patient information to support data-based decisions, digital interventions may also improve clinical decision making [5]. Moreover, because intervention components are delivered in a pre-programmed manner, implementation can occur with greater fidelity [21].

35.4 How Are Digital Therapeutics Being Used in Substance Use Disorder Treatment?

Interventions have been developed and implemented across a range of modalities and platforms, including computer or web-based [19]; short message service (SMS) or text messaging [22]; and mobile applications (apps) [23]. Today, distinguishing between digital health modalities is of less concern, as digital health interventions increasingly operate across platforms. For example, after an in-person motivational interviewing session (i.e., brief personalized intervention to promote change in substance use; MI), the HealthCall intervention used daily calls to help reduce alcohol and drug use among participants with HIV, but a mobile app has been developed as a replacement for the daily phone calls [24]. Similarly, the Alcohol eCheckUp to Go (e-CHUG) is a web-based intervention, but the

addition of a text messaging component showed greater reductions in drinking than the web-based intervention alone [25].

Digital health interventions have been utilized throughout the care continuum, from prevention, screening, and assessment, through treatment and recovery. Computerized prevention interventions, for example, may target communication or self-efficacy skills in adolescents or their parents [26]. Digital screening and assessment tools for SUDs are available to aid in the identification of problematic substance use. For example, computerized substance use screening tools have been successfully implemented in primary care settings, permitting identification of problematic substance use among individuals who are not presenting for SUD treatment [27]. More intensive digital health interventions may be incorporated alongside traditional treatment models or offered as standalone treatments.

35.4.1 Digital Treatments Integrated with Traditional Care

Many examples of digital health tools for substance use have been integrated into existing care models. Such tools may be offered as a supplement to existing treatment or used to replace a portion of usual care.

35.4.1.1 Intensive Digital Interventions Alongside Care

Digital therapeutics offered alongside clinical care offer advantages over traditional therapy alone. Adding a digital health component improves treatment retention and abstinence rates over office-based therapy alone, often at only modest per-patient cost increases [12, 20]. Further, by replacing a portion of treatment with digital therapy, a provider may be able to see more patients by reducing face time per patient. Rigorous evaluation through randomized controlled trials (RCTs) has demonstrated the clinical efficacy and effectiveness of a number of these therapeutics for supplementing traditional office-based therapy.

The Therapeutic Education System (TES) is a customizable, web-based intervention based on the community reinforcement approach (CRA) that incorporates contingency management (i.e., incentives provided for objectively verified abstinence; CM) [12, 19]. Up to 65 interactive modules cover content such as psychosocial skills and risk reduction, and TES includes several modalities of instruction, including therapeutic content presented as text or audio, quizzing to fluency, and modeling and role play of real-world scenarios. Evaluations of TES have shown it effectively replaces up to 80% of in-person therapy, results in cocaine and opioid abstinence outcomes that exceed those of care as usual, and improves treatment retention (e.g. [12, 19],). TES has been evaluated and shown to be effective with several demographic groups, including those currently using substances when they started the intervention and those with poorer cognitive functioning [15, 19].

The TES has been adapted into a 12-week web-based intervention for cannabis use. The intervention incorporated components of cognitive behavioral therapy (CBT) and motivational enhancement therapy (i.e., interventions based on motivational interviewing; MET), along with CM, or incentives for providing cannabis-free urine samples. This web-based MET/CBT/CM intervention had nine computer-based sessions with three short, supportive therapist sessions [28]. In an RCT, participants were randomized to one of three conditions: a computer-based cMET/CBT/CM intervention with incentives for cannabis-free urine samples, an entirely therapist-delivered MET/CBT/CM treatment with incentives for cannabis-free urine samples, and a brief, two-session MI-based intervention with incentives just for providing urine samples, whether or not they were positive for cannabis use. The MET/CBT/CM treatment packages—whether delivered by therapist or computer—produced similar rates of abstinence, which were greater than those produced by the brief intervention.

The Computer-Based Training for Cognitive Behavioral Therapy (CBT4CBT) digital health intervention provides computer-based CBT in conjunction with office-based therapy [29],

though emerging evidence suggests it may also be effective as a standalone treatment [30]. The CBT4CBT program addresses topics such as cravings, problem solving, and decision making in six modules. Relative to treatment as usual, the addition of CBT4CBT has been shown to reduce days of substance use and increase continuous abstinence among participants with cocaine, opioid, marijuana, and alcohol dependence [29].

The Self-Help Alcohol and other drug use and Depression (SHADE) program is a computer-delivered intervention incorporating components from CBT and MI to target comorbid depression and substance use [17]. The SHADE program features nine weekly computerized sessions followed by a brief follow-up with a therapist. An RCT comparing the SHADE program, a therapist-delivered CBT/MI intervention, and a person-centered therapy control condition in Australian adults found that both the SHADE program and therapist-delivered CBT/MI intervention reduced depression and alcohol use more than person-centered therapy at three-month follow-up [17]. For depression, there were no differences between the SHADE program and the therapist-delivered CBT/MI intervention, but those in the SHADE program had greater reductions in alcohol use than those in either therapist-delivered intervention.

An app-based treatment for those leaving residential treatment, the Addiction-Comprehensive Health Enhancement Support System (A-CHESS) uses a smartphone app to provide information, adherence strategies, decision-making tools, and social support for adults with alcohol dependence who are transitioning out of inpatient treatment [23]. The A-CHESS app also includes a risk assessment component to deliver targeted messages and social support, as needed. Relative to usual continuing care, patients randomized to receive A-CHESS had fewer self-reported risky drinking days (i.e., >3/>4 drinks for women/men) in an RCT.

To address the limited availability of mental health services in Asian countries, the S-Health China app was developed for smart phone [31]. S-Health China incorporates cognitive-behavioral elements, such as trigger recognition, coping, and self-management. In a pilot study with participants who used heroin or other drugs, users of the app reported fewer drug use days relative to an educational text-messaging control condition, but there were no between-group differences in positive urine samples at the weekly drug screens during the four-week intervention period.

A web-based treatment for cannabis use, Can Reduce incorporates elements of CBT and MI and features eight online modules plus access to a therapist [32]. An RCT compared Can Reduce with and without the inclusion of up to two counselor chat sessions with a control condition, and results suggested that the availability of the chat component was necessary for reductions in cannabis use at three-month follow-up, even if participants did not take advantage of the chat sessions.

Other treatment approaches have used new technology to remotely verify abstinence and deliver incentives. For example, a secure website and webcams were used to video record participants' breath carbon monoxide (CO) samples and readings because breath CO provides an objective measure of smoking [33]. In a 6-week RCT, rural participants were randomized to an intervention in which they received monetary incentives contingent on providing CO samples below an abstinence threshold or to a control condition in which participants provided CO samples on video but received noncontingent incentives. Participants receiving the incentives contingent on abstinence were more likely to provide CO samples that were negative for smoking and had greater levels of continuous abstinence.

35.4.1.2 Digital Health Following Brief In-person Interventions

Other digital interventions have been designed to follow in-person brief interventions to enhance or extend their effects. For example, the HealthCall intervention was developed to reduce drug and alcohol use among persons living with HIV, though not all studies have shown evidence of clinical effects. After a single session of in-person MI, the HealthCall intervention featured automated daily calls that incorporated elements of MI, self-monitoring, and personalized feedback.

An RCT showed that MI + HealthCall—but not MI alone—reduced alcohol use more than an educational control condition, and among alcohol-dependent patients, MI + HealthCall reduced alcohol use relative to both MI alone and control [34]. However, challenges were identified with the repetitive nature of the calls and engagement with HealthCall. More recently, a pilot study tested the efficacy of a smartphone app to replace the automated daily phone calls [24]. The app-based intervention included more interactive content, such as videos, and resulted in improved engagement relative to the phone calls. The app-based HealthCall intervention significantly reduced drug use, but not alcohol use, relative to motivational interviewing alone.

The MOMENT intervention follows two in-person sessions of motivational enhancement therapy (MET) to target adolescents' cannabis use [35]. Designed as an ecological momentary intervention (EMI), MOMENT features momentary assessment of cannabis use followed by support and coping strategies delivered through text messaging. Relative to MET alone, the MOMENT intervention demonstrated reductions in cannabis desire and cannabis use following targeted contexts or events.

35.4.2 Standalone Digital Treatments

Digital health interventions provided outside of traditional care have the potential to reach populations unlikely to present for treatment in standard clinical settings. Because major barriers to SUD treatment involve treatment availability and stigma [8], online interventions accessible outside of traditional care models can fill an unmet need. For example, the Can Reduce intervention for cannabis use identified key differences between users of its online, self-directed intervention and traditional clinic-based therapy [32]. Namely, the Can Reduce users were older and reported more cannabis use days. Similarly, the treatment-seeking population of cocaine users recruited into an RCT to evaluate Snow Control was older and more educated than individuals typically entering outpatient treatment for cocaine use disorder [36].

35.4.2.1 Brief Standalone Digital Interventions

Although digital screening and assessment tools may focus solely on identification of substance use problems [27], several direct-to-consumer digital tools include screening and brief treatment components that are available in one or more brief, online sessions. These brief interventions typically assess an individual's use patterns and then provide personalized feedback addressing topics such as social norms and the health and financial consequences of substance use. Brief online interventions often target alcohol use by college students, with findings generally supporting short-term efficacy for reducing alcohol consumption (e.g., [25]). A one-session online brief intervention called Drinker's Check-up has been tested in adults and has produced short-term reductions in alcohol use, consistent with those produced by in-person brief motivational interventions [37]. A brief online intervention has also been developed to reduce cannabis use among college students, but the intervention resulted only in changes to perceptions about cannabis but not use [38].

Relatively few brief interventions address substance use beyond alcohol or cannabis, but the Motivational Enhancement System (MES) has been used to target multiple substances in a single session, computer-delivered brief intervention that incorporates elements of MI [39]. Developed for use in perinatal women, MES features three components: assessment and feedback, advantages and disadvantages of changing substance use, and a summary of the individual's interest in change and optional goal setting. Although the effects of the intervention do not seem to maintain long term, MES has produced short-term reductions in use of most drugs in RCTs [39].

35.4.2.2 Intensive Standalone Digital Interventions

Intensive standalone digital interventions are designed to deliver treatment spanning several

weeks but outside of traditional care settings. These interventions feature multiple sessions or modules focusing on skill development and coping skills and behavior change strategies. Other components may include social support or progress tracking. Many of these intensive digital interventions have been developed for alcohol and tobacco, although some programs target cannabis, cocaine, or amphetamine-type stimulant (ATS) use.

Some online digital interventions feature multiple self-directed modules designed to be accessed over the course of several weeks. The DEpression-ALcohol Project (DEAL Project) is a four-week, web-based intervention for young adults with depression symptomology and hazardous alcohol used [16]. Based on the SHADE program, the intervention features four modules covering topics such as assessment and goal setting, behavioral activation, cognitive restructuring, and mindfulness. In an RCT, Australian young adults were randomized to the DEAL Project intervention or to view a website featuring informational health modules. Relative to the health information website, those receiving the DEAL Project intervention showed reductions in alcohol use and depression symptoms post-treatment. These reductions were maintained up to 6-months post-treatment, but differences between the intervention and control group were no longer significant, limiting conclusions that can be made about longer-term effects.

For treatment to decrease cannabis use, Reduce Your Use delivers six modules of a web-based intervention based on MI and CBT that includes motivational feedback, goal setting, and skill development focused around urges, withdrawal, and expectancies [40]. In an RCT comparing Reduce Your Use with web-based educational information, Reduce Your Use resulted in lower cannabis use at six-week follow-up and fewer, less-severe cannabis dependence symptoms at three-month follow-up.

Web-based interventions have also been developed for treatment of cocaine and stimulant use, but to date, their effects have been limited. Snow Control is a 6-week, internet-based, program to reduce hazardous and harmful cocaine use with techniques from MI and CBT [36]. In an RCT, the eight Snow Control modules were no more effective than an informational website at reducing cocaine use among Swiss participants. Breakingtheice is a web-based program with three modules that incorporates elements of both MI and CBT to reduce amphetamine-type stimulant (ATS) use [41]. An RCT comparing Breakingtheice to a waitlist control group showed Breakingtheice increased help seeking and reduced days out of role but did not reduce ATS use among Australian adults.

35.4.2.3 EMI

Some standalone treatments leverage the unique accessibility provided by mobile devices to provide treatments in the patient's daily life in real time. These EMIs show promise as a method to encourage use of new skills in the times and places where they are most needed. Some EMIs include both in-the-moment intervention and other components. For example, the Location-Based Monitoring and Intervention for Alcohol Use Disorders (LBMI-A) is a standalone smart phone intervention using techniques from CBT-based treatments for alcohol use disorders [42]. The app featured seven psychoeducational models, progress tracking, and tools that could be accessed in the moment, such as coping strategies. In a pilot study comparing LBMI-A to brief MI with bibliotherapy, participants receiving LBMI-A increased their percent of days abstinent over the course of 6 weeks. Moreover, greater use of LBMI-A in a given week was associated with fewer drinks per week and lower percent heavy drinking days.

Other EMIs focus solely on a text-messaging component without additional modules. For example, Riordan and colleagues examined an EMI that used SMS messages to describe the negative consequences of alcohol consumption on heavy drinking days during a college orientation week in New Zealand [22]. In an RCT, students in one of two colleges at a university showed reduced drinking during orientation week and across the academic year, but significant differences were not obtained at the other

college [22]. Although such EMI messages may show promise for reducing alcohol use, the discrepant results suggest that variables such as context and demographics need to be further examined. By contrast, another EMI study used implementation intentions, which focus on prompting non-substance use alternative behaviors in the presence of substance use contexts [13]. In an evaluation of this implementation intentions EMI, adults with alcohol use disorder were randomized to receive text messages of their pre-specified implementation intentions, which linked high-risk drinking situations with alternative responses or a control condition in which these situations and responses were not linked. At the end of the two-week intervention, participants in the implementation intentions condition reduced their number of drinks per occasion more than those in the control condition, but these effects did not maintain at a one-month follow-up. Although EMIs generally show promise for producing short-term reductions in alcohol use, the relatively early nature of this type of intervention calls for more research to determine how frequency, content, and demographic variables influence responses to these interventions.

Several text messaging interventions have targeted tobacco cessation. For example, the Happy Quit text messaging intervention examined frequency of CBT-based text messages to promote smoking cessation among a sample of adults throughout China [43]. The text messages focused on motivational messages and behavior change techniques, and participants could text to request additional supportive messages. In a 12-week RCT, participants were assigned to a high-frequency messaging group (three to five messages per day), a low-frequency messaging group (three to five messages per week), and a control group that received a single message each week featuring study information but no cessation-related content. Participants in both the high- and low-frequency text messaging groups were more likely to be abstinent than control participants at 12-week follow-up, but there were no differences in abstinence between the high-frequency and low-frequency groups.

35.4.2.4 Gaming Elements

Other digital interventions have begun to incorporate game-like elements [44, 45]. One game-based intervention, Alcohol Alert, features three sessions of a web-based game in which adolescents navigate role-play situations dealing with the negative consequences of binge drinking [44]. Adolescents receive personalized feedback for their in-game responses, as well as advice about real-world drinking situations. Among Dutch adolescents recruited from schools, Alcohol Alert showed potential to reduce short- and long-term binge drinking relative to a no-intervention control, but issues with attrition limit conclusions about the intervention. The QuitIt Coping Skills Game gives patients who smoke the opportunity to role-play coping strategies in situations that are relevant to smoking relapse [45]. Tobacco-dependent cancer patients scheduled for surgery were recruited for an RCT. Although more participants who played the game were abstinent relative to those in a standard care control group, the small sample size and issues with retention limit the generality of these findings. Game-based interventions show promise for reducing use of alcohol and tobacco, but the small size of the pilot studies to date limits the conclusions and generality of these findings to broader populations.

35.5 What Can Help Guide the Use of Digital Therapeutics?

The rapid growth in technology and its reach have been accompanied by growth in digital health applications. Although digital health shows promise for improving aspects of SUD treatment, several concerns associated with digital health applications merit consideration prior to adoption for SUD treatment. For providers, general guidelines for digital health, though not focused on substance use, can help guide and inform considerations for use of digital health tools. For example, the WHO's Report on Monitoring and Evaluating Digital Health provides guidance for monitoring processes and

evaluating outcomes when implementing and scaling up digital health [7]. Such reports can inform practical considerations for implementation, but such guidelines do not replace research- and evidence-based best practice.

One example of regulating and disseminating digital interventions comes from the Food and Drug Administration (FDA) in the United States, which recently launched an authorization program for prescription digital therapeutics that directly treat a disease [46]. This program offers a certification framework for digital health interventions that have demonstrated safety and efficacy via RCTs. The FDA authorization process situates these products into existing prescription and reimbursement structures, offering greater potential to promote use of digital therapeutics among providers and their patients. Because digital therapeutics will need to demonstrate clinical efficacy through a rigorous investigation process to receive authorization, this program is an important step in offering both providers and consumers an avenue to verify safety and efficacy of digital treatments. Unfortunately, because few individuals with SUD go to a provider for treatment [8], prescription digital therapeutics may still leave unmet need among those individuals who do not seek professional help. Researchers and developers should continue to consider other flexible models of deployment for their digital health treatments.

The wide availability of technology and the increasing penetration of smartphones may increase the likelihood that individuals seek self-help solutions through commercial outlets, such as the Apple App Store or Google Play. Although some apps available through such sources can be helpful, recent reviews of apps targeting smoking and alcohol use suggest the quality and content of available apps can vary dramatically, with only 5% of smoking cessation apps being judged as high quality using the Mobile App Rating Scale [47]. In 2018, the American Psychiatric Association published guidelines specifically for providers seeking to evaluate mobile phone mental health apps for their clients [48]. These recommendations include considerations about privacy and security; the evidence for the tool; its ease of use; and its interoperability with clinical care. Although helpful, these recommendations may change over time as new research becomes available and technology continues to advance, introducing new concerns.

35.6 What Are Concerns and Limitations of Digital Therapeutics?

Although digital health shows promise for the treatment of SUDs, limitations should be considered with use of these technologies. One major concern involves equity in access to digital interventions. Data suggest that more than half of the world's population are internet users, but internet access rates of the most developed nations are approximately four times those of the least-developed countries [1]. Most digital health interventions for substance use have been evaluated with participants in a single, developed country, though some have recruited participants internationally [40]. The generality of such findings to contexts that differ in financial resources and culture remains underexamined.

Within developed and developing countries, economic inequality represents one of the greatest barriers to internet access. Although the introduction of smartphones has extended internet access to more individuals and groups, within both developing and developed countries [1, 2], an internet access divide still exists. For example, in the United States, 98% of people with high incomes use the internet, compared to only 82% of those with low incomes [2]. Although growing internet access rates across groups are promising, lingering differences in internet access may contribute to inequity in digital treatment availability. Even with internet access, however, individuals vary in their comfort using technology and have differing skillsets that may be necessary to access some digital health treatments, such as numeracy or literacy. Some digital interventions present treatment content as text (e.g., [43]), meaning that individuals need a minimum level of literacy to use such interventions. Although past research has suggested that indi-

viduals with varied skillsets can successfully navigate and benefit from digital health treatments, user skillsets need to be considered before incorporating digital health interventions. Particularly relevant are questions relating to comfort navigating technology and skills required to benefit from a selected intervention. Providers may consider selecting digital interventions that have options to improve accessibility, such as larger text size or content presented in audio or video formats. Other options improving access might involve additional trainings and supports, either within the digital intervention or as an adjunct to treatment.

Other considerations involve the use and implementation of digital interventions outside research settings. Problems with engagement and attrition have been identified with digital health interventions [49]. Specifically, engagement with digital interventions may be limited or start high but fall over time, whereas attrition issues may manifest as high study dropout rates from baseline to follow-up [49]. Attrition can not only make it difficult to assess the effectiveness of an intervention but may also suggest limited generality of the treatment to non-research contexts. Although strategies that may improve engagement have been proposed, more research needs to be done to determine their effectiveness. Incorporating provider contact may reduce attrition in digital health studies [50], and incorporating social aspects into treatments may enhance their effects. Some interventions have shown improved efficacy with some provider contact or the option for therapist contact [32], whereas other interventions have included social components, such as peer contact and support [23]. The relative contribution of these social aspects to SUD treatment effectiveness remains underexamined. Another major consideration is how to transition digital health interventions to broader implementation. In a UN Parliament survey of European experts in the field of SUDs, 64.4% indicated that they never or rarely use technology-based interventions for SUDs, broadly defined to include telehealth, online therapy, and self-help interventions [6].

Other limitations are related to privacy and security of the technologies themselves [50]. Well-publicized breaches of both commercial and healthcare data highlight the very real security and privacy concerns inherent to use of any digital health application. Those who develop technology will continue to grapple with improving the privacy and security of their applications, but providers using digital health technology will need to evaluate the risks and benefits of a given intervention, keeping issues of security in mind. Acquisition of samples for biochemical verification of abstinence may also raise privacy issues. Although the entire process of obtaining a breath CO sample to verify smoking abstinence can be video-recorded to ensure the sample was given reliably and by the appropriate individual [33], other objective measures of abstinence cannot be remotely verified due to privacy concerns.

35.7 Conclusion

Applications of technology to health care, broadly called digital health, show promise in promoting access to and availability of SUD treatment. Digital treatments for SUDs have been developed for various digital platforms and treatment settings, and these treatments have been demonstrated to be effective through RCTs across substances and demographic groups. Technological innovation is enabling novel, promising treatment approaches, such as JITAI and EMI, that can extend treatment into patients' everyday lives. Despite these intriguing advances in digital health for SUD, barriers to use and adoption of digital treatments, such as privacy issues, remain. Despite these barriers, digital health treatments for SUD show promise for increasing the availability of effective SUD treatment.

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36 Cultural Adaptation of Empirically Validated Therapies for Treating Drug Dependence: International Considerations

Felipe González Castro, Manuel Barrera Jr, and Flavio F. Marsiglia

Contents

F. G. Castro (✉)
Edson College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ, USA
e-mail: felipe.castro@asu.edu

M. Barrera Jr
Department of Psychology, Arizona State University, Tempe, AZ, USA

F. F. Marsiglia
School of Social Work, Arizona State University, Phoenix, AZ, USA

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Abstract

This chapter examines issues and challenges in the local and cultural adaptation of evidence-based interventions (EBIs) and empirically validated treatments (EVTs). We examined the prior Fidelity-Adaptation Dilemma from the contemporary perspective that regards both *fidelity* and *adaptation* as equally important intervention imperatives. This approach involves implementation fidelity in congruence with the theory-based and empirically validated core therapeutic thrust of the intervention, while also exercising flexibility in conducting planned adaptations that are responsive to the "real world," needs of diverse cultural subgroups of clients. The need to develop pretreatment "integrative modules" is described as an innovative feature of contemporary EBI design, to aid in integrating the EBI for effective "function and fit" within various communities and health service delivery settings. The goal is to facilitate EBI widespread dissemination and implementation to thus improve the health and well-being of diverse clients and community residents. The implications for international dissemination and implementation across nations, cultures, and among diverse clients are described.

Keywords

Cultural adaptations · Evidence-based interventions · Empirically validated treatments · Integrative modules · Fidelity · Adaptation

36.1 Introduction

36.1.1 The Case for the Cultural Adaptation of Drug Abuse Treatments

Interest in the *adaptation* of model treatments—*evidence-based interventions* (EBIs) and *empirically validated therapies* (EVTs)—has increased in recent years [7, 13]. This chapter examines issues, perspectives, and approaches in the cultural adaptation of original EBIs or EVTs, respectively, as examined within two research areas: (a) prevention interventions with adolescents and (b) drug abuse treatments with young adult and middle-aged clients. It also examines (c) issues of intervention "fit and function" within a community or health service agency seeking to adopt that EBI.

The strategy of adapting a validated model treatment, as opposed to its delivery with total fidelity and thus without adjustment [18], has emerged as a significant and controversial approach. Some research investigators have argued that evidence-based interventions (EBIs) and evidence-based treatments (EVTs) [7] should be disseminated widely to diverse client groups, and when implemented with high fidelity should work as designed, thus obviating any need for adaptation. By contrast, evidence from a study of school-based drug abuse prevention curricula [40] reveals that classroom teachers who administered manualized model prevention interventions frequently modified the original intervention because they saw significant limitations in the original model intervention. These teachers generally sought to modify the original EBI to make it more culturally relevant for their adolescent students. Similarly, among drug abuse counselors and therapists, fidelity in the delivery of original and validated EVTs has also been remarkably low [7].

Regarding efforts at local adaptation, teachers from schools populated by high percentages of racial/ethnic minority students have been most active in making relevant adaptations. These adaptations have focused on three major content areas: (a) adding content on preventing youth violence, (b) accommodating limited English proficiency students, and (c) addressing issues relevant for racial and ethnic minority students [40]. Although this issue relates to substance use preventive interventions for adolescents within

the United States, these adaptation issues parallel similar concerns in the adaptation of drug abuse treatments within the United States, as implemented with major racial/ethnic minority populations—African Americans, Hispanics/Latinos, Asian Americans, and Native Americans.

Furthermore, adaptations conducted not only to accommodate cultural variations within nations but also conducted to make interventions developed in one nation more suitable for use in other countries [27]. The complexities of international adaptations will also be discussed later in this chapter.

36.1.2 Issues Involving Fidelity and Adaptation

Fidelity refers to the extent to which a treatment is delivered as originally developed and implemented by the treatment's manualized procedures that have been validated within one or more randomized controlled trials [19]. By contrast, the *adaptation* of a model treatment refers to modifications in one or more treatment components or activities to increase treatment *relevance* and *effectiveness* for a specific cultural subgroup of clients [9]. Such modifications often focus on treatment contents, activities, or forms of implementation that neglect or conflict with the needs of a cultural subgroup of clients. Ideally, such adaptations will increase intervention *reach*, *participant engagement*, as well as intervention *efficacy*, and *sustainability* [1]. Presently, this Fidelity-Adaptation Dilemma [13] has been reframed from the original polarized perspective that pitted fidelity against adaptation, to an integrative perspective that acknowledges the importance of both approaches. This reframed view asserts that implementation fidelity to the theoretical foundations of the intervention is important, yet so it well planned flexibility to adapt certain aspects of the EBI to respond to "real-world" issues, particularly in response to issues central to the lives of individuals from culturally diverse populations.

In principle, each EBI should be broadly disseminated, thus making that treatment readily available to many communities and consumers [44]. Nonetheless, and as noted, in practice this broad-based dissemination and implementation have not been fully realized [7]. Since the emergence of fidelity-adaptation controversies, efforts to adapt model treatments have become "the rule rather than the exception" [40]. This suggests that there may exist few truly "universal" or "one-size-fits all" interventions that work well for nearly everyone, and thus not in need of local adaptations. This universality appears to diminish when treating more complex health and mental heathy problem, such as obesity reduction or the treatment of post-traumatic stress disorder. A more realistic scenario is that some form of *local adaptation* will be necessary, at least in the form of a linguistic translation, although it is likely that other cultural modifications will likely be necessary.

36.1.3 Lessons Learned From the Clinical Trials Network

Regarding efficacious outcomes from drug abuse treatments, Carroll and collaborators summarized the lessons learned from 10 years of research from the National Institute on Drug Abuse Clinical Trials Network [7]. Regarding emergent issues that affect empirically validated therapies (EVTs) for drug abuse treatment, these investigators noted that (a) retention in treatment remains a major problem in substance abuse treatment, since treatment retention is critical to treatment success; (b) EVTs are still not broadly implemented in practice, (c) when implemented are often delivered with low fidelity; and (d) at the agency level, effort, support, and commitment are essential factors for adopting and sustaining an EVT, given the costs of implementation, staff training, and supervision [7]. Given the importance of client retention, along with the problem of low utilization of EVTs, these issues should be addressed in the design of future EVTs to promote client retention by enhancing the treatment's cultural relevance as this can increase client engagement [26].

36.1.4 Intervention Dissemination and Implementation Within Diverse Settings

A major problem that has limited the widespread dissemination and implementation of evidence-based interventions (EBIs) is that despite their established effectiveness, these EBIs have attained limited adoption and utilization within various community and healthcare service settings [25]. Thus, the design of future EBIs could benefit from the addition of a preintervention "integration module," for effectively "grounding" the EBI within any of several service delivery settings. This integration module would focus not on intervention *content*, but instead on the intervention's *structural features* to promote a seamless "fit and function" within a given setting [20], by integrating the EBI in congruence with the structure and operations of a local community or service agency.

This integration module may also enhance the EBI's *acceptability* among the local community of consumers, while also enhancing the interventions capacity for *engagement* among these consumers, across the various forms of engagement: attendance, enrollment retention, consumer satisfaction, in-session participation, and home practice [1]. This integration module could build upon and operate as an abbreviated form of the *Planned Intervention Adaptation Framework* that involves conducting one or more preintervention studies to inform forthcoming adaptation activities [46]. The difference would be that these integration modules would aim to promote EBI fit and function within a short period of time thus preparing the EBI and the agency (intervention-setting congruence) for the EBI's effective implementation within as short a time as possible.

Generally, this integration module would be designed to align with: (a) the *interventions of structural characteristics*, for example, adaptability, design quality and packaging, cost, etc.; (b) the healthcare treatment setting's *inner setting characteristics*, that is, structural characteristics, communication networks, institutional culture, implementation climate, readiness for implementation; and (c) the *characteristics of participating individuals*, for example, their knowledge and beliefs about the intervention, self-efficacy, individual stage of change, among other relevant personal characteristics [15].

In summary, the issue of significant limitations in EBI dissemination and implementation into "real-world" community and healthcare delivery settings, as has occurred within the United States, may be regarded as a subset of the larger and more complex issue that involves the dissemination and implementation of EBIs across diverse nations, cultures, and settings worldwide. This emerging challenge can be addressed with the use of the community participatory approach to organize stakeholders from the nation or community interested in adopting a specific EBI, in collaboration with stakeholders from the United States (or another nation) that has developed the original EBI. Much interesting and greatly needed research and planning can be conducted in developing these preintervention "integration modules," for improving the widespread dissemination, implementation, adoption, utilization, and sustainability of these EBIs, thus to hasten their availability for prevention and treatment to improve health outcomes worldwide.

36.1.5 Cultural Considerations in Drug Abuse Treatment

In 1999, the National Institute on Drug Abuse (NIDA) published *NIDA's 13 Principles of Drug Addiction Treatment* [34]. It is noteworthy that none of these 13 principles directly addressed issues of *culture* in the treatment of drug-dependent clients [12]. A few years earlier, issues of culture and ethnicity have been recognized as important for the complete and culturally sensitive treatment of many clients, and primarily for those from racial/ethnic backgrounds [24, 47]. Terrell [47] discussed several strategies for the design and implementation of efficacious alcohol and drug abuse treatments for racial/ethnic minority clients. These strategies include (a) assessing the client's immigration and acculturation experiences including *acculturation stress*, as a factor that can erode

the protective effects of the client's traditional or native culture, (b) assessing a client's experiences with *discrimination*, and (c) developing *culturally responsive* treatment interventions [47]. Today, the contextual factors of race, ethnicity, gender, sexual orientation, and other cultural factors or contextual factors are important for a more complete treatment of diverse drug-dependent clients [10, 12, 46].

Beyond cultural issues, some of these 13 principles may be regarded as elements of a drug abuse treatment that can operate as core treatment components. The multiplicity of these NIDA principles also underscores the complexities inherent in the delivery of a comprehensive drug abuse treatment. Such treatment also includes the need for ongoing monitoring of client progress, and the ongoing clinical need to make relevant adjustments to optimize treatment by tailoring it to the client's needs [6].

36.2 Description of Approach

36.2.1 Exemplar of a Tested and Effective Drug Abuse Treatment Program

The Matrix Model is a manualized multicomponent model treatment. In its basic form, the Matrix Model consists of a 16-week program delivered in 3 sessions per week for a total of 48 sessions [35]. The Matrix Model treatment includes (a) 12 family therapy sessions, (b) 4 social support group sessions, (c) 4 individual treatment sessions, and (d) a weekly breath alcohol testing and urine testing protocol. This treatment is nonjudgmental and nonconfrontational and includes positive reinforcement from therapists and peers for appropriate behavior change [23, 38].

The Matrix Model was developed from the integration of empirically based interventions and "grassroots" clinical experiences [38]. This manualized treatment includes patient handouts and a patient workbook that introduce evidence-based recovery activities as developed from the integration of five theory-based treatment approaches: (a) motivational interviewing, (b) early recovery phase treatment activities, (c) cognitive-behavioral therapy (CBT) including contingency management, (d) family therapy, and (e) 12-step facilitation [35]. As developed from these five treatment approaches, the formal *core components* of the Matrix Model consist of (a) early recovery phase treatment activities, (b) individual sessions, (c) urine testing, (d) family and conjoint sessions, (e) family education groups, (f) social support groups, (g) relapse analysis, and (h) relapse prevention training.

The Matrix Model is guided by eight *treatment principles*: (a) create explicit structure and expectations; (b) establish a positive collaborative relationship with the client; (c) teach information and cognitive-behavioral concepts; (d) reinforce positive behavior change; (e) provide corrective feedback when necessary; (f) educate the family regarding stimulant/drug abuse recovery; (g) introduce and encourage self-participation; (h) use urinalysis to monitor drug use ([38]; J. Obert, personal communication, April 2, 2013).

36.2.2 Cultural Adaptation of the Matrix Model

In principle, the cultural adaptation of the Matrix Model or any EVT begins by identifying problems in treatment implementation, and also by identifying sources of client-treatment mismatches (non-fit) [9]. This is followed by making planned adaptations in treatment content, activities, or forms of delivery, as recommended by consumer feedback from key informants, stakeholders, and as reviewed by a Cultural Advisory Committee. These adaptations would be accomplished: (a) while seeking to maintain identified core treatment components (essential program activities); (b) increasing the cultural relevance of the treatment for local consumers (clients and subcultural groups); (c) increasing client motivation, engagement and treatment involvement; (d) sustaining the efficacy of the treatment effect (i.e., maintaining the "effect size" on targeted outcomes); and (e) ideally increasing the treatment's "effect size" [8], that is, producing a

greater and clinically significant magnitude of improvement on targeted outcome variables.

Moreover, effective cultural adaptation can ideally advance "beyond the black box," meaning that these adaptations would introduce: (a) a greater understanding of how cognitive-behavioral theory or the treatment's *logic model* produces therapeutic improvements on targeted outcome variables, and (b) greater knowledge of how cultural treatment factors improve the treatment's relevance for addressing client needs, while also increasing the treatment's effect size.

Reducing client-treatment mismatches Conceptually, the greater the gap or *mismatch* between the EBI's core concepts and activities, and the needs and preferences of a clients, the greater the adaptive changes necessary to fit the needs of a targeted group of clients. For implementation in international venues, a relevant question is, "In what ways should an original EVT developed for American drug dependent clients be modified for application with specific groups of clients from another country?" In this regard, within the United States, certain "mainstream treatments," which were designed for middle class White American clients, have been shown to be insensitive to the needs of many low-income African American and other racial/ethnic minority clients [5, 10]. This observation led to calls not only for *cultural sensitivity* in treatment development [45] but also for greater *cultural competence* [41] among the counselors or therapists who would deliver these treatments. Such observations ultimately prompted the development of stage models for adapting model treatments (an original EBI) to better fit the needs of specific cultural subgroups [3].

Need for gender sensitivity Historically, one example regerding the need to adapt prior drug abuse treatments is that they were originally developed for treating drug dependent *male* clients, thus inadvertently insensitive to the needs of many *female* drug dependent clients [22]. Such treatments did little to address certain critical issues affecting drug-dependent women, such as their victimization from domestic violence. Thus, gender-sensitive programs were developed for delivery to drug-dependent women. Unfortunately, these treatments, when compared with conventional mixed-gender treatments, in randomized controlled trials have *not* been shown to be more effective in promoting recovery among drug-dependent women. Nonetheless, these gender-sensitive treatments have shown greater acceptability in addressing the common needs of drug-dependent women [22].

36.3 Evidence to Support the Approach

36.3.1 Evidence Regarding the Effects of Core Components

In principle, intervention activities and procedures that constitute a treatment's "core components" are based on theory and on clinical procedures shown empirically to produce desired therapeutic effects. For example, a treatment that utilizes principles from Social Cognitive Theory and cognitive-behavioral procedures, for example, contingency management, might exhibit near-universal effects on human behavior, and thus generally applicable for treating clients from many parts of the world [25].

Given that the Matrix Model is based on Social Cognitive Theory, as well as on principles from cognitive-behavioral therapy (CBT) and family systems therapies, its major core components are (a) family sessions, (b) enhancing social supports, (c) individual treatment sessions, and (d) breathalyzer and urine testing. Furthermore, in principle, within an adapted version of this model treatment, none of these core treatment components should be eliminated or modified. For example, the Matrix Model treatment might lose some of its treatment effectiveness if breathalyzer and urine testing were eliminated within a culturally adapted version of the original Matrix Model.

36.3.2 Evidence on the Need for Assessing Cultural Factors

A study in Belgium illustrates several core issues were examined in an international setting regarding the role of cultural factors in drug abuse treatment. That study conducted a qualitative analysis using in-depth interviews with drug treatment center staff and clients [48]. First, these investigators reported on problems emerging from the existing treatment system's client database it did not distinguish the construct of "ethnicity" from "nationality." This omission lacked information on ethnic issues, as these were conflated with very different issues that involve clients' nationality. From ethnic themes emerging from these interviews, ethnic clients complained that the drug treatment lacked cultural responsiveness. Another theme involved cultural barriers in communication with the therapist, as these barriers became detrimental to progress in treatment. Other barriers included clients' perceptions that their own treatment needs conflicted with their therapist's Westernized world views.

Ironically, most of these clients and therapists recommended that developing a separate ethnic-specific treatment program would *not* be useful. Clients recommended retaining the conventional treatment, although supplemented with attention to cultural factors and issues [48]. This outcome underscores the need to base drug abuse treatment on established scientific principles of recovery from addiction, while also attending to issues of culture and local client needs. Such cultural issues can be addressed without replacing the treatment in its entirety, by adding one or more modules to the original treatment, to address specific cultural issues. Although data are limited, evidence exists that adaptations that are additions to core components are associated with positive intervention outcomes, but changes to components and their deletions are not [1].

36.3.3 Evidence Regarding Engagement and Retention

Issues in reducing the number of sessions As noted previously, in drug abuse treatment, several challenges exist involving client engagement and retention [7]. One approach to increase treatment engagement and retention among youth and families is to reduce the total number of program sessions, for example, from 12 to 8 sessions. However, some evidence indicates that reduction in sessions can also diminish program effectiveness [26], as clients retain less essential knowledge and skills due to this reduction in sessions.

Indices of treatment outcome Based on research conducted with the Matrix Model, major indicators of client retention are (a) *engagement*—staying in treatment as assessed at the 2-week and 1-month observations; (b) *retention*—staying in treatment as measured by the number of weeks remaining in treatment, with a maximum of 16 weeks, and also as measured by staying in treatment for 90 days or more, versus less than 90 days; (c) *abstinence*—as indicated by the average number of drug-free urinalysis tests collected during treatment, and the occurrence of three consecutive drug-free urine analyses during treatment; and (d) *completion*—the completion of the 16-week Matrix Model treatment with no more than two consecutive missed weeks of treatment versus noncompletion of this 16-week program [23]. These indices of client treatment participation are likely correlated, although each provides slightly different indicators of treatment effects.

36.4 International Considerations

36.4.1 General Considerations in Dissemination and Implementation

A major Matrix Model treatment goal involves its broad dissemination to enhance the availability for treating drug-dependent clients [43]. The successful dissemination and implementation of evidence-based interventions (EBIs) and of empirically validated therapies (EVTs) offer great potential for enhancing public health and well-being [44]. This approach, identified as "Type 2 translation research," involves generating scientific evidence on best approaches for (a)

building community and agency infrastructures to deliver EVTs and EBIs, (b) creating practitioner-scientist partnerships, and (c) establishing effective implementation procedures for adopting, implementing, and sustaining EBIs and EVTs within diverse community settings [44].

As an exemplar of this pursuit, the Matrix Model has been translated into nine languages, and disseminated to over 6000 therapists or counselors in the United States and internationally, as taught by 320 key supervisors. These supervisors have conducted Matrix Model training in 21 countries and in all 50 of states of the United States, resulting in staff training conducted in over 2500 treatment agencies (J. Obert, personal communication, April 2, 2013).

Based on challenges from Matrix Model dissemination efforts as conducted in Thailand, Mexico, and in other countries worldwide, the developers of the Matrix Model offer several observations to guide future dissemination and implementation efforts. First, despite the availability of a published Matrix Model treatment manual, this treatment cannot be delivered effectively from this manual alone; formal training of Matrix Model implementers is necessary. Second, at the organizational and community levels, agency and civic leaders must understand fundamental aspects of drug abuse treatment, to provide appropriate support that ensures correct treatment implementation, and avoids administrative decisions that conflict with or that undermine Matrix Model principles and activities (J. Obert, personal communication, April 2, 2013). Third, dissemination efforts are best guided by a clear dissemination plan that is monitored for quality and professionalism in its implementation. Based on prior difficulties encountered in initial dissemination efforts, the developers of the Matrix Model also designed a certification program to ensure quality in training of Matrix Model therapists and counselors. The aim is to implement this treatment with requisite fidelity and with treatment insights regarding fidelity of implementation and/or adaptation planning when encountering problems in the implementation of the Matrix Model (J. Obert, personal communication, April 2, 2013).

36.4.2 General Considerations in International Adaptations

The world is a diverse place in which cultural diversity is expressed in a multiplicity of spoken languages, variations in literacy levels, diversity of religious and cultural systems of beliefs, and a multiplicity of sociocultural attitudes, values, and norms as exhibited across nations, and even within nation (REF). Within this context, worldwide there exists a dynamic tension between the sociocultural forces of *modernization* and quests for change, versus *traditionalism* and quests for the preservation of tradition and a resistance to change [42]. Factors that promote modernism, such as international globalization, emphasize growth and standardization, and operate as forces that tend to homogenize cultural practices. By contrast, factors that promote traditionalism and its indigenous perspectives [37] tend to diversify whole populations into distinct cultural subgroups, emphasizing the retention of unique cultural and local identities and lifeways. These broad cultural influences provide a systemic context against which to consider the cultural adaptation of EBIs and EVTs.

36.4.3 Stage Models of Adaptation and Applications Across Cultures

Within the past decade, several stage models have been developed to guide the cultural adaptation of prevention and treatment interventions [2, 16, 27, 49]. Several of those models were developed for the adaptation of treatments developed initially for majority middle-class populations within the United States, as these original EBIs or EVTs could be modified for greater relevance as delivered to member of the major US subcultural groups, that is, African Americans, Hispanics/Latinos, Asian Americans, Native Americans. However, with a few exceptions [27, 49], cultural adaptation models have *not* been developed for international applications in which EVTs and EBIs created in one country have been adapted culturally for use in another country.

Segmentation: Beyond "country" or "nationality" as the unit of analysis One important way to reframe the approach to cultural adaptation is to avoid a one-size-fits all approach, such as planning to adapt the Matrix Model to be equally effective across the entire country of Mexico. A more useful approach is to consider adaptation for a *local community* or *region* of a country, given the remarkable within-country heterogeneity that exists within most countries worldwide. In other words, sensibly adapting an original EVT "for Mexico" requires a more refined approach to adaptation, one that considers a *smaller unit of analysis* rather than adaptation for an entire nation. Adaptation to a local region or to a local community is critically important. This more *micro-level* approach advances beyond an "ethnic gloss" that occurs under a more *macro-level* of analysis, that is, the nation, given that a macro-approach often glosses over important within-country variations.

For example, in considering the cultural adaptation of the Matrix Model for use "in the country of Mexico," besides a translation from English to Spanish, this adaptation would also require variations for its use within large urban and lower- and middle-class environments, such as within Mexico City and Guadalajara. By contrast, a second modified and adapted version may be needed for use with residents from rural and indigenous communities, such as with residents from rural communities from the Mexican states of Chiapas and Yucatan. For example, within indigenous Mexico, some local residents have very low literacy levels, and may not communicate well in Spanish, with some who do not speak Spanish as their preferred language. Thus, a linguistic adaptation of the Matrix Model to Spanish could render this adapted version culturally relevant only in part, when administered with an indigenous cultural subgroup from the region of rural Chiapas, Mexico. Moreover, such a linguistic adaptation alone would not address long standing cultural traditions, thus also highlighting the need for a local or regional cultural adaptation. Some rural indigenous males from this region of Mexico may also have culturally based *macho* gender role norms and expectations that confer them with considerable male authority and privilege over their family and within their community. Such traditions and cultural practices must be addressed if this treatment is to engage such clients in culturally relevant activities, and operate effectively with the male residents of this local community.

36.4.4 Approaches to International Adaptation

Planning for the cultural adaptation of an intervention A recent article has presented an international model of intervention adaptations, an approach titled, *Planned Intervention Adaptation* (PIA) [46]. The authors described PIA as a synthesis of several models that outline stages or conceptual frameworks for systematically adapting interventions for applications in new cultural contexts [46]. PIA consists of two broad phases that were inspired by Resnicow and colleagues, who distinguished between the concepts of "deep structure" elements of an intervention, from "surface structure" elements [39].

In reality, PIA is not fundamentally different than other cultural adaptation stage models (see Barrera et al. [3]). However, it does distinguish itself from others in the detail of its recommendations. For example, PIA specifies a time period for the initial adaptation stages and a sampling strategy for formative studies. Phase 1 of PIA consists roughly of a 1.5–2 year period when intervention developers and stakeholders (agency staff, potential consumers) agree to collaborate on five preliminary steps that are summarized in a table and detailed in text (e.g., language translations, tests of translated materials, focus group checks on the cultural appropriateness of intervention materials and activities). These preliminary steps help to shape the adapted intervention.

In Phase 2 of PIA, the authors recommend conducting a three-arm effectiveness study which would consist of (a) a minimally adapted intervention (solely surface structure changes such as language translation), (b) a fully adapted intervention

(both surface and deep structure changes), and (c) a control condition. However, even for this recommendation, given the complexities in conducting *conceptually equivalent* linguistic translations, a linguistic translation itself may actually involve more than just surface changes. The PIA also recommends the inclusion of appropriate measures and data analytic procedures to identify possible mediators and moderators of intervention effects [30]. Unfortunately, based on Sundell et al.'s [46] article, it is not certain that the PIA framework actually has been used in the international adaptation of an original EVT intervention.

Undoubtedly, the best examples of international adaptations involve studies of the Strengthening Families Program (SFP), a family skills intervention for the prevention of youth substance abuse [27]. SFP was initially developed and tested in the United States, and subsequently has been adapted for applications in Australia, Canada, Central America, Europe, South America, and Southeast Asia. The results of that work have been summarized with the following statement ([28], p. 176).

> Replications of SFP in non-experimental and quasi-experimental studies in about 17 countries and randomized control trials (RCTs) in nine countries (United States, Canada, Australia, UK, Sweden, Netherlands, Spain, Italy, and Thailand) with different cultural groups by independent evaluators have found SFP to be an effective program in reducing multiple risk factors for later alcohol and drug abuse, mental health problems and delinquency by increasing family strengths, children's social competencies and improving parent's parenting skills.

Kumpfer and her colleagues [29] details 10 steps that should be followed in creating an international adaptation of SFP, and perhaps for other evidence-based programs. Table 36.1 summarizes these 10 steps. Kumpfer et al. [27] illustrated the steps with examples from their extensive experience in many countries. This article contains guidance and best practices for those who are planning international adaptations of evidence-based interventions.

A case analysis of the cultural adaptation of a preventive intervention for Mexico An efficacious prevention intervention originally designed and tested in the Southwest United States was culturally adapted with and for Mexico youth. The intervention's name is *keepin' it REAL (kiR)*, a widely used prevention program in the United States with some localized cultural adaptations in Mexico [31]. This more comprehensive adaptation effort includes the three largest cities in Mexico; NIDA/NIH funded the study.

To learn from the end users what was in need of adaptation, one school in each city implemented the linguistic adapted version of the intervention. The research team collected data regarding cultural adaptation through (a) *focus groups with students:* More than 100 students participated in 21 focus groups; 73 students from 7th grade and 30 from 9th grade; (b) *focus groups with teachers:* At each site, three teachers who implemented *kiR* discussed their curriculum reactions in a focus group format; (c) *lesson fidelity observations:* The team conducted 47 classroom fidelity observations; (d) *teacher reflection forms and notes:* At the end of each lesson, all implementing teachers ($n = 9$) completed a reflection form assessing cultural appropriateness of the lessons; (e) *external Expert Reviews:* The study team sought input and feedback from five external expert reviewers to ensure the adaptations were appropriate and representative of the study sites.

The team developed a coding system and process to establish consistent meanings among the coders [33]. Six research team members—three bilingual coders from U.S. and three from Mexico conducted coding independently. By employing multiple data sources and relying on Mexican partners in this adaptation process, the surface and deep structure adaptations made to the *kiR* curriculum increased the chances that *kiR* will be successful in Mexico and provide an opportunity to extend knowledge and expertise to create a national substance use prevention programming for Mexico. This process enabled the team to preserve the core elements of the curriculum while making the necessary adaptations to enhance cultural fit across diverse settings. As a result, other researchers can employ this approach to develop culturally relevant and scientifically sound prevention interventions.

Table 36.1 Two systematic approaches to cultural adaptation

Step	Action (from Ref. [28])	Stage	Action
1	*Needs Assessment*—Collect needs assessment information from new or existing data to determine major family risk and protective factors for child developmental problems	1	*Information Gathering*—Review of the current drug treatment literature and a screening of client-treatment mismatches
2	*Literature Review*—Collect information from research literature or websites on appropriate family skills. Select the best program for age, ethnicity and risk level of families (e.g., universal, selective, or indicated prevention approaches)		
3	*Cultural Adaptation Team*—Create a cultural adaptation team including family members and the original program developer	2	*Preliminary Adaptation Design*—Propose adapted modifications of specific mismatched content or activities for the original model treatment
4	*Linguistic Translation*—Translate into local language and do minor cultural adaptations		
5	*Initial Implementation*—Implement "as is" with minimal adaptation at first	3	*Preliminary Adaptation Test*—Test this pilot adaptation to assess how well it works with clients from the targeted subcultural client group
6	*Implementation of Initial Changes*—Have implementers from local culture make gradual changes based on what works (culturally appropriate language, stories, and songs)		
7	*Ongoing Cultural Adaptations*—Continuously make additional cultural adaptations and add to curriculum with the program developer's approval	4	*Adaptation Refinement*—Using client feedback from the prior stage, make adjustments on revisions to refine the emerging adapted model treatment
8	*Ongoing Evaluation*—Continuously conduct pre-and post-test evaluations on each family group to measure if the local cultural adaptations are making the program better or worse	5	*Cultural Adaptation Test*—As viable, conduct a small scale or ideally a large scale randomized controlled trial to formally assess the efficacy of the adapted model treatment, as compared with the original model treatment, and ideally also against a treatment as usual (TAU) control group
9	*Add or Drop Adaptations*—Make adjustments to add or drop new cultural adaptations		
10	*Dissemination to Similar Groups*—Disseminate the culturally adapted version to similar cultural groups if effective		

36.5 Conducting a Streamlined Cultural Adaptation: A Five-Stage Model

We recognize that many drug abuse treatment programs in the United States, and in various communities worldwide are delivered within medical centers and in a variety of community-based agencies, large and small. These professional settings often lack the requisite research infrastructure (the program evaluation or research staff, the funding and time, and other research or evaluation resources) to conduct a formalized and months-long randomized controlled clinical trial to test the efficacy of an EVT adaptation as described by Sundell and colleagues and by Kumpfer and colleagues.

36.5.1 A Practical Approach to the Cross-Cultural Adaptation of a Treatment Program

How then might a treatment center or community-based agency conduct a cost-effective, culturally responsive, and scientifically defensible cultural adaptation of an original EVT? Within such an abbreviated cultural adaptation effort, to avoid engaging in misadaptation, we encourage rigor in the application of scientific and community-based participatory research procedures (CBPR) [32]. This abbreviated approach would aim to achieve, and perhaps enhance, certain targeted treatment outcomes: (a) treatment engagement, (b) retention in treatment, (c) abstinence from drug use, and (d) program completion [23]. In addition, as noted, another goal is to avoid introducing iatrogenic effects as consequences of misadaptation.

36.5.2 General Strategy and Procedures for a Streamlined Intervention Adaptation

An initial assessment step in the cultural adaptation of an original EVT is to establish a Cultural Advisory Committee to identify and address cultural and other forms of local problems in treatment implementation and in client-treatment mismatches. Such culturally incongruous contents or activities refer to treatment elements that are confusing, objectionable (low acceptability), or culturally offensive to members of a targeted subcultural client group. Under a community-based participatory research approach (CBPR), these forms of mismatch are identified by conducting *focus groups, key advisor, (key informant) interviews,* and interviews with *stakeholders,* as well as with individuals who represent future recipients of this treatment [36]. It would also be important to conduct interviews with agency therapists or counselors. The identification and assessment of cultural mismatches would reveal significant problems in EVT implementation within the agency or setting, as well as approaches for correcting them. If not identified and addressed initially, such sources of "cultural non-fit" can alienate members of a targeted client group and could induce them to drop out of treatment.

Castro, Barrera and Martinez [9] outlined three major dimensions of model treatment adaptation. These three major dimensions are (a) *cognitive-information processing* characteristics such as language and age/developmental or literacy levels; (b) *affective-motivational* characteristics, including gender, racial/ethnic identity and background, religious background, socioeconomic status, as these factors can influence clients' comfort in accepting the EVT's messages and activities; and (c) *environmental* characteristics, including ecological aspects of the client's local community.

Cognitive-informational adaptation This involves modifying program contents or activities so that clients can understand them. In international adaptations, this would involve a linguistic translation for equivalence in meaning (conceptual equivalence), and not in a word-for-word translation [21]. This should consider the literacy level of members of the targeted subcultural group.

Affective-motivational adaptation This involves modifications of program content or activities that can induce *cultural conflict* or that *prompt reactance* (behavioral resistance). An example might be a Westernized cultural approach requiring male clients to publicly disclose their drug dependence or to discuss sexual issues in the presence of certain family members. Without understanding the possible cultural implications, that practice might be perceived by traditional culture males as inappropriate, feeling stigmatized and resisting participation in an important treatment activity. Conversely, as a culturally modest adaptation, eliminating a discussion of stimulant use as a trigger for sexual arousal and behaviors could undermine drug treatment, given the association between stimulant use and sexual activity as a trigger of a

relapse episode (J. Obert, personal communication, April 2, 2013). Thus, a discussion of benefits and liabilities from such adaptations is critical for making sound adaptation decisions that are both culturally sensitive and that also adhere to scientific principles of effective drug abuse treatment.

Environmental adaptation This involves therapeutic changes in a client's family system, in the living situation, and within the treatment agency, thus modifying local environment conditions to aid in the client's recovery. Within this domain, two basic forms of adaptation consist of (a) modifying *program content,* which relates to the environment, and (b) modifying the *form of program delivery*. Modification of content would include shallow or deep-structure changes. Changes in form of delivery would involve presenting the same treatment content, with changes in (a) *characteristics of delivery personnel*—lay health workers rather than health educators; (b) *channel of delivery*—internet delivery rather than a group session; or (c) *location of delivery*—improving access by delivering the program within a church setting, rather than within a drug treatment center.

36.5.3 Five Basic Stages in a Local or Cultural Adaptation

In a version that parallels Kumpfer's ten-step approach to cultural adaptations, the cultural or *local adaptation* of an original drug abuse model treatment (an empirically validated therapy—an EVT) can be conducted via a basic five-stage process [3]. Ideally, this five-stage process is conducted formally under a randomized controlled trial. In the absence of that option, four of these five stages can be conducted using a community-based participatory research (CBPR) approach as overseen by a well-informed Cultural Adaptation Committee (CAC). Accordingly, this adaptation effort as conducted by a drug treatment agency would be conducted: (a) with the aid and oversight of a Cultural Adaptation Committee, and (b) using CBPR procedures to facilitate input from key advisors, stakeholders, and agency staff to review consumer feedback for a culturally sensitive and scientifically informed analysis of appropriate adaptations. The CBPR approach is a bidirectional approach involving a collective dialogue and group decisions for adapting an original EVT [17]. Table 36.1 presents these five stages as described by Barrera and colleagues [3]. Based in this framework and process, these five stages are as follows:

Information Gathering This involves qualitative research with potential participants and community experts who are familiar with working with targeted cultural groups; and review relevant drug treatment literature as background to identify implementation problems and sources of client-treatment mismatches, as linked to the three major dimensions of cultural adaptation assessment, along with proposed adaptive changes that consider (a) participant characteristics, (b) program delivery staff, and (c) administrative/community factors (see [9]).

Preliminary Adaptation Design *This involves integrating the information and data collected* by the Cultural Adaptation Committee which is staffed by (a) select stakeholders, (b) community experts, (c) developers of the model treatment, and (d) former drug treatment clients or their representatives (treatment insiders); and if needed, other important representatives from the local community or treatment center. A general aim will be to preserve the core interview components, unless there exists strong evidence that one or more aspects of a core component is detrimental to the well-being of clients from the targeted constituency.

Preliminary Adaptation Tests This involves conducting a pilot test of the preliminary adapted version of the original EVT. to assess (a) the elimination of prior implementation difficulties, (b) the emergence of problems with content or activities, (c) client satisfaction with treatment elements, and (d) planned adaptations for improving identified problems.

Adaptation Refinement This involves revising the adapted intervention. Then, if viable as a more formal adaptation activity, proceed to stage 5. That stage involves:

The Cultural Adaptation Trial Formally determine the efficacy of this adapted version by comparing it to a treatment as usual (TAU) control group, and ideally to the original EVT. It will also be important to assess the adapted version's improvements over the original EVT on indicators of client acceptability, engagement, attendance, treatment completion. Although seldom evaluated, within the cultural adaptation trial stage, intervention evaluators could also assess the effects of the adapted EVT on specified mediators and moderators [30]. For example, if a culturally adapted EVT adds a cultural pride component for a mediation analyses to determine whether the intervention was effective in enhancing cultural pride, and then if cultural pride enhancement exerts an effect in reducing drug use or in avoiding relapse. Similarly, moderator analyses could be examine if the culturally adapted EVT was differentially effective: (a) for men versus for women, (b) for clients high versus low in levels of acculturation, (c) among immigrants versus natives, or (d) for any other potential moderators of intervention efficacy [4].

Use of a mixed methods methodology This adaptation analysis could utilize a rigorous mixed methods research design [14], one that includes in-depth interviews with participants and interventionists, for an in-depth assessment of treatment outcomes that provides more complex information on intervention process, client responses to the intervention, and other aspects of this adapted version [11]. This mixed methods approach could provide a deep-structure analysis of client and therapist commentaries on factors that (a) may operate as new core treatment components, (b) may operate as sources of problems within treatment, and (c) worked very well and should be kept, along with (d) client feedback for enhancing the content or delivery of treatment modes to aid in treatment revisions as incorporated into a future enhancement of adaptation.

36.6 Some Recommendations for Adaptation of Drug Abuse EVTs

From this analysis of the cultural adaptation of EVTs and EVIs and their international considerations, we offer a few observations and recommendations.

1. *Identifying robust principles and guidelines for effective cultural adaptations*. There exists the need to identify a few principles and guidelines, such as the principle of "knowing the theories and goals at the core of each intervention component, to avoid changing the core approach when making an adaptation to address participants' cultural or other needs and preferences."
2. *Increasing treatment relevance and "fit and function" with clients and within the treatment setting*. A treatment that not designed for the needs of a specific cultural subgroup may exhibit insensitivity to that group's needs and preferences. EBI implementers can assess aspects of a treatment that lack relevance to the needs of a local group of participants, thus to consider adaptations to address those needs, while still maintaining fidelity to the EBI's major therapeutic thrusts.
3. *Recognizing the importance of cultural factors*. Recent studies have highlighted the importance of considering various cultural factors and contextual influences. These factors include gender, racial or ethnic identity, sexual orientation, levels of acculturation as influences on recovery from drug dependence. Drug abuse treatments can be enhanced by infusing cultural sensitivity and relevant cultural contents and activities to promote full recovery among diverse drug-dependent clients and to avoid relapse [12].
4. *Increasing cultural relevance without reconstructing a treatment*. Increasing an existing EBI's cultural relevance need not involve a

complete reconstruction of an existing EBI. Adding a relevant treatment module or culturally relevant content and activities may be sufficient to enhance treatment relevance and client-treatment fit.

5. *Enhancing client engagement and intervention acceptability*. Client engagement in treatment is important to promote client retention and treatment completion. Low engagement can affect treatment efficacy and the benefits that can be derived from that treatment [7]. It is thus essential that newly developed, adapted, or refined EBIs increase their capacity for client engagement.
6. *Cultural adaptation as a systematic and team effort*. The effective adaptation of an EBI benefits from a planned and systematic team effort that involves a scientist-provider partnership between the developers of the treatment and other stakeholders [17]. Organized agency structures can facilitate this partnership to promote well-planned and executed treatment adaptations. This also includes sustainability plans to fund and maintain the treatment well into the future.

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37 Multidisciplinary Management of Acute and Chronic Pain in the Presence of Substance Use Disorder (SUD)

Daniel L. Krashin, Natalia Murinova, and Jane Ballantyne

Contents

Abstract

The management of pain is greatly complicated by comorbid substance use disorder (SUD), particularly opioid use disorder. Patient with SUD may have more difficulty coping with pain, decreased response to analgesics, and higher rates of complications with pain treatment. Multimodal therapy that is personalized to the patient is much more effective for acute pain. Chronic pain treatment in the setting of SUD is particularly challenging. Chronic opioid therapy is now known to be riskier and less effective than was previously thought. Tapering high-dose opioids reduces risk and may improve functioning for some patients. Others respond poorly to taper and may respond better to buprenorphine substitution.

D. L. Krashin (✉) · N. Murinova · J. Ballantyne
University of Washington, Seattle, WA, USA
e-mail: krashind@uw.edu

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Pain · Opioids · Substance · Addiction · Tapering · Buprenorphine

37.1 Introduction

Substance abuse and addiction have created crises in many countries, rich and poor, in many areas but particularly affecting healthcare. Addiction has continued to be a highly significant public health issue for decades, while the specific drugs of abuse have changed over time. In rich countries, prescription drug addiction has become a particularly challenging issue and area of rapid growth. This development has particularly effected prescription opioids in North America, as they are prescribed in greater amounts to more patients there than anywhere else in the world, particularly for non-cancer pain. The increase in the frequency and dosage of opioid prescribing in the USA was dramatic and has only recently begun to trail off [7]. The opioid crisis in the USA became obvious and severe in part due to prescription opioid misuse [35]. Unfortunately, the high levels of morbidity, mortality, and social chaos resulting from this crisis have continued even as prescription opioid prescribing has declined [19].

The practice of pain medicine has been significantly complicated and strained by this public health crisis. While fewer chronic pain patients are being started on high daily doses of opioids, a cohort of patients on these high doses continues, sometimes known as "legacy patients," and there is no clear consensus on the best path forward for these patients' pain care. The 2016 Center for Disease Control (CDC) guidelines for opioid treatment in chronic pain were very influential in encouraging tapers of opioid medication to lower doses [14, 15]. Concerns have been raised that many patients have been tapered involuntarily and quickly in order to meet this pressure, regardless of their clinical status or whether they had shown any signs of opioid misuse. Opioid prescribers felt considerable pressure in this regard, not only from the CDC but also from state and national regulators and insurance companies. There were plentiful reports of patients suffering severe loss of function, worsening depression and suicidality, and even completed suicides [31]. At the time of this writing, the authors of the original CDC guidelines had issued a clarification stressing that the recommended ceiling dose should not be taken as a mandate for all patients, especially those legacy patients who had been functioning well on higher doses of medication [16].

The other face of pain crisis is the large population of patients who suffer from both opioid use disorder (OUD) and pain. Patients with opioid use disorder who are physiologically dependent on opioids present multiple obstacles to acute and chronic pain treatment, including lower pain thresholds and high opioid tolerance. Comorbid use of other illicit substances is also common. Patients with OUD who are in medication-assisted treatment pose other treatment challenges. In addition to these OUD patients, there are other patients for whom opioid prescribing is problematic, including patients who sell or otherwise divert their prescriptions. There are as well a large number of pain patients that have developed aberrant use of their chronically prescribed opioids. Some of these patients improve dramatically after opioid taper, but many seem to do even worse, becoming more aberrant in their medication use, more distressed, less active, and less functional in everyday activities.

37.2 Substance Use Disorder Complicates the Treatment of Pain

The argument for opioid analgesia for cancer pain remains strong, and this is the most common use of opioids worldwide, although there are some regions with significant access issues to this class of medications and subsequent undertreatment of pain. The best practices of opioid prescribing for chronic non-cancer pain are much less clear. While higher doses and longer duration of prescription are both associated with increased mortality, there does not appear a perfectly safe dosage of opioids [45]. Mounting evi-

dence suggests that receiving opioids after surgery for any length of time raises the risk of opioid misuse or OUD [25].

The interaction between pain treatment and substance use disorder can be complex and hazardous. Treatment of pain with opioids raises iatrogenic addiction risk [4]. In the USA, illicit drug use was estimated by government survey to be almost 9% [53]. While some subgroups of prescription opioid abusers, such as youth, are clinically similar to other substance abusers [8], there is a wide spectrum of illness, and many of the older pain patients who develop problems with opioids have significant physical and psychiatric comorbidities, particularly females [11]. National survey data from 2015 and 2016 suggest that of the 89 million Americans using opioids, almost 4 million (4.4%) engage in prescription opioid misuse, which frequently co-occurs with illicit opioid use, illicit benzodiazepine use, and psychological distress [39].

Patients with substance use disorders are more challenging and risky to treat for pain for multiple reasons. For patients who are actively using, there is naturally a high risk that the opioids will simply add into the mix of drugs that are being abused, with potentially lethal results, particularly in the presence of sedatives or alcohol. Active substance use also decreases adherence to treatments, and these patients are more likely to be lost to follow-up.

For patients whose substance use disorder is in remission, reexposure opioids may be a trigger for relapse in their drug of choice, and they are at increased risk of iatrogenic opioid use disorder.

37.3 Diagnosis and Assessment of Addiction in the Pain Treatment Setting

The diagnosis of addiction in psychiatry has been complicated by a distinction between substance abuse and substance dependence. This has always been a poor fit for the particulars of opioids, which cause a withdrawal syndrome in everyone who takes them chronically, regardless of addiction issues. In the DSM-5, the categories of substance abuse and substance dependence have been collapsed into substance use disorder [44]. Both the DSM-5 criteria for substance use disorder and the ASAM-APS-AAPM criteria for addiction address similar symptoms of impaired control over use or compulsive use, continued use despite harm, and preoccupation with use or cravings [23]. The DSM-5 criteria for opioid use disorder specifically exclude consideration of opioid tolerance and withdrawal, since these will develop in all patients who take opioids chronically [1]. The DSM-5 also specifically excludes this diagnosis in patients who are only taking their prescribed opioid medication, which provides diagnostic clarity but may result in underdiagnosis of patients with iatrogenic OUD.

Addiction can be challenging to recognize in many settings but is particularly difficult in pain clinics, where the majority of patients are in some degree of emotional distress; there is high psychiatric comorbidity with depression and anxiety, frequent occupational and interpersonal problems, and many patients are seeking or are already prescribed habit-forming medications. Studies suggest that clinicians may overestimate their ability to recognize substance abusers "by feel" and that they are prone to fall into prejudicial misapprehension, overestimating prevalence of substance abuse in minority patients and failing to detect it in other population groups. The use of best practices for safe opioid prescribing has risen from a low baseline in an uneven manner, for example, laws have been passed in many states mandating that opioid prescribers check the prescription monitoring program report before writing a new prescription, but the actual adoption of this evidence-based practice has varied [52].

However clinicians can reliably observe two important sets of clues to addiction: risk factors

Table 37.1 Opioid aberrancies

Escalation of medication dosage
Requesting early refills
Doctor-shopping
Losing prescription medications
Tampering with prescriptions

and aberrancies. Aberrancies cover a wide spectrum of undesirable, unsafe, or boundary-transgressing patient behavior (see Table 37.1). The use of prescription monitoring programs and urine drug screenings can also be very helpful in identifying aberrant behavior. Once identified, whether by a physician, support staff, or lab, it is important to consider the anomalies in context of the clinical picture. The differential for addiction includes major mental disorders, delirium, misunderstanding, and interference by family members, roommates, or romantic partners.

Risk factors can be obtained from the patient, his other providers, and family. Several standardized questionnaires, such as the SOAPP and ORT, allow providers to identify known risk factors for addiction by self-report at time of intake.

It is important not only to make an accurate pain diagnosis and detect substance abuse in patients but also identify any other psychiatric comorbidities they may have. Once a patient has been identified as having a complex pain problem with addiction or dual diagnosis issues, they need to be evaluated more thoroughly to develop a good understanding of their psychosocial situation, their social and other resources, and significantly their limitations and challenges, including limited resources, legal issues, and family problems [12].

37.4 Acute Pain in Addicted Patients

The evidence suggests that nonaddicted patients in acute pain who have not had opioids before are at low risk for developing addiction during a short course of treatment with low-potency opioids [50]. However, brain changes of unclear significance are observable after as little as a month of treatment with opioids [56]. Clinical observations suggest that it is quite difficult for patients to discontinue opioids after 90 days of continuous treatment, which is also the threshold for pain conditions to be considered chronic. It is not unusual in academic pain centers to encounter patients who have undergone procedures and been prescribed pain medication for 1, 2, or even 3 months before they are referred to the pain service for a subacute problem which is rapidly becoming a chronic condition. Particularly when discharge is looming, the patient may not be safe to be discharged on high doses of opioids, but abrupt taper prior to discharge may result in a crisis and failure of disposition planning.

This situation requires close assessment to determine what is happening, as this clinical picture may represent reactivation of addiction and medication overuse, an inadequately treated pain condition, or diversion. Ideally, in the case of elective procedures, these issues can be identified beforehand and incorporated into treatment planning; however, a significant proportion of acute pain patients, particularly those with substance abuse issues, will present with pain secondary to trauma occurring due to assault, injury, or motor vehicle collision with no advance warning. When these issues are identified, they should be incorporated into treatment planning for their care of that acute pain episode and beyond. This can also be an excellent time for substance abuse interventions, particularly if the patient's injury was related in some way to their addiction, as this provides a clear adverse consequence to use as a platform for motivational interviewing or other interventional techniques. Motivational interviewing (MI) has been beneficial for preventing alcohol-related reinjury [18] and for increasing exercise in fibromyalgia patients [3], but there is no solid evidence for MI-based interventions for opioid dependence at this time. At the same time, further psychiatric assessment may be indicated, particularly if there is concern for suicidality prior to hospitalization or during the hospital stay. Some hospitals will have 12 step-based program meeting on their grounds, and this may also be an option for motivated and mobile patients to attend.

For pain specialists, the greatest challenge in acute pain in patients with substance use is finding safe and adequate treatments in patients who may have elevated opioid tolerance, lower pain threshold, and difficulty coping with stress and discomfort. Perioperative management must take into account patients' use of prescribed opioids, illicit opioids such as heroin, and potentially patients on chronic buprenorphine or methadone for opioid dependence who will have high tolerance and, in the case of the buprenorphine patient,

some initial difficulty in getting adequate analgesia due to the partial antagonism of the buprenorphine [38]. The provider must also be watchful for signs of other substance toxicity or withdrawal, such as stimulant-inducted psychosis or benzodiazepine withdrawal.

For the pain relief provider, it is important to determine, or at least estimate, their baseline opioid dosage and then maintain them on a regimen of opioids close to this in potency, with additional opioids available as needed for the acute pain. This may require conversion to parenteral opioids, and frequently the use of IV PCA analgesia is the safest and most effective strategy for managing their acute pain needs. In cases of thoracic or abdominal surgery or trauma, neuraxial anesthesia using epidural catheters to deliver local anesthetics or opioids can be very effective. Epidural morphine, for example, is ten times more potent than systemic morphine. Where the pain has a focal source, particularly in an extremity, regional anesthesia, such as using nerve catheters, can block much of the nociception from the injury and thus reduce the need for opioids overall as well as improve perfusion and recovery time. When patients with extremely high opioid tolerance require systemic opioids, a switch to methadone can often allow a decrease of overall dose. Very high doses of opioids raise the risk of respiratory depression and opioid-induced hyperalgesia, a condition characterized by whole-body pain that only worsens with increased opioid dosing.

37.5 Treating Chronic Pain with Opioids

Chronic pain is a highly significant and growing problem as the world's population gets older and more people are surviving significant illness or injury. Addicts are more likely to have all kinds of comorbidities, psychiatric and physical, and have a higher rate of physical injury and chronic pain as well [29]. The phenomenon of so-called self-medication for chronic pain is another mechanism by which patients may be exposed to these medications and develop addiction [46]. Chronic pain has been defined variously as pain lasting more than 3 or more than 6 months; for our purposes, the ASA description of chronic pain as pain lasting longer than "the expected temporal boundary of tissue injury and normal healing and adversely affecting the function or well-being of the individual" is most germane [2]. Perhaps the most important fact about chronic pain is that it is chronic; in other words, it should be managed without the expectation of complete resolution, a quick return to premorbid function, or a short horizon for treatment. The effectiveness of chronic pain treatments is also less than those for acute pain, with average effect size of 40–50% and a substantial minority of patients who receive no benefit from treatment. Any treatments offered for chronic pain should be safe and sustainable in terms of availability and affordability.

The most vexing question in the treatment of chronic pain, particularly chronic pain in addicts, is that of chronic opioid therapy. Patients prescribed opioids for pain are also likely to use opioids nonmedically. This finding has been seen in military veterans and in the general population [5, 17]. A history of substance use disorder makes it less likely that primary care patients will have good relief after 12 months of treatment for musculoskeletal pain including opioids [42]. Some systematic reviews of chronic opioid therapy for non-cancer pain have failed to present strong evidence for the effectiveness of chronic opioid therapy [9].

"Adverse selection" is the phenomenon of the sickest and highest-risk patients receiving more opioids for longer and often receiving the bulk of opioid prescriptions in any given population. This phenomenon has been demonstrated in multiple settings [54]. Similar findings have also been reported among US military veterans and HIV patients [41, 48].

The APS-AAPM guidelines published in 2009 for treatment of non-cancer chronic pain may be helpful in guiding treatment, although they are not specifically focused on substance abuse patients [10]. These patients are often more complex, with layered conditions including substance use disorders, one or more primary pain conditions, and frequently psychiatric comorbidities as well. Although these complex pain patients have been shown to respond better to intensive treat-

ment, the healthcare system rarely allows them to receive it [43]. Interdisciplinary pain care, which includes treatment by allied professionals and mental health, is rarely available in the USA due to coverage and access issues. The more recent and conservative CDC guidelines for opioids in chronic pain are also helpful and recommend low doses of opioids on a trial basis, with a ceiling dosage of 40 mg morphine equivalents [14, 15].

37.6 Treating Chronic Pain in the Setting of Substance Use Disorder

In this patient population, opioids should be prescribed cautiously if at all, in the knowledge that this is intrinsically risky, and more as a last resort than a first step. Providers without the requisite training or experience, or who do not have adequate support, are recommended to avoid opioid prescribing entirely in this population. If the patient is enrolled in substance treatment, or about to enter treatment, opioids may be incompatible and actually sabotage the patient's placement in a treatment program and should be avoided. These patients should first have the benefit of alternative treatment methods to the greatest extent possible, including non-opioid pain medications, nerve medications that are not addictive, behavioral interventions, and physical interventions such as physical therapy, TENS units, and injections where appropriate.

The initial intake for pain treatment should routinely include risk assessment, and this should be repeated regularly during treatment. Once risk factors such as a past history of SUD have been identified, or current aberrancies suggestive of SUD are seen, the decision must be made how to respond. Seeing potential problems of this nature or taking no action is not ethical or professionally advisable for the prescriber; in an older study of disciplinary actions taken against physicians related to opioid prescribing, 12% of the charged physicians had recognized SUD issues in their patients and continued prescribing without taking any action.

If opioids are felt to be a necessary part of pain treatment, they should be prescribed at the lowest dose possible. Many experts recommend short-acting opioids used on a schedule. If the patient is converted to a longer-acting opioid, it is recommended that they are not also prescribed short-acting opioids on an as-needed basis. This practice of treating "breakthrough pain," while very helpful in cancer pain, often results in patients taking both their scheduled and as-needed medications daily to the maximum extent possible, increasing risks and total opioid dosage [33]. It is predictable that some patients will overuse or misuse their medications. Many patients, after an initial good response, will quickly develop tolerance to at least part of the analgesic effect of the opioids and will escalate use on their own or request dosage increases. Increasing opioid doses tends to be a temporary solution only and increases morbidity and mortality risks.

Treatment should be individualized; however, there are many best practices that should be routinely followed in pain treatment, particularly as these risk factors and aberrancies may not be identified initially. Patients with fewer risk factors and less severe aberrancy may not require specific changes in treatment beyond closer monitoring. For high-risk patients and those whose aberrancy is more concerning, practices including a written, explicit treatment agreement, compliance checklists, and randomized urine drug screens may be helpful and should be used in every case. Early intervention with behavioral treatments may also be helpful [27], but there is little strong evidence to guide treatment in these high-risk patients. For patients with ongoing substance use issues or serious aberrancies, such as obtaining opioids from multiple prescribers for routine care or diversion, there may be no better option than stopping the opioids entirely. A taper should be done if safety allows, possibly with referral for consideration of medication-assisted treatment.

37.7 Problems with Tapering and Stopping Opioids

When opioid therapy is tapered or discontinued in patients who have been on opioids chronically, patients often experience at least transitory distress and increase of pain symptoms. Patients

with comorbid depression or anxiety may have exacerbations of these symptoms. A particularly challenging constellation of symptoms occurs in those pain patients who have been on chronic opioids for some time and have developed aberrancies or behavioral complications, which only seem to worsen when the opioid dosage is decreased. At worst, this can lead to a catastrophic scenario where the patient's distress becomes uncontrollable, placing patient and provider in a dilemma as neither further taper nor return to high-dose opioids seems a workable option [34]. This is hypothesized to result from physiological changes in the nervous system with prolonged opioid which make the patient unable to tolerate opioid tapering. This has been called "complex persistent dependence" and has been observed to respond well to buprenorphine therapy. In the USA, this treatment may be difficult to access, particularly if the patient does not meet formal criteria for OUD; some patients are also understandably resistant to this diagnosis, which is highly stigmatized and may have negative impacts on their employment and access to health insurance. In addition, relatively few pain specialists prescribe buprenorphine, and most addiction treatment programs do not feel comfortable addressing pain in addition to SUD.

If not treated with buprenorphine or methadone, chronic pain patients with SUD histories are more likely to relapse, particularly those with OUD [24]. A manualized treatment program emphasizing behavioral treatment including cognitive-behavioral therapy and acceptance and commitment therapy has been developed for veterans with comorbid pain and SUD [26]. Some patients in this position will complain that they are being driven to seek illicit drugs. For ethical and professional reasons, it is recommended to continue to offer these patients the full panoply of non-opioid pain treatments to the extent that they are appropriate.

37.8 Palliative Care in Addicted Patients

Palliative care was defined by the WHO as an approach to treatment which improves the quality of life of patients and their families facing the problems associated with life-threatening illness [47]. In this specialized arena of healthcare, the mandate to provide comfort may take precedence over concerns about addiction. While it is rare for patients in this clinical context to develop new addiction issues, preexisting psychiatric and addiction issues may be reactivated or worsen under the stresses of serious illness and may go unrecognized by providers. Untreated alcohol dependence, for example, is linked to other substance misuse and worse outcomes in pain patients [13]. Some cancer patients are provided with pain medications in larger quantities and dosages toward the end of life than any other types of patient. In addition to addiction, misuse or simple incorrect use due to misunderstanding can put patients at risk. These patients, who may be dependent on others for the management and administration of their medications, are also more vulnerable to diversion of medications by people near them. At the same time, many cancer patients do not receive adequate pain treatment due to access to care issues and also due to patient reluctance to use these medications for fear of addiction [49].

Following best practices in these patients can help track their medication use and identify aberrancies earlier. Close monitoring of symptoms and more frequent dispensing of opioids can be useful in harm reduction approaches. In larger, well-staffed cancer care centers, even daily dispensation of pain medications may be a useful intervention for selected patients. Pill safes and enlisting family members to dispense daily dosages can also improve safety and reduce the risk of misuse/overuse/diversion. In many cases, the medication misuse is also being driven by complex physical and emotional distress, with combined factors of depression, anxiety, worry about the future, impending death, being a burden on family, how family will fare after the patient's death, and non-pain forms of suffering such as dyspnea, fatigue, constipation, or immobility [32].

37.9 Best Practices for Risk Management

All patients may be potentially at risk for addiction, and current approaches to risk stratification are very limited. For example, there is consensus

that there is a large genetic component in predisposition to addiction, with abnormalities of the endogenous opioid system in particular being linked to increased risk of opioid abuse. However, no standard, evidence-based genetic testing protocol has been introduced. While family history may provide some clues to genetic predisposition, addiction is well known to "skip generations" and is often not openly discussed within families, so that the patient may not be aware of relevant history.

Therefore, the concept of universal screening in pain medicine, similar to the use of universal precautions for infection control, is becoming more popular [20]. This universal approach may also serve to reduce stigma and improve the detection of misuse. For example, opioid dependence is more likely to be overlooked in older adults and in Whites [6, 55]. This screening and risk stratification may also help use scarce community mental health, pain management, and substance abuse treatment resources more effectively, as low-risk patients remain in the primary care setting as long as they are doing well, while riskier patients are able to access more specialized and interdisciplinary care. Patients with serious psychiatric issues, substance dependence, or both should generally be seen in a setting with the availability of mental health consultation. This model tends to apply most to large cities and areas near academic medical centers; however, telemedicine applications may extend the reach of these specialties into rural areas and isolated regions [36].

Several useful screening tools for determining risk factors for patients include the COMM, SOAPP, and ORT. These are all brief, self-administered tests. The COMM has 17 items, while the ORT 8 and the SOAPP come in a full 24-item version and briefer versions [37]. The full version of the SOAPP may be the most effective at predicting future aberrancy [40]. Note that even a high score does not automatically translate into "do not prescribe opioids"; these tests must always be interpreted using clinical judgment. Since they are self-reported screens and do not attempt to conceal the nature of the assessment, they may underestimate risks in patients who are unreliable historians or deliberately deceitful.

The use of an opioid treatment agreement is also widespread, although there is very little evidence to support its efficacy. The greatest usefulness of this measure is to provide a transparent means of disclosing treatment policy to patients in advance. It is important to discuss the agreement with patients, along with obtaining fully informed consent for any treatments and documenting same. Since the risks of opioid therapy are much better appreciated now than they were even a decade ago, it is not safe to assume that a patient who is seen already on chronic opioids has full understanding of the implications and risks of this treatment. Any specific policies regarding prescription monitoring, pill counts, and urine drug screens should also be discussed at this time.

Urine drug testing (UDT) offers the promise of letting the prescriber know what the patient is exactly taking. Simple immunoassays have high false-positive and false-negative rates and should be followed up with confirmatory gas chromatography/mass spectrometry testing. Since even monotherapy with some opioids may result in numerous metabolites, these results should be reviewed with an expert, such as a pain specialist, pharmacist, or pathologist, before taking clinical action. UDT is most helpful in demonstrating that patients are not taking prescribed medications or taking additional, non-prescribed medications or illicit drugs. A policy should be developed to guide providers consistently on what actions to take in the event of an unexpected UDT result. Some studies have shown that even when UDT is obtained and shows unexpected results, prescribers continue to prescribe opioids [21]. In some states, where state law recognizes a role for medical marijuana, providers may choose to obtain UDT without checking routinely for THC. UDT is not able to reliably determine whether a patient is taking the full dose of their prescribed medication. These limitations aside, UDT helps providers recognize aberrancy that would not be identified by behavioral monitoring [30]. In the USA, many health insurances will not cover the cost of UDT, so providers must make smart choices about when and how often to order them. Systematic reviews suggest that the benefit for patients of standard UDT policies is modest [51].

37.10 Cooperation with Allied Providers

Primary care providers and pain specialists cannot be expected to master the fields of psychiatry and addiction but must understand enough to recognize patients with these issues, make appropriate referrals, and collaborate with the appropriate allied providers. It is important to provide solid information to colleagues about the nature of the patient's pain diagnoses and their treatment. For patients with addiction issues, some medications such as benzodiazepines and opioids may be both inadvisable and incompatible with their addiction treatment. In this case, prescribing these medications for the patient may unknowingly sabotage their addiction treatment or provoke relapse.

In patients who have been diagnosed with opioid dependence, a possible option for them may be opioid agonist therapy, namely, methadone or buprenorphine. In the USA, methadone may be prescribed freely for pain but only prescribed for the treatment of addiction by federally recognized methadone clinics. In addition, methadone clinics provide patients with a single larger daily dose of methadone, rather than dosing three times a day as is done for pain. Buprenorphine, in the form of Suboxone, may be prescribed for opioid dependence and (off-label) for pain. Buprenorphine is also available without the combination of naloxone and as a long-acting transdermal patch, Butrans. Both of these forms are more prone to abuse. Since buprenorphine is a partial opioid agonist, it may be less prone to abuse than other opioids, and it is also not suitable for combining with other opioids and may precipitate withdrawal in a patient who has been taking other opioids chronically. Bupropion treatment has been shown to be an effective treatment of opioid dependence and also reduces the rush experienced by patients who do relapse and use other opioids on top of the buprenorphine [28]. Naltrexone is also effective for OUD but has no analgesic effect and may worsen mood disorders; this medication, particularly in its long-acting injectable form, will complicate acute pain treatment due to the opioid blockade. A recent review by Harrison et al. provides an excellent overview of perioperative care in patients receiving medication-assisted treatment [22].

37.11 Conclusion

Substance dependence is a large and growing problem in developed countries. Prescription opioid misuse appears to have crested as a public health problem but remains significant, and the wider opioid crisis continues unabated as of this writing. Pain medicine has become intimately involved with this opioid crisis. Many pain patients have comorbid conditions including depression, anxiety, and SUD which complicate their treatment and worsen their prognosis. These patients should be offered the full range of pain management services, with particular emphasis on behavioral interventions; opioids should only be considered, if at all, after reasonable trials of other, safer treatment approaches. Early recognition of the patients by identifying their high-risk status and detecting aberrancies can help with early referrals to mental health and substance abuse providers and cautious, closely monitored prescribing practices. Many patients fall into this overlap between disorders, and there is an acute need for providers who are able to manage these challenging conditions. Specifically, a subset of patients who seem unable to tolerate opioid weaning and discontinuation has been identified. While they may not meet formal criteria for OUD, they may respond to behavioral treatment and buprenorphine.

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Part IV

Main Systems Components in Addictions Treatment

Ambros Uchtenhagen and Giuseppe Carrà

38 Main Elements of a Systems Approach to Addiction Treatment: An Introduction

Ambros Uchtenhagen and Giuseppe Carrà

Abstract

The focus of this section is mainly on the treatment system and on the community, at a regional or national level, as a comprehensive network of different approaches, services, and actors, covering all types of addictive behaviors. This implies the preference for a public health perspective, combining the care for the individual patients in their diversity with the intention to cover the treatment needs in a specific catchment area and for a given population. In addition, there are some chapters focusing on diagnostic issues and reviews of specific therapeutic approaches.

This aim has to consider the availability, affordability, and accessibility of appropriate and qualified treatment. It has to build on effective treatment, provided in an efficient and cost-effective way. It has to stress connections among services, shared concepts of different indications, and routine rules for patient pathways through treatment phases, ranging from first contact, screening, and assessment to treatment planning and monitoring, rehabilitation, and aftercare. Pathways may also follow models of stepped care in an attempt to avoid misplacement of patients and to make best use of the available human and financial resources. Quality of intervention is embedded in evidence based also in the field of drug addiction treatment.

A comprehensive network goes beyond formal therapeutic regimes, by including low-threshold approaches for establishing contact by outreach activities and by harm reduction interventions in support of those still actively engaging in addictive behavior. This includes measures to reduce the risks of injecting, of acquiring blood-borne infectious diseases, and of overdose-related mortality. Such interventions are not in contradiction to others offering a structured regime of substitution medication (e.g., for opiates or nicotine) or even aiming at abstinence from substance use and full recovery. The system has to integrate all these approaches in order to best meet the needs and preferences of the equally diverse people with substance use disorders. Everyone should be able to find what is appropriate and suits him or her best under present conditions.

Such a comprehensive network is work in progress, as addictive behaviors and treatment populations change over time. New therapeutic methods and instruments also ask for adaptation

A. Uchtenhagen (✉)
Swiss Research Foundation for Public Health and Addiction, Zurich University, Zurich, Switzerland
e-mail: ambros.uchtenhagen@isgf.uzh.ch

G. Carrà
Mental Health Department, University of Milano-Bicocca, Monza, Italy
e-mail: giuseppe.carra@unimib.it

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and suited implementation at the system level. Where no such network is in place, the relevant steps for building up a system responding to the needs are recommended. All this goes not without a political support to provide adequate and sustainable resources, in the framework of a treatment policy which is in line with an overall drug policy.

The structure of this section in its revised format can be divided into two parts: The first is about the principles and aspects of the systems approach to addiction treatment, presented in the text above. In the second part, the reader will find information on the individual chapters in this section. This is presented in the following text.

Chapter 39 by Babor TF, "Treatment Systems for Population Management of Substance Use Disorders: Requirements and Priorities from a Public Health Perspective," is a systematic analysis of what has to be considered in a treatment system, in order to best serve all in need of treatment in a given population. *Method:* It is based on relevant previous publications by the author and others, providing additional information on the various aspects, also in a historical perspective. The *Text* focuses on concepts, requirements, and priorities recommended for building up an adequate treatment system, starting out with definitions and rationale, going on to conceptual developments, and finally listing priorities. The *Conclusions* ask for an appropriate resource allocation if the treatment system should allow to cover the treatment needs, including good service quality and access to care.

Chapter 40 by Saunders JB and Latt NC, "Screening, Early Detection, and Brief Intervention for Alcohol Use Disorders," starts out from the observation that alcohol problems are frequently diagnosed too late before becoming chronic and disabling conditions. Therefore, secondary interventions such as providing help for self-recognition, early diagnosis, self-management of use, and therapeutic approaches to change behavior are essential. *Method:* The aim is to provide screening instruments and information on their usefulness, with bibliographic details, rather than a systematic literature search. *Text:* Besides providing evidence for the observations made, the focus is how to implement the use of screening instruments and of brief intervention techniques into clinical practice, including Internet and mobile phone techniques for interactive support.

Chapter 41 by Bobes-Bascaràn T et al., "Clinical Assessment of Alcohol Use Disorders," describes how to evaluate the type and extent of alcohol use and the type and extent of psychiatric comorbidities, of neuropsychological performance, and of psychosocial functioning and quality of life. *Text:* Besides reviewing the necessary elements of a comprehensive clinical procedure, a description of the most relevant psychometric instruments is provided, covering symptomatology; legal, economic, and occupational problems; coping behaviors; and readiness to change.

Chapter 42 by Wurst FM et al., "Biological State Marker for Alcohol Consumption," has a strong focus on the various direct ethanol metabolites and the use of their measurement, adding an overview of the traditional biological markers on consumption. *Method:* systematic description of the various biomarkers and their advantages and limitations. *Text:* Epidemiological data justify the need for better implementation of how to assess alcohol consumption by using biological markers. The main part is a detailed, literature-based description of direct ethanol metabolites and their assessment and value for clinical use. *Conclusion:* advancements in diagnosis and therapy, new perspectives for prevention, and interdisciplinary cooperation due to extended use of direct biomarkers.

Chapter 43 by Assanangkornchai S and Edwards G, "Clinical Screening for Illegal and Prescription Drug Misuse and Nicotine Use," covers screening instruments used in detecting substance use in medical, psychiatric, and forensic services, with a view of providing subsequent treatment. Specific tests utilized are discussed, along with their psychometric properties, intended screening populations and validity, as well as the importance of proper and ethical use. Conclusion: Despite its limitations, screening is a first, small step toward providing successful treatment outcomes.

Chapter 44 by Tremonti C, "Drug Testing in Addiction Medicine," explains in detail how a range of psychoactive substances can be detected in body fluids and tissues for medical and legal purposes, how findings are interpreted on the basis of appropriate knowledge about pharmacokinetics, and characteristics of the various samples to be analyzed. *Method:* Technologies and their applicability are described on the basis of best known standard procedures. *Text:* Drug screening is explained in a range of different contexts, such as hospital toxicology, workplace drug testing, forensic toxicology, postmortem toxicology, sports toxicology, and drugs of abuse testing. *Conclusion:* Close collaboration with laboratory specialists is essential for obtaining adequate results.

Chapter 45 by Harland J, Henry-Edwards S, Gowing L, and Ali R, "Brief Interventions for Illicit Drug Users," focuses on brief interventions as an effective and targeted tool, in the interest of the individual and of public health. *Method:* extended use of updated literature. *Text:* concise description of the nature and the effectiveness of brief interventions, for both legal and illegal substances of abuse, adding specificities of working with illicit drug users and the key principles to be followed. Settings for brief interventions are described. *Conclusion:* Including knowledge and training of brief interventions in medical school and nursing schools, as well as continued education later on, is considered a must.

Chapter 46 by Rush B, "Screening and Assessment of People with Substance Use Disorders: A Focus on Developed Countries," is about best practice procedures including a staged approach and subsequent monitoring of outcome, in order to maximize efficiency. *Method:* selected essential literature. *Text:* Various collaborative models in screening and assessment facilitate such procedures early in contact of persons with psychiatric and especially substance use problems with the treatment system. Best practices are based on an individual's needs and strengths, adhering to a bio- and psychosocial model of understanding disorders, cultural differences and characteristics of a given service, and research evidence of usefulness. *Conclusion:* A more proactive concerted effort to screening for mental health problems and at-risk consumption of alcohol and other drugs is recommended.

Chapter 47 by Uchtenhagen A, "Stepped Care in Addiction Treatment," deals with models and procedures on how treatment intensity can be determined by a systematic screening of patient characteristics, in order to make best use of available human and financial resources in a given treatment system. *Method:* Available literature describes and compares two models. *Text:* Procedures to start out with the least intensive intervention, progressing to more intensive ones if ineffective, are known from psychiatry and other medical disciplines. In the case of addiction treatment, two outstanding models have been developed, one by the American Society of Addiction Medicine ASAM and the other by a Dutch group as a national project MATE (Measurements in the Addictions for Triage and Evaluation). The first developed special models for adolescents and patients with psychiatric comorbidity and the later for patients with legal problems. The implementation meets some resistance from services used to take on patients even if those do not need this type of service. *Conclusion:* Further use and development of stepped care models needs political support.

Chapter 48 by De Leon G et al., "Therapeutic Communities for Addictions: Essential Elements and Cultural and Current Issues," describes community as a method, its various applications worldwide, its outcomes according to research, and challenges and how to meet those. *Method:* based on the extensive knowledge of the authors. *Text:* Besides the explanation of the TC model and its unique role in the treatment system as a recovery-oriented therapeutic method, available knowledge on its effectiveness and adaptations and modifications for special populations and settings are presented. Details on implementing a TC include funding, workforce, duration of treatment, research, challenges, and fidelity to treatment. *Conclusion:* defending the TC model and its unique mission for a recovery-oriented treatment.

Chapter 49 by Galanter M, "Spiritual Aspects of the Twelve-Step Method in Addiction," is

directed at defining the nature of spirituality and its relationship to empirical research and clinical practice. *Method: based* on the extensive knowledge of the author. Text: Diverse theoretical and empirically grounded sources provide an initial understanding of spirituality. More concretely, the movement of Alcoholics Anonymous illustrates the impact of spirituality on addiction in different cultural and clinical settings. Subjective spiritual experience can be assessed systematically by employing empirical techniques, thereby studying an important aspect of recovery. *Conclusion:* more integration into professional treatment needed.

Chapter 50 by Best D and Hamer R, "Addiction Recovery in Services and Policy: An International Overview," emphasizes the growing role of recovery as a treatment goal and a policy vision, aiming at healthy lifestyle and good quality of life. *Method*: based on the authors' knowledge of relevant literature. *Text:* Addiction is a chronic condition, and recovery needs a continuing care approach. Emerging service models and peer-driven recovery supports are described. The aim goes beyond changes in addictive behaviors, to improved overall functioning of the person and his/her quality of life. *Conclusion:* strategies recommended for medical professionals on how to promote recovery in substance-using patients.

Chapter 51 by Smith DE and Davidson LD, "Strategies of Drug Prevention in the Workplace: An International Perspective on Drug Testing and Employee Assistance Programmes (EAPS)," describes the diverse regulation mechanisms and instances for drug testing in the workplace, in the USA and Europe, especially for improving workplace safety by preventing or reducing substance use in staff. *Method:* based on the authors' knowledge of relevant literature. *Text:* A detailed and extensive description of regulation diversity and practices, including statistical information on findings from workplace testing, is provided, as well as much background information in graphs and figures. Same for employee assistance programs. *Conclusion:* The advantages of employee assistance programs for employers and employees are highlighted.

Chapter 52 by Hedrich D and Hartnoll R, "Harm Reduction Interventions, Policies, Settings, and Challenges," is a comprehensive description of all approaches to minimize the impact and negative consequences of substance use in persons unable to quit their substance use or having no access to effective treatment. *Method:* based on the authors' knowledge of relevant literature. Bibliography includes recommendations for further reading. *Text:* Main types of drug use-related interventions to reduce harm are described in detail. Best policy favors combination interventions, illustrated by integrated approaches at the local level. Further topics are enabling environments, prison settings, and ways to overcome barriers. *Conclusion:* Single interventions have best outcomes if they are part of a comprehensive policy to reduce harm from substance use and other addictive behaviors.

39 Treatment Systems for Population Management of Substance Use Disorders: Requirements and Priorities from a Public Health Perspective

Thomas F. Babor

Contents

Abstract

This chapter describes the requirements and priorities of service systems designed to treat persons with substance use disorders. Research and theory are reviewed to inform policymakers, program administrators, and treatment providers about the best ways to organize or to expand treatment services using a public health systems approach, which is concerned primarily with how services contribute to the health and welfare of a population. The requirements of a service system include sound policies (especially stable financing); appropriate structural features, such as facilities and trained personnel; and services that are effective, accessible, affordable, and integrated. The priorities for establishing such a system will depend on the assessment of population needs, as well as needs-based planning and the support of mutual help organizations. It is concluded that a public health approach to the development of treatment systems provides a useful way of responding to the changing needs of the population in relation to substance use disorders.

Keywords

Treatment · Systems · Alcohol · Drugs · Public health

39.1 Introduction

At the time when health-care delivery is changing rapidly throughout the world and new substance abuse treatment services are being developed, it is

T. F. Babor (✉)
Department of Public Health Sciences, University of Connecticut School of Medicine, Farmington, CT, USA
e-mail: Babor@uchc.edu

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critical that services for persons with alcohol and drug problems be delivered in the most effective as well as in the most efficient manner. The focus on treatment system issues represented in the title of this chapter is designed to direct attention at the growing body of research and theory that can be used to inform treatment planning and quality improvement at the community and national levels. The development of an effective treatment system is a crucial part of a country's public health response to the problems associated with substance use disorders. Although a great amount of research has been conducted on treatment of substance use disorders, most of it deals with clinical issues, such as the efficacy of different psychotherapies or pharmacotherapies, rather than the larger treatment service issues that often result from tradition, budget constraints, procurement procedures, or political decisions. As described in a conceptual paper by Babor et al. [8], what is now needed is a comparable effort to use systems-level research to inform policymakers and program administrators about the best ways to configure and expand their treatment services to maximize their impact at the population level.

This chapter deals with the requirements and priorities of the treatment system, which are approached from a public health perspective. The requirements of a service system include sound policies (especially stable financing); appropriate structural features, such as facilities and trained personnel; and services that are effective, accessible, affordable, and integrated. The priorities of such a system include the accurate estimation of population needs through service mapping and needs assessment, as well as rational service planning that includes an emphasis on community support networks such as mutual help organizations.

39.2 Concepts, Requirements, and Priorities

39.2.1 Definitions and Rationale

A treatment system for persons with substance use disorders is an arrangement of facilities, programs, and personnel that is designed to function in a coordinated way. Such an arrangement includes linkages between specialized care and other types of services, such as mental health, primary health care, social welfare, criminal justice, and mutual help organizations [8]. The focus on the arrangement and coordination of services, rather than just the personnel, programs, and therapeutic aspects of treatment, raises a new set of questions for clinicians, program administrators, and policymakers. Can systems concepts help to reduce the gap between population needs and the current availability of substance abuse services? How can treatment services be made more accessible to those in need? Are the needs of affected populations being met by the current array of services? Are services being distributed and accessed appropriately? Are screening and referral conducted at gateway institutions, such as primary health care, schools, and employment settings? Are there appropriate diagnostic capabilities? What are the most effective administrative linkages between substance abuse services and criminal justice, mental health, primary care, and other human services? Are specialized services coordinated in a continuum of care? Are evidence-based services available and relevant? What is the policy support for integrated structures? What can be done to build stronger community support networks (e.g., Alcoholics Anonymous (AA), family social clubs)? To what extent can mental health and general medical services be better integrated with addiction treatment? Are there advantages to having separate systems for substance abuse, or should they be integrated administratively with mental health care or services for other health conditions or social problems?

These questions define issues that can be addressed by a public health systems perspective, which is concerned primarily with how services contribute to the health and welfare of a population. Services for substance use disorders expanded dramatically in developed countries in the 1970s but often in a fragmented and arbitrary way. Resource allocation decisions and treatment policies have a major effect on the development of services for persons with substance use disorders, but there is little research to guide service planning or to indicate whether services achieve their public health objectives. Low- and middle-

income countries are now investing in services as substance use prevalence rates increase with new epidemics or rising national incomes, but there is little systematic knowledge to guide the development of service systems that would best address the needs of their populations.

39.2.2 History and Conceptual Developments

Conceptual, theoretical, and empirical work on treatment systems is a recent development, but substance abuse treatment has a long history that can be traced back at least 200 years in some countries [55, 63]. A rudimentary set of treatment services, mostly specialized residential programs, emerged from the nineteenth-century asylum movement originally designed for mental patients but which also served large numbers of alcoholics [63]. Since the 1960s in the industrialized countries, there has been a steady growth of specialized medical, psychiatric, and social services for individuals with substance use disorders [32]. Although each country developed a different mix of services and administrative structures, there were some commonalities across national systems in the types of service settings (residential, detoxification, and outpatient) and therapeutic approaches [25]. As treatment services became more numerous and specialized, new concepts were developed to describe how they related to the different types of population needs. These concepts include the continuum of care, broadening the base of treatment, the chronic care model, and service system levels.

The *continuum of care* concept, as described by Rush et al. [49], refers to the mix of services available to patients and the way patients are expected to pass through it. The services are generally arranged sequentially beginning with screening and diagnostic assessment. Patients are then assigned to different settings and services depending on acuity, severity, and complexity. The main services that have been incorporated into the systems framework in most countries are withdrawal management (including detoxification), residential rehabilitation, outpatient counseling, continuing care, harm reduction programs, and community support networks such as Alcoholics Anonymous. Variations of the continuum of care concept are the core-shell model and the stepped-care approach. In the core-shell model, core functions, such as intake assessment and treatment assignment to the most appropriate type of care (the shell), are facilitated by case management [15]. In the stepped-care approach, patients are assigned to the least intensive level of care initially. If outcomes are not optimal, they can be "stepped up" to a more intensive level, and if outcomes are positive, they can be "stepped down" to appropriate continuing services.

Another innovation that has contributed to the systems concept is SBIRT, which refers to screening, brief intervention, and referral to treatment, typically in the context of early intervention in primary health-care settings [5–7]. The SBIRT model grew out of a seminal report issued by the US Institute of Medicine [23], called *Broadening the Base of Treatment for Alcohol Problems*. SBIRT is a comprehensive and integrated approach to the delivery of early intervention and treatment services through universal screening for persons with substance use disorders and those at risk. Beginning in the 1980s, concerted efforts were made by the World Health Organization (WHO) to provide an evidence base for alcohol screening and brief intervention in primary health-care settings, in order to *broaden the base of treatment* in countries where specialized services were unavailable. With the development of reliable and accurate screening tests for alcohol, more than a hundred clinical trials were conducted to evaluate the efficacy and cost-effectiveness of alcohol screening and brief intervention in primary care, emergency departments, and trauma centers [5–7, 24].

Just as SBIRT attempts to integrate specialized substance abuse treatment services with outreach to the general health-care system, the *chronic care model* addresses the needs of more serious cases of substance dependence by coordinating specialized services over time under the assumption that once substance dependence has developed, there is a need for continuing care and management, as is done with chronic conditions like diabetes and hypertension. The chronic care model has been adapted to substance abuse by

Rush [48, 49] who has defined a series of "tiers" that constitute the most important elements of a continuum of services for the management of chronic substance users (see also Rush and Urbanoski [50]). Five tiers are defined on the basis of their functions, which are higher-order groupings of similar services or interventions, such as early intervention, detoxification, outpatient counseling, and residential programs. Tier 1 refers to health promotion and prevention functions targeted at the general population. This tier recognizes the likelihood that public policies, the regulatory environment, and lifestyle factors contribute to the risk of substance abuse and the need for treatment. Tier 2 consists of early intervention and self-management functions directed at persons at risk. This incorporates the SBIRT activities that have provided an important link to other health-care settings. Tier 3 consists of treatment planning, crisis management, and support functions for persons with identified substance-related problems. Tier 4 includes specialized care for people in need of more intensive services, such as residential programs, outpatient counseling, and pharmacotherapy. Finally, Tier 5 comprises highly specialized care functions for individuals with complex problems, such as inpatient withdrawal management, forensic services, and long-term psychiatric care. The tiered framework is designed to be used as a planning tool for the development of an integrated system of service functions for substance abuse, mental disorders, and gambling problems that takes into account problem severity and complexity.

Despite the growth of treatment services and systems of care in many countries, the services in most parts of the world are fragmentary and lack coordination. Four development levels have been proposed to account for the range of systems that have evolved in different countries [3]. Level I refers to services that are "minimal" in relation to population needs. If they exist at all, services tend to be fragmentary, with rudimentary care available in some settings (e.g., emergency departments or psychiatric wards) and perhaps specialized services in medical and psychiatric settings where a residential unit might provide care for a limited number of patients. Level II is described as "limited" in terms of systems development, with some specialized services in medical and psychiatric settings. Level III refers to a "modest" level of development where a variety of services are delivered in most settings and there is some regional coordination and planning. Level IV refers to "mature" systems, with a variety of integrated services in a range of settings and stable financing for these services. The specification of these levels is useful for suggesting ways in which a system at a particular level of development can be improved and for monitoring changes in systems development over time.

39.2.3 Requirements of an Optimal Treatment System

Babor et al. [3, 8] have described the components and dynamics of an optimal treatment system from a public health perspective. These are the basic "building blocks" of a service system [22]. As illustrated in Fig. 39.1, the first requirement is a set of policies that make the governance of the service system and its constituent parts possible. The second component is the system's structural resources, including infrastructure, technologies, personnel, programs, and facilities. The third component consists of system qualities, such as accessibility, economy, and efficiency, which contribute to the smooth functioning of the service system.

According to this model, the policies, resources, and qualities of the system should not only translate into the effectiveness of services on individuals exposed to them, it should also contribute to population health through reductions in death, disease, and disability.

The components of this model and the research supporting it are discussed in the remainder of this section in order to indicate how a systems model might best contribute to population health.

39.2.3.1 Policies

The first requirement of an effective treatment system is appropriate treatment policies that provide a statutory basis for designing treat-

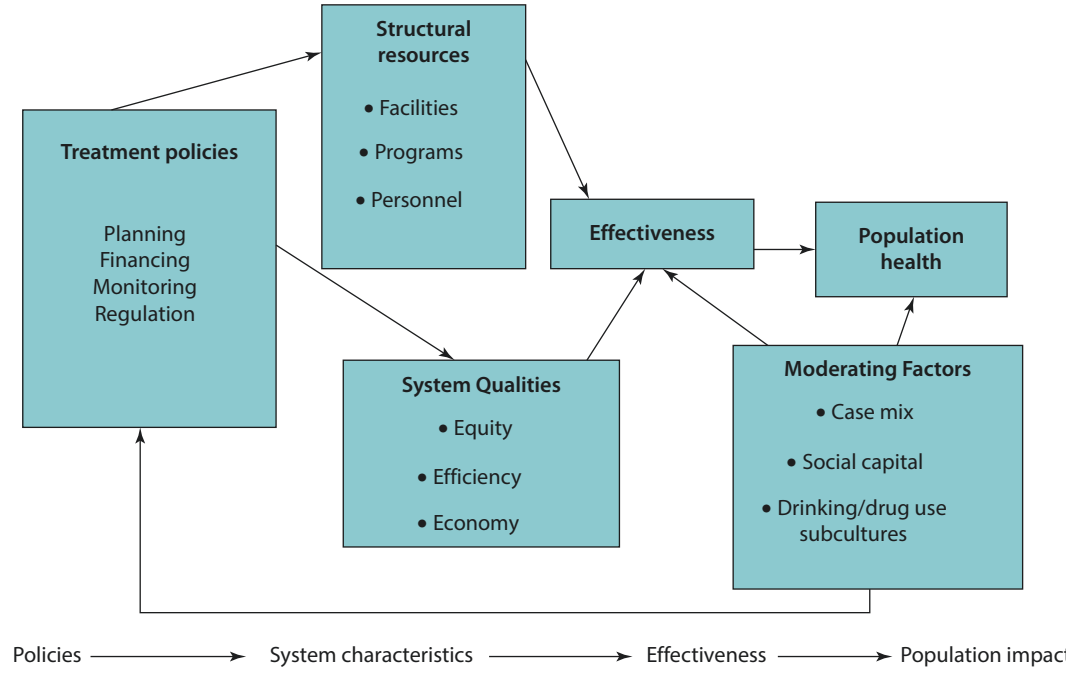

Fig. 39.1 Conceptual model of service system policies, resources, and qualities and their potential impact on population health. (Source: Adapted from Babor et al. [8])

ment programs, licensing of treatment providers, and funding for programs and personnel. Policies determine the size, the administrative location, and the organization of the treatment system. They provide a framework for the allocation of resources. There is a great deal of legislation for the treatment and rehabilitation of persons with substance use disorders, but much of the legislation is concerned with provisions for compulsory treatment or for treatment in lieu of jail [46]. Other kinds of policy include national standards for clinical practices and licensing requirements for treatment personnel.

According to a survey conducted by the World Health Organization [64], 66.2% of the 145 countries surveyed have a government unit or government official responsible for treatment services for substance use disorders, but fewer than half of these countries have a specific budget line for these services. Financing mechanisms vary but most countries use tax revenues, user fees, and private insurance to pay for alcohol and drug services. User-based funding models depend on private financing for services or insurance coverage. Population-based financing relies on public funding of services and is typified by the inclusion of addiction treatment in the social welfare systems of the Nordic countries.

Resource allocation and financing decisions have had a major effect on the development of these services. For example, the number and variety of services increased dramatically in the United States when the US Public Health Service invested in treatment services as part of a broader public health approach to reduce the burden of disease, disability, and social problems that accompany substance use [63]. The rapid development of federally supported residential and outpatient treatment programs, along with an expansion of insurance coverage for private programs, established the feasibility of serving large numbers of alcohol- and drug-dependent patients within a specialized set of services.

Treatment policies and financing mechanisms affect the degree of centralized management of treatment services and their incorporation into other human service areas, such as social welfare,

mental health, general medicine, and criminal justice. In Denmark, policies were used to decentralize treatment services, whereas in Norway, they moved the system toward a more centralized, medically oriented structure [57]. In Canada and the Netherlands, mental health and substance abuse treatment systems have been integrated [48]. In Finland, mental health and addiction outpatient services were merged, and patients were also managed in primary care [29]. Although policy changes designed to reform the organization of treatment services may have sound assumptions and a good rationale, they are rarely accompanied by systematic evaluation research to inform future decisions. One exception is a study of marketization trends in the Nordic countries [58], which found that public procurement guided by a business management model may not be appropriate for addiction services.

39.2.3.2 Structural Resources

The next requirement of an effective treatment system is to have sufficient resources to meet population needs and the demand for treatment services. The core structural elements are facilities, personnel, and programs. Alcohol and drug services in "mature" treatment systems form a continuum ranging from primary prevention activities designed to ensure that a disorder or problem will not occur, through secondary prevention activities (including early identification and management of substance use disorders), to tertiary prevention activities that aim to stop or retard the progress of a disorder. In many countries, these services have generally developed separately and are rarely integrated within a single service delivery system. Figure 39.2 summarizes data from the WHO *ATLAS on Substance Abuse* [64] describing the most common settings throughout the world for the treatment of alcohol and drug disorders. In the plurality of the responding countries (39.8%), mental health services are the most common treatment setting for alcohol use disorders, whereas the main setting for the treatment of drug use disorders (51.5%) is specialized treatment services.

Approximately 10% of the countries reported primary health care to be the most commonly used setting for treating alcohol and drug use disorders.

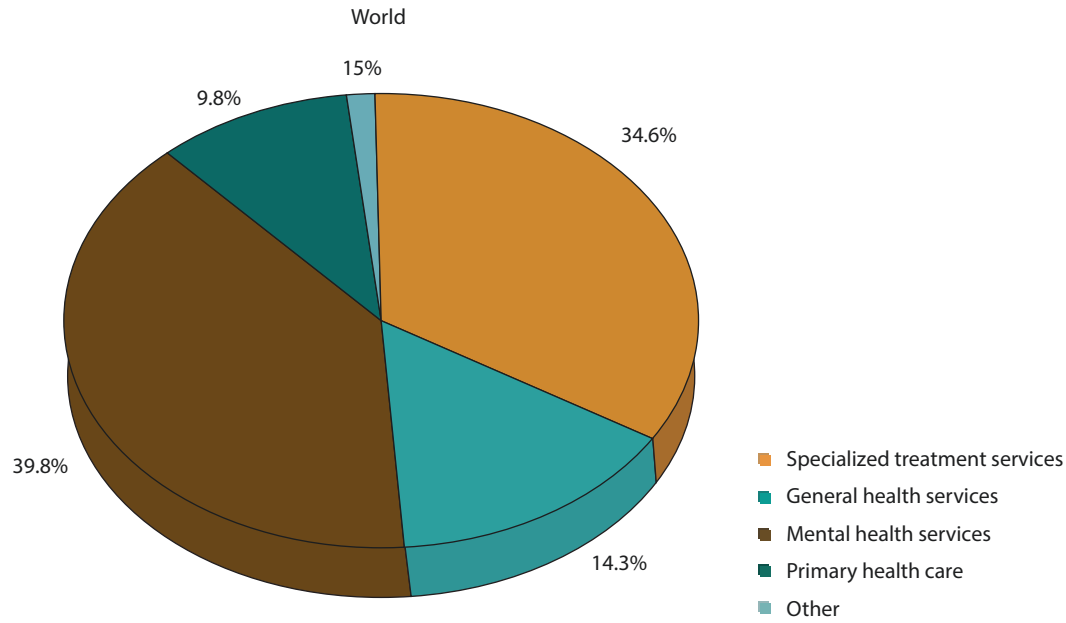

Fig. 39.2 Most common settings for treatment of alcohol and drug disorders in WHO member states. (Source: WHO ATLAS on Substance Abuse)

Another structural resource is the capacity of the system in terms of the number of beds and length of stay. The median number of beds for alcohol and drug use disorders globally was 1.7 per 100,000 population (range 0–52) [64]. The lowest number of beds was reported in the African regions, whereas the highest number was reported from countries in the European Region (10.3 beds per 100,000 population). Median length of stay for drug and alcohol detoxification was found to be 14.0 and 10.3 days, respectively, with low-income countries reporting a longer median length of stay than high-income countries.

Finally, treatment personnel have become a central feature of a country's treatment infrastructure. Among the various health professions involved in treating substance use disorders, the majority of countries reporting in the WHO ATLAS include psychiatrists, general practitioners, and narcologists as the most important [64]. That situation may be changing in the high-income countries of Europe and North America with the growth of specialized study programs for addiction treatment specialists, who are being trained at the bachelor, master, and doctoral levels to deliver services and manage programs [41, 42]. In addition to these professional addiction specialist groups, nonprofessional organizations have emerged as a critical part of the workforce in the formation of self-help organizations. Former alcoholics and drug addicts play an important role in providing community support services in many countries [64].

39.2.3.3 System Qualities

Over time, the collection of services used to manage persons with substance use disorders takes on the characteristics of a system, with unique configurations emerging not only in terms of policies and structural resources but also in terms of system qualities that characterize the functioning of a system. According to the model in Fig. 39.1, these qualities can be described in terms of equity, efficiency, and integration.

Equity refers to the extent to which services are equally available and accessible to all population groups. In South Africa, a study found inequitable access to substance abuse treatment services among the poor, with non-need factors, such as gender, mainly determining utilization [38]. Access to treatment may be as important as the type of treatment. Findings from large-scale treatment matching studies indicate that the decision to enter treatment is associated with considerable reductions in drinking, but once someone is admitted to a particular program, they do equally well regardless of the type of psychotherapy they receive [2].

Research [13] suggests that the key ingredient of the success of any therapy may be its ability to attract clients and generate enthusiasm among therapists. Instead of distinct nonoverlapping elements, different types of therapy may work through common mechanisms, such as empathy, an effective therapist-client alliance, a desire to change, ability to mobilize the client's inner resources, the creation of a supportive social network, and the provision of a culturally appropriate solution to a socially defined problem. Thus, the more that treatment services are made available to all population segments, the greater the system's effectiveness is likely to be.

Some therapeutic interventions are more cost-effective than others, suggesting that resources could be allocated more efficiently and economically without compromising effectiveness. One way to improve the efficiency of treatment is to organize treatment teams or sites to work together for a 12- to 24-month period with the aim of improving a specific area of care. This "improvement collaborative" approach combines traditional quality improvement methods of teamwork, process analysis, adoption of standards, training, and coaching. In a study by Gustafson et al. [16], the use of collaborative methods, especially coaching, was found to decrease waiting time, improve treatment retention, and increase recruitment of new patients. Humphreys and McLellan [21] found that process improvements can change the efficiency of treatment programs, but the link to better outcomes is weak, in part because outcomes are mainly influenced by environmental factors and life events outside of formal treatment.

System integration is a term that refers to the amount of interconnectedness among the organi-

zations in a network. Research suggests several ways to improve system integration: drug courts, SBIRT, integrated treatment programs for pregnant drug users, managed care, case management, and New Public Management (NPM), a market-oriented approach used in the Nordic countries to improve efficiency and lower costs [27]. There is some evidence to suggest that drug courts can increase social controls, lengthen the duration of treatment, reduce criminal behavior, and lower rates of recidivism [14]. The elements of SBIRT have been evaluated in clinical trials and found to be effective [5] to such an extent that programs have been initiated in large population areas of several countries, including Finland [53], Norway [1], Denmark [10], South Africa [52], Brazil [56], and the United States [31]. Despite some successes in primary health care [56], the results of programs relying on the training of physicians and other health personnel without adequate logistical support have not been encouraging.

In the United States, a large-scale program operating in 27 states since 2005 [6, 7] has been found to enhance the states' continuum of care to include universal, adult SBIRT services in primary care and other community settings (e.g., health centers, nursing homes, university health centers, hospitals, emergency departments, and military). In an evaluation of SBIRT's system effects, the program filled gaps in services for substance users in both the medical and specialty treatment systems of care. It was also associated with improved system equity (i.e., equal access to all population groups) and efficiency by extending services to underserved populations, expanding services within facilities and across tasks, and improving system linkages [6, 7].

Another way to improve system integration is through integrated treatment programs. Examples include treatment of pregnant women who have substance use disorders and the delivery of mental health services to patients with co-occurring mental disorders. Integrated women's programs providing pregnancy and parenting services have been associated with improvements in child development [39]. To the extent that clients with co-occurring disorders tend to have a more severe course of illness, more severe health and social consequences, more difficulties in treatment, and worse treatment outcomes than clients with a single disorder, research suggests that these outcomes might be improved when treatment modalities are offered in combination within an integrated treatment plan that simultaneously addresses substance abuse and psychiatric problems [36].

39.2.3.4 Effectiveness and Population Impact

When the requirements for an optimal treatment system are met, treatment services are available, affordable, and accessible. Under these conditions, the system should not only deliver effective services, it should also have a population impact. Effectiveness means the extent to which one or more services are responsible for positive changes in substance use and substance-related problems. Effective services should promote abstinence (or at least reduce substance use), prevent relapse, and address such substance-related problems as unemployment and marital adjustment. As suggested in Fig. 39.1, the impact of these services should translate into population health benefits, such as reduced mortality and alcohol-related disease rates, as well as benefits to social welfare, such as reduced unemployment, disability, crime, suicide, and health-care costs. One way this may happen is through the rapid diffusion of innovation within and across systems. To the extent that a new treatment innovation is perceived as being consistent with existing values, past experiences, and the needs of the country, the treatment system's communication processes may facilitate the transfer of evidence-based approaches [27].

Can the integrative effects of prevention, early intervention, and treatment systems reduce population rates of alcohol and drug problems? This issue has not been investigated extensively. There is suggestive evidence for such an effect with treatment services but not for screening and brief intervention [17]. For example, growth in the availability of opioid maintenance treatment is associated with reductions in illicit opiate use, crime, and HIV risk behaviors in the United Kingdom, France, Norway, and the United States [12, 34]. Increases in the proportion of alcoholics in treatment have been linked to decreases in liver cirrhosis morbidity [19, 33], and increases

in AA membership and amount of treatment linked to decreased alcohol problems [54].

Given the possibility that policies, resources, and system qualities, as core requirements, can be used to provide a more effective set of services and contribute to the system's public health impact, the next section of this chapter considers the main priorities for developing such a system.

39.2.4 Priorities

Substance use services have traditionally been established without the benefit of a comprehensive, quantitative planning process that is aligned with population needs. Priorities for developing an optimal treatment service system will vary according to a country's current level of services, as well as the nature of their alcohol and drug problems. Among the highest priorities are service mapping, needs assessment, and service planning. Another priority that is often neglected despite its recognized effectiveness is the establishment and support of mutual help organizations that provide a critical community resource for the initiation and maintenance of recovery.

39.2.4.1 Service Mapping

Treatment service mapping involves the documentation and description of system structures and qualities. Treatment mapping research has been conducted in Hungary, Poland, the Russian Federation, France, Switzerland, Germany, the United Kingdom of Great Britain and Northern Ireland, the United States of America, Finland, Sweden, and a variety of other countries [25, 26, 28]. Data collection tools have been developed for treatment mapping purposes, but most of these instruments do not examine the treatment system components described in this chapter.

To promote the orderly planning and dissemination of evidence-based addiction treatment within national health-care systems, the World Health Organization has designed a procedure for assessing, monitoring, and evaluating treatment systems for substance use disorders, in relation to population needs [3]. The WHO Substance Abuse Instrument for Mapping Services (WHO-SAIMS) was developed to provide information on prevention and treatment services that can be used for policy planning, service design, and service improvement. In its present form, the WHO-SAIMS has a primarily descriptive function that identifies gaps in service delivery and areas for system improvement. The primary purpose of the WHO-SAIMS is to examine the structure and functioning of alcohol and drug service systems in terms of resources, facilities, personnel, and programs. It can also be used at the national and subnational levels for monitoring and process evaluation to identify changes in the system over time and to assess the extent to which system improvement strategies have been implemented. The scope and configuration of the instrument are described in Table 39.1.

Table 39.1 Scope and configuration of the World Health Organization's Substance Abuse Instrument for Mapping Services (WHO-SAIMS)

Policy and legislative domain: This includes items about national alcohol and drug policies; legislation governing drug control, prevention, and treatment; strategic plans that address substance use disorders, workforce development for substance abuse professionals, and resource allocation to and the financing of alcohol and drug services
The substance abuse situation and current alcohol and drug service needs: This section is designed to (1) help identify whether current services match needs and (2) estimate service coverage of the current alcohol and drug treatment system. This domain described the type and mix of services provided, service integration, and system complexity
The alcohol and drug services domain. This section covers (1) other residential services for alcohol and drug problems such as halfway houses and sober living environments; (2) alcohol and drug services provided by other sectors such as mental health facilities, primary health-care services, and the criminal justice sector; (3) the linkages between these services; (4) the availability of psychosocial treatments and psychotropic medications; and (5) drug substitution therapies and harm reduction services for opioid users
The primary care domain. Items in this category refer to interventions used in primary care settings. The human resource domain. This describes the quantity of human resources as well as human resource development, including mutual help organizations and recovering communities such as AA and NA

Source: Babor and Poznyak [3]

39.2.4.2 Estimating Demand for Treatment and Treatment Needs

Demand for treatment refers to the number of people who want to access treatment, including those who receive treatment (met demand) and those who want treatment but cannot access it (unmet demand). Unmet demand may exist because services do not exist, are not available, are too expensive, or are inaccessible [44, 45]. Need for treatment refers to the number of people in a geographic region who meet the criteria for dependence or harmful use and who would benefit from treatment but do not access it. Some of these people want treatment but cannot access it (for the above reasons), while others do not want treatment nor do they seek it [44, 45]. The numbers of "unmet need" are likely to be greater than the numbers of "demand for treatment" because "unmet need" includes those people who do not perceive the need for or do not desire any treatment.

There are several methods to identify unmet treatment need, some involving primary data collection and others relying on secondary analysis of existing data sources. The simplest procedure is to use population surveys to estimate the number of people in need of treatment (see [43–45, 61]). If the rates of dependence and harmful use are used, these can translate into the potential demand for specialized services (residential and outpatient) as well as early intervention services in other health-care settings. These services can be directed at patients with dependence and harmful use, respectively. Because of the limitations of using survey measures of diagnostic criteria, population survey data should be supplemented by obtaining prevalence estimates from settings where substance users are likely to be encountered, such as prisons, emergency departments, and HIV clinics. The need for substance abuse services among the general population can also be estimated through the use of health and social indicators, such as substance-related mortality, morbidity, social problem statistics, and expert opinion on treatment needs. A major difficulty in using population data to estimate treatment need is the occurrence of "spontaneous remission," which refers to the changes in substance use that occur without treatment. Because of these problems, some experts suggest focusing on treatment demand, which can be measured through self-reported intentions to seek treatment or client perceptions of the need for treatment [44, 45]. Another option is to use waiting list data. If these data are not available or are difficult to obtain, harm indicators derived from administrative databases can be used as well. For alcohol, the harm indicators that have been used include arrests for alcohol-impaired driving and alcohol-related morbidity rates for different diseases and conditions. Although these indicators of treatment need or demand have limitations, a combined approach is sometimes used to provide greater confidence in the estimates [61] and to help direct resources to those services that conform best to the various indicators of severity (e.g., opiate withdrawal) and complexity (e.g., psychiatric co-morbidity).

39.2.4.3 Needs-Based Planning

For service systems at a modest (Level III) or mature (Level IV) stage of development, it may be more fruitful to use the "needs-based planning" approach described in Fig. 39.3. This model uses population prevalence data to estimate the types of treatment services to be received by subgroups in the population. As such, it is more advanced than the SAIMS methods because it takes into account different types of treatment and respective "need" by treatment type.

In the "Rush model," help-seeking populations are allocated across three treatment service categories: withdrawal management, community services and supports, and residential treatment services. Projections of need and required service capacity for Canadian health planning regions were derived by synthetic estimation according to age and gender. The model and gap analysis was piloted in nine regions of Canada, producing the following national distribution of need across the five categories: Tier 1, 80.7%; Tier 2, 10.4%; Tier 3, 6.1%; Tier 4, 2.6%; and Tier 5, 0.2%.

The "Rush model," initially developed in the early 1990s [47] to estimate treatment needs in Ontario, Canada, has been followed by similar

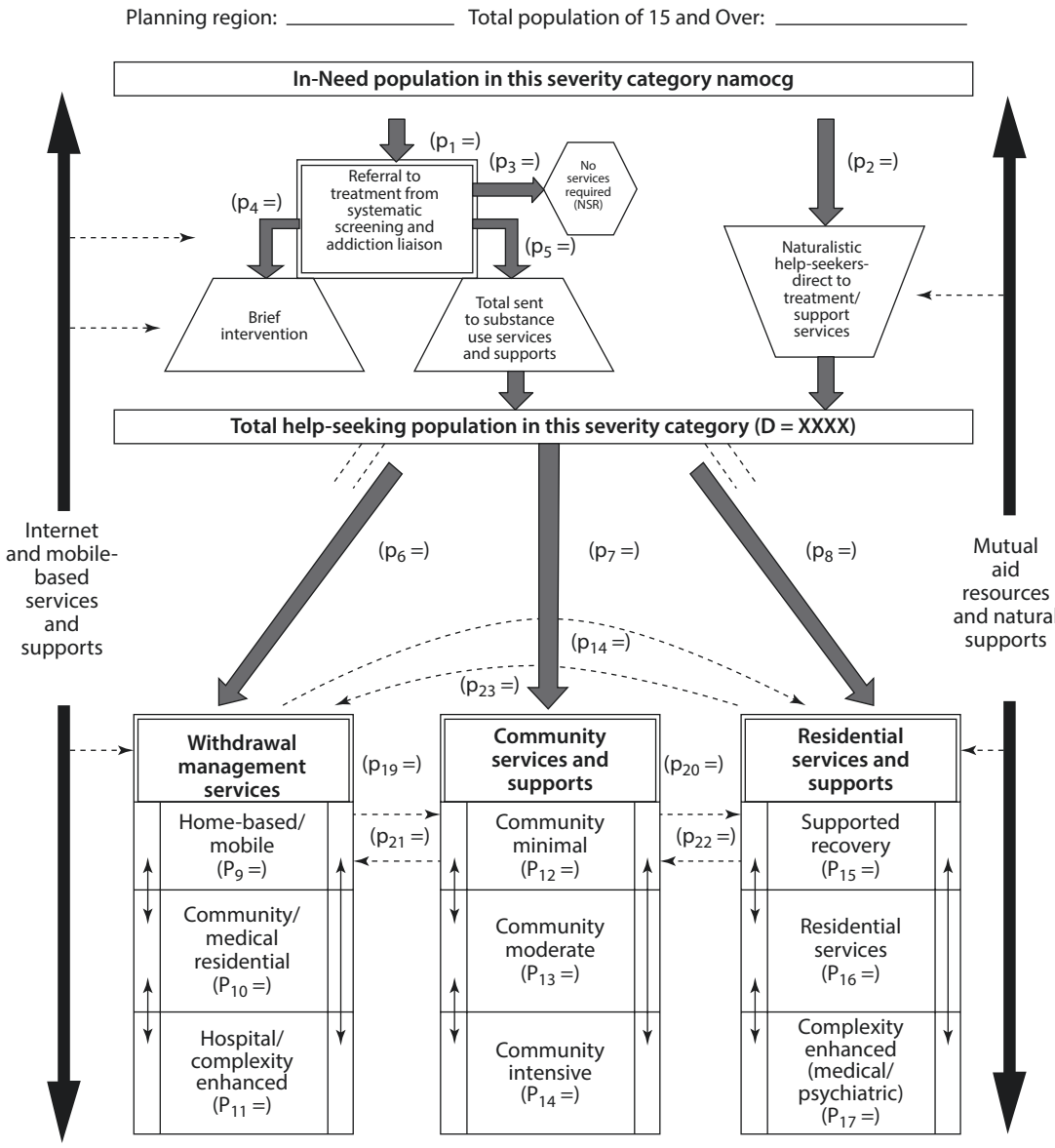

Fig. 39.3 Schematic diagram of needs-based planning model for substance use services and supports. (Source: Rush et al. [51])

approaches in Australia [44, 45]; the UK [11]; Brazil [37]; and Quebec, Canada [60]. As noted by Babor et al. [9], these initiatives differ in key features such as the substances of concern, populations of interest, criteria to define need for treatment, as well as methodological details. Nevertheless, they share several common features, such as the use of epidemiological measures of need and help-seeking to estimate the demand for treatment and postulating an "ideal" system design composed of evidence-based interventions.

Another commonality is the assumption that "treatment need" and the "treatment gap" should be estimated at the level of different services and client characteristics, rather than reported only as an undifferentiated measure of overall treatment coverage. In the past, diagnostic criteria derived

from health statistics or epidemiological surveys have typically been used as an indicator of the "treatment gap." In some cases, the estimates are so crudely constructed that they grossly overestimate total need without specifying how those estimates map on to specific service components and population groups [9]. An example is the use of the AUDIT and AUDIT-C that are sometimes used to estimate the need for early intervention services despite the number of false positives that can be included in such estimates [18].

39.2.4.4 Mutual Help Organizations

Alcoholics Anonymous and other mutual help organizations represent a critical resource both in countries with mature systems and in those with limited resources. Not only do these approaches provide continued support in the community, they do so at minimal cost. A variety of mutual help models have been developed throughout the world [20], many of them seemingly capable of managing some of the most difficult cases of drug and alcohol dependence. With an estimated 2.2 million members affiliated with more than 125,000 groups in 180 countries, AA is by far the most widely utilized source of help for drinking problems in the world [20, 30]. And the AA recovery program has been applied to a variety of other addictive behaviors, including drug use and problem gambling [30].

Although it is regarded as one of the most useful resources for recovering alcoholics, the research literature supporting the efficacy of AA is limited [35]. Attendance at AA tends to be correlated with long-term abstinence [20, 59], but this may reflect motivation for recovery. Several large-scale, well-designed studies [40, 62] suggest that AA can have an incremental effect when combined with formal treatment, and AA attendance alone may be better than no intervention. When AA is combined with a 12-week individual therapy called Twelve-Step Facilitation (TSF), one study [2] found that TSF not only increased affiliation with AA, it also had a demonstrable effect on clients whose social networks contained many drinking companions. This study suggested that AA is effective because it helps to change the drinker's social environment rather than through some form of spiritual conversion.

Similar mutual help organizations have been developed in a number of other countries, such as Danshukai in Japan, Kreuzbund in Germany, Croix d'Or and Vie Libre in France, Abstainers Clubs in Poland, Family Clubs in Italy, Links in the Scandinavian countries, Pui Hong self-help organizations in Hong Kong, Oxford House in North America and Australia, and Narcotics Anonymous worldwide [4, 20, 63].

39.3 Conclusion

Treatment systems for substance use disorders are a significant part of national responses to the burden of disease and disability resulting from substance abuse. In well-resourced countries, a relatively integrated system of services has been developed in response to population needs. In less-resourced countries, treatment services are often inadequate and fragmentary. Regardless of development level, appropriate population health-care management requires the allocation of resources to preventive, curative, restorative, and rehabilitative services, using the most effective and efficient evidence-based practices. By organizing service providers into networks, it should be possible to shift utilization to lower cost settings or the most appropriate level of care.

Despite the lack of systems research in low- and middle-income countries, some progress has also been reported in emerging economies where treatment services are expanding. For example, the implementation of needs assessment and performance measurement protocols has been found to be feasible and helpful for treatment systems planning in countries like Brazil and South Africa [9, 37]. These developments suggest a shift in the ability of governments and public health authorities to estimate need and plan services in countries where the epidemiological tools and the necessary service elements already exist.

A system-wide holistic approach to the planning and coordination of services for substance use disorders is more than the mere sum of gains attributable to discrete interventions and technologies, such as new screening tools, better diagnostic instruments, improved intervention

techniques, and more numerous services. The systems approach goes beyond capacity building and technical innovation. It is designed to coordinate services so that they are capable of responding to the changing needs of the population.

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40 Screening, Early Detection, and Brief Intervention of Alcohol Use Disorders

John B. Saunders and Noeline C. Latt

Contents

J. B. Saunders (✉)
National Centre for Youth Substance Use Research, University of Queensland, St Lucia, QLD, Australia

Formerly Disciplines of Psychiatry and Addiction Medicine, Faculty of Medicine, University of Sydney, Camperdown, NSW, Australia
e-mail: mail@jbsaunders.net

N. C. Latt
Disciplines of Psychiatry and Addiction Medicine, Faculty of Medicine, University of Sydney, Camperdown, NSW, Australia

Formerly Northern Area Drug and Alcohol Service, Royal North Shore Hospital, St Leonards, NSW, Australia
e-mail: noelinelatt@bigpond.com

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Abstract

Self-recognition of an alcohol use disorder is often late in the natural history of this condition. Because of this and the limited impact of treatment for patients with late-stage complications of their alcohol problem, there has been considerable effort made to identify alcohol consumption where it has reached a hazardous or risky stage or is starting to cause problems, before dependence becomes entrenched and complications irreversible. The approach of screening and brief intervention represents a secondary intervention approach, which aims to help people reduce their alcohol consumption to low-risk levels and thereby avoid progression to dependence and the development of harmful physical and mental sequelae and social problems. This chapter describes the development of screening instruments such as the Alcohol Use Disorders Identification Test (AUDIT) and several derivatives and alternatives. The performance and applicability of these screening instrument is reviewed. Following this, there is an account of brief intervention approaches which aim to provide succinct information on alcohol use and risks to the individual, often combined with brief motivational and behavioral strategies. There is considerable evidence from scores of randomized controlled trials and meta-analyses for the effectiveness of brief interventions in reducing hazardous alcohol consumption and alcohol-related problems. In the long-term follow-up studies, there is also evidence for reduced rates of hospitalization and mortality. The latest developments in screening and brief intervention are their presentation in various electronic formats. Online screening with feedback and brief intervention has shown to be efficacious and has the potential to be accessible to a greater section of the general population than face-to-face interventions in healthcare settings.

Keywords

Hazardous alcohol use · Harmful alcohol use · Alcohol dependence · Alcohol use disorders · Screening instruments · Early intervention · Brief intervention · Electronic screening · e-SBI

40.1 Broadening the Spectrum of Intervention for Alcohol Use Disorders

Self-recognition of an alcohol use disorder is often late in the natural history of the condition. Frequently, patients seen in healthcare services have well-established alcohol dependence and often physical, neurocognitive, psychiatric, and social complications when they present for treatment. At this stage, the road back to reasonable health and well-being is a long and sometimes uncertain one, requiring considerable personal resources and involvement in treatment, support, and lifestyle changes.

An important movement in recent years has been to broaden the spectrum of responses so that people with hazardous, harmful (or unhealthy) alcohol consumption and those with less severe alcohol use disorders, as well as those with alcohol dependence, have an opportunity to be alerted to the risks of their drinking and to change their consumption patterns in a healthy direction. Screening and brief intervention has its origins in the work of a World Health Organization (WHO) Expert Committee in the late 1970s. In its report, the Expert Committee recommended "the development of methods for identifying and modifying potentially harmful patterns of alcohol consumption before dependence developed and disease was entrenched."

Arising from this report was a WHO program of work on development of techniques for early detection and intervention for hazardous and

harmful alcohol consumption. Parallel work in the area was undertaken by pioneers such as Kristenson [41] and Heather [33]. Since those early days, there has been a substantial effort to develop screening instruments, such as the Alcohol Use Disorders Identification Test (AUDIT) [67], and brief structured therapies designed to be used at the time hazardous and harmful alcohol use is identified.

This approach has been endorsed by many authorities. In 1990 an influential report from the US Institute of Medicine [35] recommended that healthcare responses should extend beyond the provision of treatment for people with established alcohol dependence (or "alcoholism") to encompass early detection and treatments in primary care and in other nonspecialist settings. It noted the evidence accumulating for the effectiveness of opportunistic screening and brief intervention for hazardous and harmful alcohol consumption. Since that time, a national alcohol screening day has been introduced in the USA, and screening and brief intervention is identified as an essential approach for primary healthcare services. The US National Institute on Alcohol Abuse and Alcoholism (NIAAA) has issued a clinician's guide on "Helping patients who drink too much" [52]. The UK's National Institute for Health and Care Excellence's (NICE) guideline on the prevention of alcohol use disorders [53] and the World Health Organization's intervention guide for mental, neurological, and substance use disorders [80] support the widespread screening and implementation of brief intervention approaches in people with nondependent hazardous and harmful drinking.

Screening and brief intervention is analogous to screening for asymptomatic hypertension, hyperlipidemia, and a range of medical, mental, and social disorders. It is predicated on the basis that early detection and treatment of a disorder in its developmental stage has advantages over treatment of severe alcohol use disorder or dependence disorder in terms of reduced morbidity, better and more guaranteed response to treatment, and the avoidance of the costs of treating the advanced disorder and prevention of premature mortality.

This present chapter will (1) review the current criteria for nondependent hazardous/unhealthy alcohol consumption, harmful alcohol consumption, and mild alcohol dependence/mild alcohol use disorder, (2) examine the available screening instruments (focusing on instruments specifically derived to screen for a range of hazardous consumption and alcohol use disorders), (3) review the evidence for the effectiveness of brief alcohol interventions, (4) review the key therapeutic components of brief interventions, (5) examine the implementations of such interventions in healthcare systems, and (6) examine electronic screening and brief intervention approaches which have been developed to further broaden the access of people with hazardous or unhealthy patterns of alcohol consumption to information and advice, who otherwise might not be engaged in the healthcare system.

40.2 The Spectrum of Nondependent Alcohol Use Disorders

Alcohol use and misuse exists as a continuum, and an important realization is that harm can occur at many points along this continuum. Excess alcohol use is a significant cause of morbidity, mortality, and social problems. Accidents can occur due to a single episode of excessive consumption; they are more likely to occur with repeated bouts of drinking; social problems can arise due to intoxicated behaviors, and acute medical disorders may also arise from periodic binges. Many chronic disease states are linked to regular consumption of alcohol that may not reflect alcohol dependence. Although the risks of all these are multiplied in people who have alcohol dependence, and it is right that much attention be paid to this group, it is important to capture a broad range of consumption patterns and alcohol disorders.

Alcohol consumption may be facilitated by external factors such as cultural norms and practices, peer pressure, work culture, and work pressure or internal factors such as the person's feelings and mental state or desire to experience the euphoria and state of intoxication that alcohol can cause.

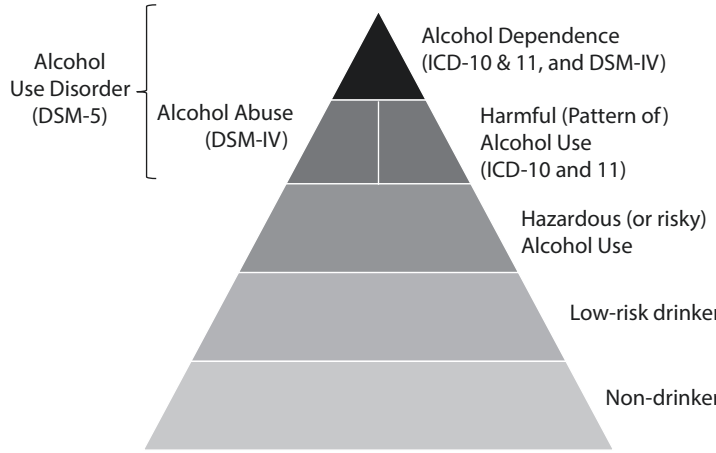

Fig. 40.1 The spectrum of alcohol use disorders

Nondependent alcohol use disorders include the following diagnostic terms from the World Health Organization's International Classification of Diseases (ICD) system: hazardous alcohol use [79], harmful alcohol use [78], and harmful pattern of alcohol use [79]. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) includes alcohol abuse [1] and mild alcohol use disorder [2]. "Unhealthy alcohol use" is an umbrella term referring to that spectrum of alcohol use that can result in health consequences and broadly covers hazardous use, harmful use, and alcohol abuse and dependence and all grade of alcohol use disorder [64, 65] (See Fig. 40.1).

40.2.1 Hazardous Alcohol Use (ICD-11)

Hazardous alcohol use is defined as a pattern of alcohol use that appreciably increases the risk of harmful physical or mental consequences to the drinker or to others [79]. Hazardous use has not yet reached the level of having caused harm. "Risky use" is similarly defined as alcohol consumption in amounts that increase the likelihood of health consequences, e.g., injury, interpersonal problems, and medical consequences [64, 65].

The risk of harm is related to the level of alcohol consumption and the frequency and duration of consumption. In addition, psychosocial, environmental, and genetic influences may play a role [69, 72, 73]. Examples of national criteria for hazardous or risky alcohol use are as follows:

(a) *USA*: for women and men aged 65 years and older, drinking more than 7 drinks in a week or more than 3 drinks per day; for men under age 65 years, drinking more than 14 drinks in a week or more than 4 drinks in a day (1 drink being approximately 12–14 g of alcohol) [50, 52].
(b) *UK*: regular drinking of more than 14 units a week but less than 35 units a week for women; drinking more than 14 units a week but less than 50 units for men (1 unit is approximately 8 g or 10 ml of ethanol). Regular drinkers are advised to spread the amount evenly over 3 days or more, with some alcohol-free days per week [53]. In the UK risky drinking is sometimes graded as low risk, increasing risk, or higher risk. A single episode of heavy drinking, e.g., five to seven units in a 3–6-hour period (binge), increases the risk of accidents and injury two to five times [75].
(c) *Australia:* more than two standard drinks on any day (for both men and women) or more than four standard drinks on a single occasion (one standard drink being approximately 10 g of alcohol). For those under the age of 16 years or if a woman is pregnant or planning to become pregnant or breastfeeding, the safest option is not to drink alcohol [51].

Hazardous drinking includes any use of alcohol in pregnancy, when driving or working with machinery, when taking medications that interact with alcohol, and in certain medical conditions, e.g., chronic hepatitis C. Women should be warned that consumption of alcohol in early pregnancy carries the risk of fetal alcohol spectrum disorder (FASD) [68].

40.2.2 Harmful Alcohol Use (ICD-10) or Harmful Pattern of Alcohol Use (ICD-11)

Harmful (pattern of) alcohol use is a repetitive pattern of use at levels which have caused damage to a person's physical or mental health or resulted in behavior leading to harm to the health of others but does not fulfill the criteria for dependence of alcohol [78, 79]. The harmful effects may be acute (e.g., trauma) or chronic (e.g., alcoholic liver disease, depression). An episode of harmful alcohol use is a new ICD-11 diagnostic term for situations where harm has resulted from drinking, without information on whether the consumption represents a pattern of repeated use or a one-off episode [23, 29, 78, 79]. In DSM-IV TR, the term "alcohol abuse" is defined as a maladaptive pattern of alcohol use over a 12-month period leading to clinically significant failure to fulfill major obligations at work, school, or home and legal problems or interpersonal problems or which is physically hazardous [1].

40.2.3 Alcohol Use Disorder: Mild (DSM-V)

The DSM-V replaced the terms alcohol abuse and alcohol dependence under a broad term "alcohol use disorder." It is defined as a cluster of cognitive, behavioral, and physiological symptoms following a problematic pattern of alcohol use leading to clinically significant impairment or distress, manifested by at least 2 of 11 criteria within a 12-month period. The severity of the disorder is graded on the number of criteria met, viz., mild, two to three; moderate, three to four; or severe, six or more [2]. Nondependent alcohol use disorder lies in the lower end of this spectrum.

40.3 Alcohol Dependence (ICD-10, ICD-11, DSM-IV TR)

The DSM-V moderate to severe range of alcohol use disorder may conveniently be considered a counterpart to the ICD-10, ICD-11, and DSM-IV TR definition of alcohol dependence. Alcohol dependence is defined as a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated alcohol use which tends to be self-perpetuating. The psychobiological syndrome is best understood as a disorder where there is impaired control over alcohol use and a persistent internal drive to consume alcohol such that alcohol increasing takes "center stage" or priority in the person's life and other enjoyments, activities, and responsibilities are pushed to the periphery. It reflects enduring changes in key neurocircuits that subserve reward, alertness, response control, and salience in the ventral tegmental area of the midbrain, the nucleus accumbens, and related structures of the lower forebrain and with projections to and from the prefrontal gyrus and the circulate gyrus of the cortex. It is more "disease-like" than any other form of repetitive alcohol use and tends to be self-perpetuating and to run true when active at different periods in the person's life. Physiological features indicative of neuroadaptation are manifested by tolerance, withdrawal symptoms following cessation or reduction of drinking, repeated use to prevent or alleviate withdrawal symptoms, and continued use despite harmful consequences.

Once alcohol dependence sets in, the patient may require prolonged treatment in a continuing care program. This includes inpatient or ambulatory detoxification followed by a comprehensive relapse-prevention program involving pharmacotherapy, a variety of psychosocial interventions, as well as self-help and mutual aid group therapy and family therapy. Where medical, psychiatric, or social complications have arisen, referral to appropriate specialties is required. In severe

cases, the patient may eventually require long-term residential or inpatient treatment.

There are more people with nondependent hazardous or harmful alcohol consumption than those with established alcohol dependence/moderate to severe alcohol use disorder. Approximately 15–20% of adults consume alcohol in a hazardous/harmful manner and 5% have alcohol dependence [68]. In England, alcohol dependence affects 2% of women and 6% of men, while over 24% of the English population consume alcohol in a way that is potentially harmful or actually harmful to their health and well-being [54] (see Fig. 40.1). Because of the greater prevalence of hazardous and harmful alcohol use in the population, more alcohol-related problems are attributable to hazardous and harmful alcohol use than to alcohol dependence. Screening and identification of nondependent hazardous and harmful drinking and provision of brief intervention are effective and cost-effective preventative approaches in preventing progression to more severe alcohol dependence, other alcohol-related harm, and death [31, 68].

40.4 Screening

For the spectrum of nondependent hazardous alcohol use, harmful alcohol use, and mild alcohol use disorder, there is a need for reliable methods of screening and brief intervention. Screening and early detection can also be applied to alcohol dependence, and brief interventions can be adapted and used in therapy at the start of treatment for persons with alcohol dependence. The 10-question Alcohol Use Disorders Identification Test (AUDIT) is a useful screening instrument in differentiating alcohol dependence from nondependent hazardous or harmful alcohol use: A score of 8 or more is associated with hazardous or harmful drinking, while a score of 15 or more is likely to indicate alcohol dependence [5, 7, 15, 18, 67, 68].

40.5 Development of the AUDIT

The modern era of screening for hazardous and harmful alcohol consumption and alcohol use disorders began with the development of the AUDIT [4, 5, 66, 67]. Prior to this, alcohol screening instruments focused on the detection of alcoholism. They were not designed to detect the range of alcohol use disorders or hazardous/unhealthy alcohol consumption, the reason being that these concepts had not gained general acceptance at the time the older instruments were introduced. These older instruments include the Michigan Alcoholism Screening Test (MAST), developed in 1971 which exists in several versions including brief ones, and the four-item CAGE, this being an acronym of Cut down, Annoyed, Guilty, and Eye-opener [30, 46]. The T-ACE is a variant of CAGE with guilt being replaced by tolerance (Tolerance, Annoyed, Cut down, Eye-opener), to identify excess drinking during pregnancy [71].

Given the increasing focus on identifying hazardous and harmful alcohol use before dependence has become entrenched, the MAST and the CAGE have become less widely used as they perform poorly as screens for less severe unhealthy hazardous or harmful drinking.

The AUDIT has its origins in the WHO collaborative work that was initiated by the Expert Committee and was derived from findings in a World Health Organization Collaborative Study [66, 67, 4, 5]. The AUDIT was developed from the empirical selection of items contained in a WHO assessment instrument, comprising more than 150 questions. Participating centers from six countries around the world (which represented different cultures, healthcare systems, stages of economic development and political systems) were involved. The 10 items which formed the AUDIT were those which had the following characteristics:

1. They had the highest or comparably high item-total correlations with the domains they represented.
2. Individually and collectively they had the greatest discriminatory value between patients who had hazardous or harmful consumption and/or alcohol use disorders and those who did not.
3. The questions not only conformed to the then bidimensional concept of alcohol dependence

and its consequences but extended it to a tridimensional concept of (i) intake measures, (ii) measures of the urge or drive to consume alcohol (and putative dependence), and (iii) direct or proxy measures of alcohol-related consequences.
4. The sensitivity and specificity and positive and negative predictive values for the AUDIT in clinical and also general populations indicated a high degree of accuracy of classification and therefore practical utility.
5. Likewise the sensitivity and specificity of questions in the three individual domains were psychometrically acceptable.
6. The questionnaire as a whole and questions within the three domains had acceptable psychometric performance as judged by measures such as Cronbach's alpha coefficient.
7. Each individual question had high-face validity, the meaning of the question was clear, and it explicitly mentioned the link with alcohol consumption.
8. Each question was suitable in providing a means of exploring further the patient's experiences with alcohol, and the questionnaire as a whole was suitable as a framework for intervention.
9. The individual questions could be translated readily and accurately (both grammatically and idiomatically) into major world languages.

Subsequent studies showed that the AUDIT:

1. Performed as well as a stand-alone questionnaire as it did when the questions were embedded in a general health screening instrument.
2. Had high acceptance among populations being screened.
3. It could be adapted easily to an electronic format including interactive media where feedback on the AUDIT score and on responses to individual questions could be provided.

The AUDIT questionnaire offers a simple and systematic way of assessing alcohol intake (Questions 1–3), alcohol dependence (Questions 4–6), and alcohol-related harm (Questions 7–10). The questionnaire may be self-administered while the patient is awaiting the consultation or may be used by the clinician during the assessment. Responses in the AUDIT are quantified from 0 (far left column) through to 4 (far right column) for Questions 1–8 and 0, 2, and 4 for Questions 9–10. The AUDIT score may range from 0 (for an abstainer of alcohol) to 40. A presumptive diagnosis of hazardous or harmful consumption is made if the AUDIT score is 8 or above. More severe harm and dependence is likely when the score is 15 or more and to be extremely likely if the score is 20 or more. The scores on the AUDIT can also point to the intervention required, if any. Scores of 0 and 1–7 may result in some feedback but otherwise no specific intervention. A score of 8 or more merits a brief intervention, with scores of 15 or more (and certainly 20 or more) alerting the clinician to the need for detoxification and referral for specialist treatment. Assessment by completion of the AUDIT questionnaire itself is reported to reduce hazardous drinking [42].

AUDIT screening for early diagnosis of hazardous and harmful alcohol use is recommended as part of a routine examination in the Accident and Emergency Department, during pregnancy, prior to prescribing medication that interacts with alcohol and where there is evidence of alcohol-related harm, e.g., cardiac arrhythmia, dyspepsia, liver disease, hypertension, depression, anxiety, insomnia, and trauma [13, 54].

40.6 Derivatives of the AUDIT and Alternative Screening Instruments

Several derivatives of the AUDIT have been published over the years. The most popular of these is the AUDIT-C, a three-item questionnaire which comprises simply the first three questions of the AUDIT consumption measures. The AUDIT-C and the single-item AUDIT-3 (which comprises the third question on heavy episodic drinking alone) have been shown to be more convenient, brief, and effective instruments for diagnosing alcohol use disorders in a primary care setting [15, 19, 70].

40.6.1 AUDIT-C

1. How often do you have a drink containing alcohol?
2. How many standard drinks containing alcohol do you have on a typical drinking day?
3. How often do you have four drinks (women) and six drinks (men) or more on one occasion?

A score of 3 or more in women and 4 or more in men has a sensitivity of 73% and 86% and a specificity of 91% and 89%, respectively [16]. A score of 7–10 or more suggests there may be alcohol dependence [60].

The Fast Alcohol Screening Test (FAST), a four-item questionnaire based on the AUDIT, is another useful screening tool. The first question is, "How often do you have eight (for men) or six (for women) or more standard drinks on one occasion?" A response of monthly or more is considered a positive answer. Three further questions make up the FAST [34] with a score of 3 or more indicating hazardous alcohol drinking.

The WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) is a combined screen for drug and alcohol misuse and is available for self-completion while the patient is in the waiting room or hospital clinic. It is designed to inquire about alcohol use in context of health enquiries to detect problem or risky alcohol and other substance use in primary healthcare. It is linked to a brief intervention based on the acronym FRAMES (Feedback, Responsibility, Advice, Menu, Empathetic interviewing and Self-efficacy) and incorporates motivational interviewing [57, 77].

40.6.2 Screening in Special Populations

Some alcohol screening instruments have been developed to identify hazardous consumption and alcohol use disorders within specific populations such as pregnant women, youth and adolescents, ethnic minorities, and the elderly. These include the TWEAK, a quick five-item screening and assessment tool for alcohol use during pregnancy [62, 63] and an acronym of Tolerance, Worried, Eye-opener, Amnesia and Cut down (K). A review of alcohol screening in women suggests that the TWEAK appears to be the optimal screening questionnaire for identifying women with excess alcohol use in racially mixed populations with the AUDIT as a reasonable alternative [14].

The CRAFFT, a six-item screening tool and an acronym for Car, Relax, Alone, Family, Friends, and Trouble, was developed specifically to screen for problematic substance use in teens [40] and found to be a suitable alternative to AUDIT in adolescents and young adults, with excellent sensitivity and no gender-based or race-based differences [22]. Another questionnaire for adolescents called the POSIT (an acronym for Problem-Oriented Screening Instrument for Teenagers and a lengthy 16-item screening questionnaire) was found to perform better than the CRAFFT [61]. The MAST-G, an "elderly-specific" questionnaire, and the CAGE were reported to be better than the AUDIT in a study of elderly male veterans [48]. The MAST-G and the CAGE are appropriate screening instruments for alcohol abuse and dependence in the elderly [10]. The CAGE is reported to be superior to the MAST in the elderly [6]. However, the AUDIT remains a more useful tool for identifying nondependent hazardous and harmful alcohol use in the elderly.

40.7 Brief Interventions: Background and Evidence

Once a person has been identified, through screening or clinical enquiry, as having unhealthy alcohol use, a brief, focused form of therapy is beneficial. The usual term to describe this is "brief alcohol intervention." As described above, brief intervention aims to engage with people who have hazardous or harmful alcohol consumption and offer simple advice on the harmful

physical, mental, and social consequences of excess alcohol. In the ICD system, this means people with hazardous alcohol use (use which confers the risk of future harm) or harmful alcohol use (use which has already caused physical, mental, or behavioral problems). In DSM-5, the nearest counterpart would be mild alcohol use disorder. The focused advice and therapy is provided before the person has developed a more severe alcohol use disorder or more severe physical, mental, or personal harm.

Brief intervention is therefore a proactive strategy comprising of provision of brief advice on the consequences of hazardous/harmful drinking or alcohol use disorder feedback of harm and relating this to the patient's excess drinking, setting goals for safe levels of drinking, outlining benefits obtained from cutting down drinking, and setting strategies to overcome "at-risk" times. The intervention may take only 4–5 minutes. If a structured brief intervention does not lead to reduction of hazardous or harmful drinking, it may be extended to 30–40 minutes to include motivational interviewing techniques [17, 47, 54].

While there is limited evidence on the effectiveness of brief interventions for young people under the age of 16 years [54], there is a wealth of evidence attesting to the effectiveness of brief alcohol interventions in reducing alcohol intake and alcohol-related problems in adults with alcohol use disorders. Approximately 50 randomized controlled trials of various forms of brief intervention compared with no intervention or an alternative form of intervention have been published. Furthermore, several meta-analyses have been published since the early 2000s.

Systematic reviews have shown that brief intervention reduces mortality over a 10-year follow-up, with a relative risk of 0.47 (95% CI 0.25–0.89) [24, 76].

Systematic reviews and meta-analysis confirm the effectiveness of brief intervention in reducing excess alcohol consumption and alcohol-related harm in a primary care setting [8, 58]. In a UK multicenter SIPS (Screening and Intervention Program for Sensible drinking) trial, 3562 primary care patients were screened for hazardous/harmful drinking using either the FAST or the single alcohol screening questionnaire. Patients randomized to three interventions were compared, each of which built on the previous one, namely, (i) a patient information leaflet control group, (ii) 5 minutes of structured brief advice, and (iii) 20 minutes of brief lifestyle counseling linked to motivational interviewing. The WHO screening instrument AUDIT (score of <8) was used as a primary outcome measure at 6 months**.** There was no difference in benefit between the three arms although patients in the 20-minute intervention reported greater satisfaction with treatment. The authors concluded that screening followed by simple feedback and written information may be the most appropriate strategy to reduce hazardous and harmful drinking in a primary care setting [27, 28, 39].

Meta-analysis of 22 randomized clinical trials of 5800 participants not seeking help for alcohol problems in a primary care setting showed that brief intervention was effective in reducing alcohol consumption in men with hazardous and harmful alcohol consumption but unproven in women [37]. Further supportive evidence was provided in a more recently updated Cochrane collaboration systematic review of 69 studies on a total of 33,642 participants with primary meta-analysis of 34 trials of 15,197 participants in general practices or emergency care. Brief intervention reduced alcohol consumption in hazardous and harmful drinkers compared to minimal or no intervention in both men and women, compared to controls after 1 year [11, 38].

Brief interventions, typically lasting 5–15 minutes (and no longer than 30 minutes), included feedback on alcohol use and health-related harms, identification of high-risk situations for heavy drinking, simple advice about how to cut down drinking, strategies to increase motivation to change drinking behavior, and the development of a personal plan to cut down drinking. Short advice-based intervention is as effective as extended counseling- based intervention [11, 37, 38, 49].

The efficiency of screening and brief intervention will vary according to the prevalence of hazardous alcohol consumption in general practice. A degree of effort is required to provide brief intervention in practice although information on alcohol consumption is relevant to much of the healthcare when other issues such as the potential for interactions with medications and advice needed for pregnant women and people with a range of chronic medical disorders are taken into consideration.

40.8 Implementation of Screening and Brief Intervention in Clinical Practice

There is a wealth of evidence that demonstrates that brief interventions reduce hazardous and harmful alcohol consumption, as judged by overall alcohol consumption, reduced frequency of binge drinking, alcohol-related problems, and various secondary measures such as healthcare utilization. Some of the findings vary from study to study and among the meta-analyses. However, the overall message is clear that for these interventions benefits are clear and the strength of the evidence would suggest that their general availability in the healthcare system should be assured. The reality is somewhat different.

Brief interventions are some of the most consistently effective and potent interventions directed at individuals, and considerable effort is being made to incorporate them into the healthcare system. This is proven to be more difficult than originally anticipated. Very often screening and brief intervention can be established as a brief project, but it tends not to be continued in systematic way when external support and interest ceases.

It is fair to say that screening and brief intervention remains under utilized. Certainly systematic screening in primary care and the delivery when appropriate of a brief therapy remain unusual, even in healthcare systems that have a strong primary prevention and population health orientation. Various barriers to implementation have been reported by health professionals and include (i) reluctance to inquire about alcohol consumption, (ii) poor role adequacy, (iii) inadequate resources to address alcohol use and problems, and (iv) poor role support [56]. There remain significant issues regarding training and confidence in providing brief interventions, issues of remuneration, and competition for the time of medical practitioners and other health professionals given their overall responsibilities. Ethical considerations have also been raised as to the appropriateness of introducing a health issue which is not on the patient's agenda when he/she booked the consultation. More broadly there is debate about which healthcare professionals have the capacity to provide these interventions.

Detection and diagnosis of alcohol use disorders remains low, and it is estimated that of the 15–30% of patients in primary care or hospital settings who have an alcohol use disorder, in only one-third of the cases is it diagnosed. It must be emphasis that screening and early detection therefore has a greater role than leading to a brief intervention. Early detection can often result in the correct diagnosis being expedited, with the patient being spared unnecessary investigations. Equally importantly, knowledge of the alcohol use disorder may prevent months or indeed years of inappropriate or ineffective treatment for patients who have disorders that may be related to alcohol consumption, such as hypertension, esophagitis and gastritis, anxiety, depression, and recurrent headache. It can also often provide an answer for patients who have multiple nonspecific and seemingly unconnected symptoms.

Examples of policy recommendations and directives include the expectation that screening and brief intervention will be provided in all healthcare settings in the recommendations of the US Preventive Services Task Force [50], the guidelines published by the UK National Institute of Clinical Excellence [53] and the British Medical Association (BMJ) Best Practice

Alcohol Use Disorder Guidelines [13], and the National Preventative Health Taskforce, Australia [55].

Opportunities for screening, early detection, and brief intervention for unhealthy alcohol use exist in many settings. These include general medical/family medical practice, other primary care settings (nurse, psychologist, social worker delivered), emergency departments and acute care clinics, student health services, work place health programs, and also certain public areas such as shopping centers.

In addition to these primary care or community contact settings, brief interventions can be offered in hospital wards (general and psychiatric) and in a range of specialist services such as diabetes, hypertension, and liver clinics. A large number of hospital outpatients who are not seeking treatment for their drinking could benefit from early intervention [36]. There is mixed evidence for the effectiveness of brief intervention in hospital wards, while significant reduction in alcohol consumption and less likelihood of alcohol-related injury have been reported following screening and brief intervention for alcohol use disorders in the emergency department [26, 32, 45].

These settings are of course quite diverse, and the extent to which a person can be engaged in any alcohol intervention will vary according to the primary task of a particular setting. Still, given that few people specifically request treatment and assistance in an alcohol use disorder, any attempt to identify these and to place alcohol on the healthcare agenda is to be welcomed.

Throughout this period, there has been a tendency for patients who have actual alcohol use disorders to present for care at an earlier stage than was the case a generation ago. Furthermore, developments in general practice mean that questions on alcohol as well as cigarette smoking are more commonly part of the routine enquiry when patients attend primary care for the first time or are part of a periodic annual or biannual assessment. Even though the systematic approach of brief intervention may be less common than had been anticipated by those working in the area, nonetheless in various areas of the world it is more common for inquiry about alcohol use to be made.

In addition to screening instruments, good history taking, physical examination, and laboratory tests help to provide useful diagnostic information. This includes measurement of alcohol levels in the breath or blood, full blood count (macrocytosis), and liver function tests: GGT (gamma-glutamyl transpeptidase), ALT (alanine aminotransferase), AST (aspartate aminotransferase), and CDT (carbohydrate-deficient transferase) [21].

40.9 Brief Intervention in Practice: The Techniques

Brief intervention techniques vary widely in content and duration [12, 52, 65]. A structured brief intervention begins with personalized feedback regarding a person's alcohol intake and/or experience of problems and an indication that the level of consumption puts them at risk of future harm and/or that problems have arisen due to their alcohol intake. This is followed by recommendation for behavior change and advice to reduce consumption to approved guidelines for low-risk intake. These latter vary from country to country but typically would be under 20 g daily for men and 10–20 g daily for women Finally, negotiation and confirmation of goals and arrangement for follow up is made. This information and advice is typically conveyed to the patient over 5 minutes.

Many brief interventions incorporate other strategies. They include:

- Normative feedback, in which the person's alcohol intake is compared to that of the population at large and the risk levels and harmful effects of excess alcohol
- Brief motivational enhancement approaches, which may employ techniques of empathic feedback and cognitive dissonance

– Strategies for limiting alcohol consumption which are typically brief, cognitive behavioral interventions and may focus on avoiding high-risk situations for drinking and managing emotions such as frustration and boredom
– Measures aimed at moderated or controlled drinking such as always eating some food before any alcohol consumption, spacing drinks and extending the interval between drinks and counting drinks, and having alternate alcoholic and nonalcoholic drinks.

Based on motivational interviewing techniques [47], two popular approaches to brief intervention are set out below.

The first, FLAGS, an acronym for Feedback, Listen, Advice, Goals, and Strategies [68], is derived from the intervention developed from the WHO brief intervention collaborative study [3, 5].

FLAGS

Feedback: Problems experienced or likely to occur and link this with unhealthy drinking

Listen: Listen to the patient's response and assess his/her readiness to change (use motivational interviewing techniques as required [59])

Advice: Give clear advice to change and/or reduce unhealthy levels of drinking; list the benefits of change

Goals: Negotiate goals to reduce drinking to recommended limits

Strategies: Discuss practical methods and strategies, for example, how to determine at-risk times, and develop coping strategies

The second, FRAMES, an acronym for Feedback, Responsibility, Advice, Menu, Empathetic interviewing and Self-efficacy, is an intervention which has a major component of motivational interviewing and enhancement. It is derived from the work of Miller and colleagues and is an abbreviated form of a more extended intervention which has been developed for psychological practice [68].

FRAMES: (brief intervention with motivational interviewing)

Feedback: about personal risk and impairment

Responsibility: emphasis on personal responsibility for change

Advice: to cut down, abstain if indicated, because of severe dependence or harm

Menu: of alternative options for changing drinking pattern and, jointly with the patient, setting a target; intermediate goals of reduction can be a start

Empathic interviewing: listening reflectively without cajoling or confronting, exploring with patients the reasons for change as they see their situation

Self-efficacy: an interviewing style which enhances peoples' belief in their ability to change

[12]

40.10 Electronic Screening and Brief Intervention

Worldwide, 70% of the adult population has ready access to the Internet typically through smartphones or numerous other electronic devices. In some countries, the coverage of the Internet reaches 98% of the population. Communication of information is easier than ever before. In addition, the interactivity that is possible electronically means that intervention can be offered in real time. In many areas of healthcare, this technology has been put to use for the provision of screening and assessment and the provision of relevant information and advice. Screening and brief intervention for alcohol use has been part of this.

Electronic screening and brief intervention (e-SBI) has its origins in the late 1990s when the

potential of the technology became apparent and also when there was interest in the widespread dissemination of health advice about alcohol. Soon, pioneering efforts in the provision of alcohol screening and brief intervention were made, and the first systematic studies appeared in the early 2000s. A series of controlled studies in student populations, both in individual campuses and national studies, have shown significant effect sizes on measures of overall alcohol consumption, binge drinking, alcohol-related problems, measures of academic performance, and healthcare utilization. The effect size does appear to be slightly less for electronic interventions than that seen for clinician-provided interventions [44]. In several other populations controlled trials have since shown electronic screening and brief intervention to result in significant changes in alcohol consumption and associated problems [25, 43]. However, given the high acceptability of electronic interventions and the potential reach to the at-risk population, electronic interventions have far greater capacity to be disseminated universally than could be achieved realistically through the dissemination of clinician-provided interventions.

Screening and brief intervention have high levels of acceptability particularly among populations (such as young people) who are electronically literate. Studies among university and college students show acceptability levels exceeding 80%, and receiving information electronically is preferred among young people to receiving such information from a health professional. A pilot project has shown that while implementation of self-administered electronic screening and brief intervention is acceptable and feasible in primary care practices, its use is rather limited without human support. This could be improved by training of desk personnel or practice nurses [9].

Based on evidence from a systematic review of 31 studies showing the effectiveness of electronic screening and brief intervention in reducing excessive alcohol consumption and alcohol-related problems [20, 74], the use of electronic devices (computers, telephones, or mobile devices) is recommended to facilitate screening and personalized feedback about the risks of excessive drinking. However, a randomized double blind controlled study of e-SBI to adults with hazardous and harmful drinking was not found to be effective in a hospital outpatient setting [36].

More broadly, screening and brief intervention including its electronic forms offers the prospect of reducing alcohol-related harm at a population level as an alternative to primary prevention approaches based on control of per capita alcohol consumption. These latter approaches, although empirically sound, are difficult for governments to enact into effective policy as they impact on the availability and access to alcohol of the entire population and not just those whose drinking is hazardous and causing problems. In the modern world, governments have been reticent to impose tax imposts and restrictive legislation on alcohol consumption generally for fear of electoral unpopularity and economic considerations, particularly in those countries where the production of alcohol drinks is a significant part of the national economy. Screening and brief intervention therefore offers a population-wide and more politically acceptable approach to reducing harm from alcohol in the population at large. Both clinician-provided and electronic interventions have important roles to offer in the fulfillment of this goal.

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Resources

https://www.auditscreen.org. This website provides an electronic version of the AUDIT, with immediate feedback based on the score. Translations into 50 languages are available.

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Clinical Assessment of Alcohol Use Disorders

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M. Teresa Bobes-Bascarán, M. Teresa Bascarán, M. Paz García-Portilla, and Julio Bobes

Contents

M. T. Bobes-Bascarán
Servicio de Salud Del Principado de Asturias (SESPA), Oviedo, Spain

Department of Psychology, University of Oviedo, Oviedo, Spain

INEUROPA-ISPA, Oviedo, Spain

CIBERSAM, Oviedo, Spain

M. T. Bascarán
INEUROPA-ISPA, Oviedo, Spain

CIBERSAM, Oviedo, Spain

M. P. García-Portilla · J. Bobes (✉)
INEUROPA-ISPA, Oviedo, Spain

CIBERSAM, Oviedo, Spain

Department of Psychiatry, University of Oviedo, Oviedo, Spain
e-mail: bobes@uniovi.es

Abstract

Alcohol use disorder assessment needs different strategies depending on whether screening/early use or severity and depth of the condition is yielded. The former implies the simpler and agile instruments while the latter complex and sophisticated instruments that usually require specific training. An efficacious clinical treatment starts with an integrative comprehension of the individual. Ongoing assessment and monitoring are crucial because clients' symptoms and functioning may change throughout treatment and so do priorities and targets of intervention. Alcohol use is known to interfere with neuropsychological performance, psychiatric symptomatology,

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and social and personal functioning, so it is strongly recommended to conduct multiple evaluations to determine a better approach of patient's genuine mental health and cognitive performance. An all-embracing assessment should appraise multiple domains of need and delve into the following areas: historical and recent patterns of drinking, dependence and withdrawal symptomatology, alcohol craving and impulsiveness, alcohol-related problems (i.e., legal, economic, occupational), self-efficacy and confidence in relapse prevention, readiness to change, other drug misuse including prescribed and under-the-counter medication, comorbid mental health disorders, comorbid physical health conditions, neurocognitive performance, social and personal functioning, quality of life, and disability. This information may be obtained by a precise clinical interview, but standardized tools and measures should be administered as well. This chapter will enumerate and briefly describe the most relevant psychometric instruments to evaluate alcohol use disorders and related problems, psychiatric comorbid symptomology, neurocognitive performance, and social functioning and quality of life issues.

Keywords

Alcohol assessment · Alcohol clinical assessment · Alcohol screening test · Alcohol use detection · Alcohol evaluation · Clinical evaluation of alcohol use

Screening and early detection of alcohol use disorders should be the initial step in the process of identifying possible conditions (see Chap. 40)**.** After a person has been detected and diagnosed, an in-depth assessment, which involves both integrative comprehension of the patient and monitoring of patient's progress, is needed. Ongoing assessment and monitoring is important because clients' symptoms and functioning may change throughout treatment and so do priorities and targets of intervention. For instance, a patient may report anxiety symptoms or dysphoric mood upon treatment intake and have these symptoms attenuated after achieving abstinence. By the same token, another person could enter treatment with apparently no mental health symptomatology but develop them after a period of reduced use, if self-medication with alcohol existed [18]. At the same time, it should be noted that recent alcohol abuse may influence neuropsychological performance, psychiatric symptomatology, and social and personal functioning, so it is strongly recommended to conduct further evaluations to determine a better approach of patient's genuine mental health and cognitive performance. It is fundamental to bear in mind that the primary benefit of assessment is not only to accurately and efficiently determine the treatment needs of the patient but to build rapport. For this reason, it is the heart of the assessment to avoid confrontative approaches and adopt a motivational one instead (see Chap. 24).

An all-embracing evaluation should appraise multiple domains of need and delve into the following areas:

- Alcohol consumption:
  - Historical and recent patterns of drinking
  - Dependence and withdrawal symptomatology
  - Alcohol craving and impulsiveness
  - Alcohol-related problems (i.e., legal, economic, occupational)
  - Self-efficacy and confidence in relapse prevention
  - Readiness to change
- Other drug misuse, including prescribed and under-the-counter medication
- Comorbid mental health disorders
- Comorbid physical health conditions
- Neurocognitive performance
- Social and personal functioning
- Quality of life and disability

This information may be obtained by a precise clinical interview, but standardized tools and measures should be administered as well (see Table 41.1).

This chapter will enumerate and briefly describe the most relevant psychometric instruments to evaluate alcohol use disorders and related problems, psy-

Table 41.1 Distinctive features in instrument selection

Feature	Characteristics
Clinical utility	Screening Diagnosis Assessment of drinking behavior Treatment planning Intervention monitoring Outcome appraisal
Time frame	Recent/short-term/current use vs. chronic/long-term/lifetime use
Specific subgroup	Adolescent, adult, elderly Women (pregnant) Imprisoned Homeless Inpatient vs. outpatient Cultural issues/ethnicity
Sensitivity/ positive predictive value (PPV)	Proportion of patients with the condition correctly classified as "diseased"
Specificity/ negative predictive value (NPV)	Proportion of individuals without the condition who are correctly classified as "disease-free"
Validity (test measures what is intended to measure)	Content (comprehensiveness) Construct (conceptual components, internal structure) Convergent (similar to other tests to assess that construct) Discriminant (different to tests that assess other constructs) Criterion (correlation with gold standard measures) Concurrent (similar measures obtained to comparative tests at same time frame) Predictive (ability to predict future outcome)
Reliability (accuracy of assessment)	Test-retest (correlation at two different time points) Inter-rater (degree of agreement by different raters) Internal consistency (items of test measure same aspect)

chiatric comorbid symptomology, neurocognitive performance, and social functioning and quality of life issues. Chapter 40 on Screening, Early Detection & Brief Intervention for AUD and Laboratory Tests for Alcohol Chap. 42. Biological State Marker for Alcohol Consumption may be searched through for further information. Regarding physical and mental health comorbidities, Part VIII is an exhausted revision on Medical Disorders, Complications of Alcohol and Others, and Pain Section, and Part IX addresses Psychiatric Comorbidities and Complications of Alcohol and Other Drugs.

41.1 Evaluation of Alcohol Use

There are no specific instruments to diagnose alcohol misuse, so fundamental diagnostic methods consist of an accurate anamnesis and a meticulous clinical exam. Albeit this fact, psychometric tools are of considerable aid to appraise addictive disorders when used by trained specialists.

41.1.1 Clinical Severity of Addiction

- Addiction Severity Index [45]. The ASI is a semi-structured interview designed to address seven potential impairments and problem areas in substance-abusing patients: medical conditions, employment and support, drug use, alcohol use, legal issues, family/social relationships, and psychiatric disorders. It consists of 200 items, which gather information on recent (past 30 days) and lifetime problems in all of the problem areas. Last version (ASI 6.0) [13, 44] is composed of 15 scales: 9 primary scales (related to main problem areas) and 6 secondary scales (perceived support and conflicts with partner, family, and friends). There is a follow-up version (ASI-FU follow-up) designed to monitor patients' evolution and treatment outcomes and several adaptations to adolescent population: Teen-ASI [36], T-ASI-2 [11].
- Alcohol Use Inventory [35]. The AUI is a self-administered instrument which includes 24 scales that intend to describe different ways in which individuals use alcohol, benefits and negative consequences derived from such use, and awareness and readiness for help. It consists of 228 items grouped in primary scales regarding benefits, styles, consequences and concerns and acknowledgments of alcohol use, and other second-order factor scales.
- Comprehensive Drinker Profile [48]. The CDP is a structured interview that contains 88 questions inquiring different areas of interest: alcohol use, everyday problems, most common drinking settings, people with whom they drink, beverage preferences, reasons for drinking, effects and life problems related to alco-

hol use, and patient's concerns and issues. Three instruments were derived from the CDP: the Brief Drinker Profile (BDP), the Follow-up Drinker Profile (FDP), and the Collateral Interview Form (CIF).

41.1.2 Dependence/Withdrawal Symptoms

- Severity of Alcohol Dependence Questionnaire [69]. The SADQ is a self-administered questionnaire designed to measure severity of dependence. There are four items in each of the five scales that gather information on a 6-month time frame: physical withdrawal, affective withdrawal, withdrawal relief drinking, alcohol consumption, and rapidity of reinstatement. Scores range between 0 and 60 points, and scores greater than 30 are suggestive of severe alcohol dependence. It has demonstrated adequate content and criterion (predictive) validity and test-retest reliability.
- Alcohol Dependence Scale [66, 67]. The ADS consists of 25 items that interrogate alcohol withdrawal symptoms, impaired self-control over drinking, awareness of compulsive drinking, tolerance to alcohol, and salience of drink-seeking behavior. It has shown good predictive value, content and construct validity, and test-retest and internal consistency reliabilities. A computerized version is also available. It is an adequate instrument for clinical and research purposes.
- Short Alcohol Dependence Data [59]. This 15-item instrument was derived from the Alcohol Dependence Data (ADD) in order to accomplish an easier and faster measure profitable for seeking-help patients, current state dependence assessment, sensitive to change over time, and cultural-free influenced. It can be self- or hetero-administered in about 2–5 minutes and has provided good reliability and validity parameters.
- Clinical Institute Withdrawal Assessment [70]. The CIWA-AD is an eight-item scale for clinical quantification of the severity of the alcohol withdrawal syndrome. It is useful to monitor patients undergoing alcohol withdrawal as it focuses on both intensity and severity of symptoms. Scores over 20 indicate a severe withdrawal syndrome, and inpatient detoxification is strongly recommended.

41.1.3 Craving/Impulsiveness

- The Obsessive Compulsive Drinking Scale [4]. The OCDS is a 14-item scale developed to reflect obsession and compulsion related to craving and drinking behavior such as drinking-related thoughts and urges to drink and the ability to resist those thoughts and urges. The OCDS has been shown to be a reliable and sensitive monitoring tool and has proven content and predictive validity for relapse drinking. There is an adolescent version, the A-OCDS [19], which discriminates between problem drinkers and experimenters and detects functional impairment associated with alcohol abuse.
- Penn Alcohol Craving Scale [27]. The PACS is a five-item self-administered instrument for assessing frequency, intensity, and duration of thoughts about drinking and the ability to resist drinking. Although it was intended for adults, it may be used in adolescent population. Good reliability and validity measures have been obtained.
- Alcohol Craving Questionnaire [64]. The ACQ-NOW is a 47-item self-administered, multidimensional state measure of acute alcohol craving. It measures four dimensions: emotionality, purposefulness, compulsivity, and expectancy. There is a 12-item short form, the ACQ-SF-R. It has demonstrated adequate reliability and is sensitive to change.
- Impulsive Behavior Scale [76]. The UPPS is a 45-item scale designed to measure impulsivity across dimensions of the five-factor model of personality. It measures four domains: premeditation, urgency, sensation seeking, and perseverance. The revised version, UPPS-P, consists of 59 items and assesses an additional personality pathway to impulsive behavior, positive urgency [17].

- Barratt Impulsiveness Scale [5, 57]. The BIS is one of the oldest and most widely used measures of impulsive personality traits. The last version, BIS-11, contains 30 items grouped in 3 subscales: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness. This scale is intended to measure six factors: attention, motor impulsiveness, self-control, cognitive complexity, perseverance, and cognitive instability.

41.1.4 Self-Efficacy and Expectancy

- Alcohol Abstinence Self-Efficacy Scale [23]. The AASE was designed to evaluate self-efficacy in 20 situations that represent typical drinking cues associated to negative affect; social/positive, physical, and other concerns; and withdrawal and urges. It may be also used to assess an individual's temptation to drink. It has shown great utility to intervene over relapse potential situations, monitor progress in treatment, and assess outcomes.
- Drinking Refusal Self-Efficacy Questionnaire [81]. The DRSEQ is a 31-item measure of drinking-related self-efficacy. It is grouped in three factors: drinking in situations characterized by social pressure, opportunistic drinking, and emotional relief. Adequate reliability and validity have been analyzed.
- Alcohol Expectancy Questionnaire [12]. The AEQ is an empirically derived self-report form designed to assess the domain of alcohol reinforcement expectancies. It consists of six subscales: positive global changes in experience, sexual enhancement, social and physical pleasure, assertiveness, relaxation/tension reduction, and arousal/interpersonal power. Total scores are predictive of current and future drinking practices, persistence and participation in treatment, and relapse following treatment.
- Negative Alcohol Expectancy Questionnaire [46, 47]. The NAEQ is a 60-item questionnaire that assesses the extent to which negative consequences are expected to occur if that person were to "go for a drink now." The expected negative consequences are held to represent motivation to stop drinking. There are three different time frames: same-day, next-day, and long-term expected consequences. Responses are measured in terms of how likely it is that a person would expect them to occur and are measured on a five-point Likert scale. A short version composed of 22 items is also available. This instrument is very useful at intake and during treatment to intervene over motivational factors during therapeutic process.

41.1.5 Motivation to Change

- University of Rhode Island Change Assessment [43]. The URICA is a 32-item self-report measure used to assess motivation for change that includes four subscales: precontemplation, contemplation, action, and maintenance. These subscales can be combined in order to yield a second-order continuous readiness to change score (C + A + M-PC). It has demonstrated adequate internal consistency as well as content and criterion validity.
- Readiness to Change Questionnaire [63]. The RCQ is comprised of 12 items and focuses on readiness to change drinking behavior. It is based on the URICA questionnaire and is founded on Prochaska and DiClemente's theory on stages of change. It is clustered into three factors: precontemplation, contemplation, and action. It has good psychometric properties, including predictive validity. There is a treatment version, the RCQ (TV), for use in patients at treatment settings.
- Stages of Change Readiness and Treatment Eagerness Scale [49]. The SOCRATES consists of 40 items grouped into 5 stages of change: precontemplation, contemplation, determination/preparation, action, and maintenance. The SOCRATES 8A is a 19-item version that yields 3 factorial-derived scale scores: recognition, ambivalence, and taking steps. There are available other forms of the SOCRATES: 8D, a 19-item drug/alcohol questionnaire for clients; 7A-SO-M, a 32-item alcohol questionnaire for significant others of males; 7A-SO-F, a 32-item alcohol questionnaire for SOs of females;

7D-SO-F, a 32-item drug/alcohol questionnaire for SOs of females; and the 7D-SO-M, a 32-item drug/alcohol questionnaire for SOs of males. These SO forms are intended to measure motivation for change of significant others (rather than patient's motivation).

41.2 Psychiatric Comorbidity Assessment

Individuals with alcohol use disorders often suffer from one (comorbid) or more (multimorbidity) psychiatric disorders. This frequent phenomenon indicates the necessity of specific assessment and treatment in the field of addictive behaviors, which has been historically narrowed and focused to the addiction per se. This section yields over basic instruments to assess psychiatric comorbidity in patients with alcohol problems (see Table 41.2). For further information on psychiatric comorbidity, consult Part IX of this book, Psychiatric Comorbidities and Complications of Alcohol and Other Drugs.

41.3 Neuropsychological Performance

Scientific literature has well established that excessive alcohol use is associated to damage and impairment of brain structure and function, yielding to poor cognitive performance and behavior disturbances. Assessment and intervention over neuropsychological performance is fundamental as it involves assimilation and understanding of information, reasoning, and problem-solving in order to prevent oneself from relapse, to develop mnesic capacity to remember therapeutic guidelines, to learn new skills and maintain abstinence, and to develop more adaptable behaviors. This section enumerates the most

Table 41.2 Psychometric instruments to evaluate psychiatric comorbidity

Construct	Instrument	Author
Psychiatric comorbidity	Psychiatric Research Interview for Substance and Mental Disorders (PRISM)	[34]
	Composite International Diagnostic Interview (CIDI)	[78]
General symptoms	Symptom Checklist- 90- Revised (SCL 90-R)	[21]
	Minnesota Multiphasic Personality Inventory (MMPI-2)	[42]
Affective symptoms	Hamilton Depression Rating Scale (HDRS)	[33]
	Beck Depression Inventory-II (BDI-II)	[8]
	Young Mania Rating Scale (YMRS)	[80]
Autolytic risk	Scale for Suicidal Ideation (SSI)	[7]
	Hopelessness Scale (HS)	[9]
Anxiety	Hamilton Anxiety Rating Scale (HARS)	[32]
	State Trait Anxiety Inventory (STAI)	[68]
	Yale-Brown Obsessive Compulsive Scale (Y-BOCS)	[31]
	Clinician Administered PTSD Scale (CAPS)	[10]
Psychotic spectrum	Brief Psychiatric Rating Scale (BPRS)	[56]
	Positive and Negative Syndrome Scale (PANSS)	[38]
Personality	International Personality Disorder Examination (IPDE)	[41]
	Eysenck Personality Questionnaire-Revised (EPQ-R)	[25, 26]
	Millon Clinical Multiaxial Inventory-III (MCMI-III)	[50, 51]
Eating behavior disorders	Eating Disorders Inventory (EDI)	[29]
	Eating Disorder Examination (EDE)	[16]
Sexual dysfunction	Changes in Sexual Functioning Questionnaire (CSFQ)	[14]
	Derogatis Interview for Sexual Functioning-Self-Report (DISF-SR)	[20, 22]
ADHD	Conners' Adult ADHD Rating Scales	[15]
	The World Health Organization Adult ADHD Self-Report Scale (ASRS)	[39]

Table 41.3 Tests to assess neuropsychological performance

Function	Subcomponent	Instrument	Author
General mental function		Mini Mental State Examination (Mini-Mental)	[28]
Attention	Span and control	Digit span (WAIS-IV)	[72, 74]
		Mental control test	[72, 74]
	Sustained or vigilance	Visual Cancellation Test	[75]
	Selective	Stroop Color and Word Test	[30]
	Alternating	Trail Making Test- – Part B (TMT-B)	[60]
Executive function	Disexecutive syndrome	Behavioural Assessment of the Dysexecutive Syndrome	[77]
	Fluency	Verbal fluency	[40]
	Working memory	Letter-Number (WAIS-IV)	[72, 74]
	Flexibility and analogic reasoning	Wisconsin Card Sorting Test (WCST)	[53]
	Interference and inhibitory control	Go/No- Go Task	
	Planning	Key Search and Zoo Map (BADS) Plan	[77]
	Decision-making	Iowa Gambling Task (IGT)	[6]
Memory	Broad function	Wechsler Memory Scale (WMS-III)	[71, 73]
	Short-term/working memory	Letter-Number, Arithmetic, and Digit Span (WMS-III)	[71, 73]
	Episodic long-term	Rey Auditory Verbal Learning Test (R-AVLT)	[62]
	Semantic long-term	Boston Naming Test	[37]
	Procedural	Rivermead Behavioural Memory Test (RBMT)	[1]
Visuospatial and perceptual abilities		Rey-Osterrieth Complex Figure	[61]
Language and communication skills		Information and Comprehension (WAIS-IV)	[72, 74]
Premorbid and morbid intelligence		Wechsler Adult Intelligence Scale-IV (WAIS-IV)	[72, 74]
		National Adult Reading Test (NART)	[54, 55]

relevant tests to evaluate neuropsychological performance (see Table 41.3).

41.4 Psychosocial Functioning and Quality of Life

Alcohol and other drug use disorders are increasingly viewed as chronic conditions. This approach addresses the impact of disorder and resources on patient's overall well-being. From this perspective, integrative intervention in addictive behaviors should aim for the broad goal of recovery, which is defined as abstinence plus improved quality of life and psychosocial functioning. These social markers are essential in treatment planning and outcome assessment as they represent the abilities and skills of the individual to function independently in the community.

41.4.1 Disability

- Disability Assessment Schedule 2.0 [79]. The WHODAS 2.0 was developed through a collaborative international approach, with the aim of developing a single generic instrument for assessing health status and disability across different cultures and settings. It is short, simple, and easy to administer, and one first-level general disability factor and six second-level standardized domains may be obtained: cognition, mobility, self-care, getting along, life activities, and participation.

41.4.2 Quality of Life

- Quality of Life Enjoyment and Satisfaction Questionnaire [24]. The Q-LES-Q is a self-

administered scale of 93 items designed to measure satisfaction and enjoyment in various domains of functioning: physical health and activities, mood state, work, household duties, academic/occupational activities, leisure and hobbies, social relationships, and general activities. There are various short forms available.

- World Health Organization Quality of Life Assessment [58]. The WHOQOL-100 includes 24 facets relating to quality of life, which are grouped into 4 larger domains: physical, psychological, social relationships, and environment. It also includes one facet examining overall quality of life and general health perceptions. There is an abbreviated, self-administered, 26-item version, the WHOQOL-BREF [65], which produces only domain scores.

41.4.3 Functioning

- Global Assessment of Function [2, 3]. The GAF is a 100-point tool rating overall psychological, social, and occupational functioning of people over 18 years of age and older. It excludes physical and environmental impairment. Scores range from 100 (extremely high functioning) to 1 (severely impaired). It has been replaced in the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) with the WHO Disability Assessment Schedule (WHODAS) which is supposed to be more detailed and objective than this brief global impression.
- Personal and Social Performance Scale [52]. The PSP is a global measure of personal and social functioning based on four domains of function: self-care, socially useful activities, personal and social relationships, and disturbing and aggressive behavior. Scores may vary from 0 to 100, with a higher score indicating a higher level of social and personal functioning.

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Biological State Marker for Alcohol Consumption

42

Friedrich Martin Wurst, Pablo Barrio, Antoni Gual, Natasha Thon, Wolfgang Weinmann, Frederike Stöth, Michel Yegles, Jessica Wong, and Ulrich W. Preuss

Contents

F. M. Wurst (✉)
Medical Faculty, University of Basel, Basel, Switzerland

Psychiatric University Hospital Basel, Basel, Switzerland

P. Barrio
Addictions Unit, Department of Psychiatry, University of Catalonia, Barcelona, Spain

A. Gual
Addictions Unit, Department of Psychiatry, University of Catalonia, Barcelona, Spain

Neurosciences Institute, Hospital Clínic, IDIBAPS, Barcelona, Spain

N. Thon
IDIBAPS Neurosciences Institute, Barcelona, Spain

W. Weinmann · F. Stöth
Institute of Legal Forensic Medicine, University of Bern, Bern, Switzerland

M. Yegles
Laboratoire National de Santé, Forensic Toxicology, Dudelange, Luxemburg

J. Wong
Klinik am Homberg, Bad Wildungen, Germany

U. W. Preuss
Vitos Hospital for Psychiatry and Psychotherapy, Kassel, Germany

Department for Psychiatry, Psychotherapy and Psychosomatic Medicine, University of Halle, Halle, Germany

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Abstract

Alcohol-related disorders are common, expensive in their entire course, and often underdiagnosed. To facilitate early diagnosis and therapy of alcohol-related disorders and thus prevent later complications, questionnaires and biomarkers are useful. Indirect state markers such as gamma-glutamyl transpeptidase (GGT), mean corpuscular volume (MCV), and carbohydrate deficiency transferrin (CDT) are influenced by age, gender, various substances, and nonalcohol-related illnesses and do not cover the entire timeline for alcohol consumption. Direct state markers such as ethyl glucuronide (EtG), phosphatidylethanol (PEth), and fatty acid ethyl esters (FAEEs) have gained enormous interest in the last decades, as they are metabolites of alcohol becoming only positive in the presence of alcohol. As biomarkers with high sensitivity and specificity covering the complimentary timeline, they are already routinely in use and contribute to new perspectives in prevention, interdisciplinary cooperation, diagnosis, and therapy of alcohol-related disorders.

Keywords

Alcohol biomarker · Ethanol metabolites · Traditional biomarkers · Ethyl glucuronide · Phosphatidylethanol · Gamma-glutamyl transferase

Introductory Paragraph

Alcohol biomarkers offer the opportunity to objectively assess alcohol intake. According to their specific characteristics, they provide different types of information: from abstinence monitoring to heavy use over time. If appropriately applied and used in conjunction with self-reports and questionnaires, they become an indispensable tool in the assessment and treatment of many conditions, such as alcohol use disorders, evaluation of liver transplant candidates, forensic evaluations, and others.

42.1 Introduction

Alcohol-related disorders are in the top ten of the most common diseases worldwide. The point prevalence for alcohol dependence in Germany, as in other comparable countries, is 5%, and the lifetime prevalence is 10%. Worldwide, approximately 4% of deaths are attributable to alcohol, greater than deaths caused by HIV, violence, or tuberculosis [1]. The yearly costs attributable to alcohol in Europe are approximately 270 billion €. Costs produced by alcohol include both direct costs (i.e., costs in which goods or services are being used or delivered such as medical care) and indirect costs (those stemming from lost productivity due to illness, death, or accidents). Another relevant source of costs attributable to alcohol is intangible costs (costs which are not related to any material loss: e.g., emotional suffering). Importantly, many of these costs are borne not only by the individual drinking alcohol but by society as a whole (the so-called social costs) [2].

Of all alcohol-dependent individuals, it is estimated that only about 10% receive specific treatment, most of them by their general practitioner (about 80%) and only a minority in specialized settings or general hospitals [3].

Thus, alcohol-related disorders are common, expensive in their entire course, and often underdiagnosed.

To facilitate early diagnosis and therapy of alcohol-related disorders and thus prevent later complications, questionnaires such as the CAGE questionnaire or the Alcohol Use Disorders Identification Test (AUDIT) are useful. Biomarkers also play an important role in many of the stages of alcohol use disorders, from screening and early detection to treatment monitoring, especially in abstinence-oriented settings [4, 5].

Indirect state markers as well as direct state markers are routinely used to detect alcohol. The indirect state markers such as gamma-glutamyl transpeptidase (GGT), mean corpuscular volume (MCV), and carbohydrate deficiency transferrin (CDT) are influenced by age, gender, various substances, and nonalcohol-related illnesses and do not cover the entire timeline for alcohol consumption, meaning that they need prolonged ingestion of relatively high amounts of alcohol to become elevated [6].

On the other hand, direct state markers have gained enormous interest in the last decades as they are metabolites of alcohol becoming only positive in the presence of alcohol. As biomarkers with high sensitivity and specificity covering the complimentary timeline, they are already routinely in use and contribute to new perspectives in prevention, interdisciplinary cooperation, diagnosis, and therapy of alcohol-related disorders.

42.1.1 Direct Ethanol Metabolites

Routinely used direct ethanol metabolites are as follows:

- Ethyl glucuronide (EtG) in serum, urine, and hair
- Ethyl sulfate (EtS) in urine and serum
- Phosphatidylethanol (PEth) in whole blood
- Fatty acid ethyl ester (FAEEs) especially in hair

Ethanol metabolites are detectable in serum for hours, in urine for up to 7 days, in whole blood over 2 weeks, and in hair over months.

42.2 Ethyl Glucuronide

Ethyl glucuronide (EtG) is a phase II metabolite of ethanol and has a molecular weight of 222 g/mol. It is metabolized by the UDP-glucuronosyltransferase.

Only about 0.5% of all the ethanol ingested undergoes this degradation pathway, but it can function as a biomarker as it is only detectable in the presence of ethanol. Moreover, EtG is non-volatile, water-soluble, and stable in storage and can, depending on the amount consumed and time spent for consumption, still be detectable in the body long after completion of alcohol elimination [7]. It can be detected of up to 90 hours in urine. There is no difference regarding the elimination rate between a healthy population and heavy alcohol consumers at the beginning of detoxification treatment [8]. Ethyl glucuronide can also be detected in postmortem body fluids and tissues such as the gluteal and abdominal fat, liver, brain, and cerebrospinal fluid and even in the bone marrow and muscle tissue.

Compared to traditional biomarkers, ethyl glucuronide displays a high sensitivity. Even small amounts like 0.1 L champagne can be detected up to 27 hours with this biomarker. Experiments with 1 g ethanol (champagne, whisky) as well as the use of mouthwash and hand sanitizer gels might yield positive ethyl glucuronide concentrations, usually with values of less than 1 mg/L in urine [9]. Measurable concentrations in urine can be found up to 11 hours after ingestion.

This aspect is of relevance regarding unintentional exposure of alcohol: Pralines, nonalcoholic beer, pharmaceutical products, fruit juice, sauerkraut, mouthwash products, and hand sanitizer gels may contain small amounts of alcohol. Even the intake of 21–42 g yeast with approximately 50 g sugar leads to measurable EtG and EtS concentrations in the urine.

Therefore, a patients' claim not having consumed alcohol may be the truth even when EtG is detectable in the urine. Since patients in withdrawal treatment should avoid even the smallest amount of alcohol, they have to be informed of such hidden sources of ethanol to avoid unintentional alcohol intake. A differential cutoff of 0.1 mg/L in cases where total abstinence is the goal and 1.0 mg/L if small amounts of alcohol intake are tolerated have been recommended for practical reasons. Applying these cutoffs, the probability of false-positive results is very low [10].

> Sometimes a positive ethyl glucuronide in the urine will be a true laboratory positive, but a false clinical positive, meaning that the patient has not intentionally ingested significant amounts of ethanol. However, using appropriate cutoffs, this would be a low probability situation.

42.2.1 Selected Applications for the Use of EtG

1. Outpatient addiction treatment programs

   Regular alcohol screening is a frequent intervention in many outpatient addiction treatment settings. Urine ethyl glucuronide has shown a higher sensitivity compared to traditional screening methods in this population, providing a more accurate feedback to both patients and professionals. In a former study, the percentage of urine positive samples screened with ethanol was less than 2%, whereas the same samples screened positive for ethyl glucuronide in almost 22% of the cases [11].
2. Specific high-risk group

   Many patients in opioid-maintenance therapy suffer from hepatitis C (HCV) infection. Alcohol consumption especially in large amounts leads to the progression of cirrhosis. Previous studies showed the usefulness and necessity of the determination of ethyl glucuronide in patients in opioid-maintenance therapy. For example, one study showed that, of all EtG positive patients, 42% ($n = 8$ of 19) would have not reported the alcohol consumption [12]. The use of direct ethanol metabolites in high-risk groups therefore allows more possibilities for therapeutic interventions,

consequently leading to improvement in the quality of life.

3. Monitoring programs

   One example for using ethyl glucuronide successfully in monitoring programs is the physician health programs in the USA which provide a non-disciplinary therapeutic program for physicians with potentially impairing health conditions as, for example, substance-related disorders. Being in the monitoring program, physicians with substance-related disorders are allowed to keep on working provided a regularly proof of abstinence has to be shown. Measuring EtG in urine, Skipper and colleagues showed that of 100 random samples collected, no sample was positive for alcohol using standard testing; however, seven were positive for EtG (0.5–196 mg/l), suggesting recent alcohol use. EtG testing can provide additional information and consequently may lead to further treatment and improvement for the patient [13].

4. Pharmacotherapeutic studies

   As an objective outcome parameter, EtG testing has shown to be useful in pharmacotherapeutic studies [14].

5. Liver transplantation

   Up to 30% of liver transplantations are related to alcohol. Postoperatively, 20–25% of patients lapse or relapse to alcohol intake. In 18 patients with ALD (alcohol liver disease), Erim et al. found no self-report of alcohol consumption. One out of 127 tests for breath alcohol was positive, whereas 24 of 49 urine samples were positive for EtG. Comparable results were reported by another study which found self-reported alcohol consumption in 3% in contrast to 20% positive urine EtG and EtS tests [15].

6. Pregnant women

   Alcohol intake during pregnancy is a well-established risk factor for developmental impairments, especially fetal alcohol spectrum disorders (FASD). It is also known that a relevant proportion of pregnant women drink alcohol. Therefore, alcohol screening during pregnancy should be routinely conducted. Alcohol intake during pregnancy can be investigated in maternal (including hair, blood, urine) and fetal specimens (meconium). Similarly to other groups, self-reports and other questionnaires tend to underestimate alcohol intake. Ethyl glucuronide both in urine and meconium has been shown to improve the detection of drinking [16].

The above mentioned applications show that ethyl glucuronide tests are complementary to self-reports and questionnaires, yielding valuable information on alcohol consumption which is relevant to diagnosis and therapy.

> Irrespective of the setting and population where it is applied, ethyl glucuronide always displays a significantly greater sensitivity for the detection of alcohol drinking when compared to questionnaires, self-reports, and traditional biomarkers. However, the information it provides must always be considered as complementary to that obtained from other sources.

42.2.2 Methodological Aspects

The gold standard for the detection of ethyl glucuronide is liquid chromatography-tandem mass spectrometry (LC/MS-MS), and it remains the only valid method of analysis in enquiries with medicolegal relevance [17]. However, availability and cost issues prevent this method to become ubiquitous.

Fortunately, a DRI ethyl glucuronide enzyme immunoassay ([DRI-EtG EIA) became commercially available a decade ago. It is a semiquantitative method with a clinical cutoff of 500 ng/ml. It also offers a low and clinically relevant analytical range (15.3–2000 ng/ml). Its validity is very similar to that of the gold standard.

The last available method of analysis has been the appearance of point-of-care EtG immunoassay dipcards, which are commercially available at a very low cost. A recent study suggests the validity of the method to be high [18].

42.2.3 Limitations

A potential problem with EtG is the potential false-negative results produced by urinary tract infections, especially *E. coli*, which is able to degrade EtG. That, however, does not happen with ethyl sulfate, which remains stable in spite of the infection. This leads some authors to recommend simultaneous analysis of both biomarkers when a false-negative result is suspected for EtG. Interestingly, a recent study reported that the bacterial degradation of EtG by *E. coli* can be prevented by the use of dried urine on filter paper.

Given the impact alcohol has on liver function, it is important to remark that liver disease does not influence on the validity of EtG, as has been shown in studies conducted in patients with liver disease, including cirrhosis. Similarly, previous studies also suggest that race, nicotine consumption, body mass index, and body water content do not influence EtG concentrations. Conversely, reduced renal function seems to prolong the elimination time of EtG. Other potential factors affecting EtG levels are age, gender, and cannabis consumption.

42.2.4 Clinical Impact of Ethyl Glucuronide

Traditional biomarker validation studies rely on cross-sectional designs where sensitivity and specificity are the cornerstone of the evidence-gathering process. Accordingly, EtG has shown a high sensitivity and also high predictive values, both positive and negative, both in experimental and clinical settings.

However, cross-sectional validation prevents linking biomarker properties to patient outcomes on a longitudinal basis. A recent publication of a diagnostic randomized clinical trial where ethyl glucuronide was compared to ethanol in a randomized design [19] enabled the connection of biomarker properties and diagnostic performance to patient outcomes, demonstrating that implementing ethyl glucuronide in the routine screening of alcohol-dependent outpatients leads to decreased drinking and increased rates of abstinence over time.

> Recent evidence suggest that the application of a highly sensitive biomarker such as ethyl glucuronide has therapeutic properties, leading to reduced drinking and increased abstinence rates, probably due to increased feedback to both professionals and patients about their drinking.

42.3 Ethyl Sulfate

Ethyl sulfate (EtS) presents a secondary elimination pathway for alcohol and is usually detectable in varying interindividual concentrations. An immunochemical detection test is currently not commercially available for EtS. For combined detection of EtS and EtG, the use of rapid LC/MS-MS procedures is routinely applied. It is normally measured in urine, although it can also be assessed in plasma.

The formation is effected by sulfonyl transferase and the breakdown by sulfatases. The molecular weight is 126 g/mol and the molecular formula $C_2H_5SO_4H$.

Currently, a LC/MS-MS method with pentadeuterium EtS as internal standard and two ion transitions can be used in forensic and medicolegal cases as well as in clinical routine. The fact that its formation route is different to that of EtG offers the opportunity of increased sensitivity when analyzing the two biomarkers together. However, the discrepancies between the two are usually low [20].

In summary, a cutoff of 0.05 mg/l for repeated alcohol intake has been suggested. As for ethyl glucuronide, there is evidence of prolonged elimination in reduced renal function. Importantly, bacterial degradation of EtS has not been described. Therefore, EtS should be analyzed in conjunction with EtG when degradation of this biomarker is suspected, in order to prevent the appearance of a false-negative result.

Ethyl sulfate is seldom analyzed alone. Usually, both EtG and EtS are assessed, in order to complement each other's information. EtS might help prevent false-negative results due to bacterial degradation of EtG, especially by *E. coli*, and it might also increase the sensitivity of EtG alone.

42.4 Fatty Acid Ethyl Esters

In recent years, the existence of fatty acid ethyl esters and non-oxidative metabolic products of ethanol in the blood and various organs with reduced or deficient capacity to oxidize ethanol after consumption has been proven. Since these esters were proven to cause damage to subcellular structures, they were postulated to be mediators of organ damage.

Two enzymes catalyze the formation of FAEE: acyl coenzyme a-ethanol o-acyltransferase (AEAT) and fatty acid ethyl ester-synthase. FAEE-synthase can be isolated from the rabbit myocardium, human brain, and rat fat tissue. Two of these FAEE-synthases were shown to be identical to rat liver carboxyl esterase. Furthermore, pancreatic lipase, lipoprotein lipase, and glutathione transferase were shown to possess FAEE-synthase activity.

Fatty acid ethyl esters are formed in the presence of ethanol from free fatty acids, triglycerides, lipoproteins, or phospholipids affected by specific cytosolic or microsomal FAEE-synthases or through acyl coenzyme a-ethanol o-acyltransferase. Detectable levels are found in the blood shortly after alcohol consumption and remain positive for more than 24 hours.

Of 15 different FAEEs in hair, the sum of four of these (ethyl stearate, ethyl oleate, ethyl myristat, and ethyl palmitate) is shown to function as a marker in hair analysis. With a cutoff of 0.5 ng/ml, a sensitivity and a specificity of 90% were reported. A differentiation between abstinent, social, and excessive drinkers appears possible [21]. However, the complex GC/MS method lacks practicability for routine use.

42.5 Phosphatidylethanol

Phosphatidylethanol is an abnormal phospholipid formed in the presence of alcohol via the action of phospholipase D. The precursor is the naturally existing lipid-phosphatidylcholine. PEth consists of glycerol which is substituted at positions sn1 and sn2 by fatty acids and a phosphate group at position sn3 esterified with ethanol. Due to the variations of the fatty acids, various analogs of PEth can be detected. The PEth analogs 16:0/18:1 and 16:0/18:2 are most prevalent, and their combined sum correlates better with PEth than PEth 16:0/18:1 or PEth 16:0/18:2 alone.

Using the original HPLC methods, repeated consumption of more than 50 g alcohol over 2–3 weeks yielded positive results, lately even with daily consumption over 40 g [22].

A drinking experiment [23] with healthy persons with a target blood ethanol concentration of 1 g/kg (1 per mille) once on each of 5 consecutive days yielded PEth values up to 237 ng/ml. Measurements were performed with LC/MS-MS. In contrast to alcohol-dependent patients, the values were reported to be up to 213,000 ng/ml [24].

Various studies found no false-positive results. A linear relationship between consumed amounts of alcohol with phosphatidylethanol values has been described [22].

Interestingly, and thanks to constant refinements in analytical methods, the sensitivity and specificity of current PEth analysis seem to be extremely high [25]. Also relevant is the fact that, besides its already known potential for abstinence monitoring, current evidence suggests PEth could be a suitable biomarker for the differentiation between light and heavy drinking, a feature that is lacking in other direct alcohol biomarkers [26].

Importantly, PEth values seem not to be influenced by liver diseases and hypertension [27].

Among the new direct alcohol biomarkers, PEth seems to be the only one capable of assessing abstinence and also differentiating between light, moderate, and heavy drinking.

42.5.1 Methodological Aspects

The current approach for PEth determination is LC/MS and LC/MS-MS methods. These methods facilitate detection and quantification of single analogs, if a reference is available.

For everyday practical use, the use of dried blood spots may be of significant relevance. This method is suggested to have results similar to whole-blood measures. Furthermore, there is no difference between venous or capillary blood collection [28]. Sampling is simplified as nonmedical staff can obtain capillary blood, the risks for HIV and hepatitis C infections are decreased, and storage and transport are simplified.

42.5.2 Clinical Applications

Similar to what has been described with ethyl glucuronide, phosphatidylethanol has shown a high degree of sensitivity and specificity for the detection of alcohol drinking. It has been applied to different populations and clinical settings, such as HIV populations, pregnant women, and alcohol-dependent patients [29].

Interestingly, it seems like PEth shows good correlations with AUDIT-C scores [30]. Therefore, PEth might be a potential biomarker of heavy alcohol consumption over time.

Finally, some authors suggest that PEth might have a role in patients who are tested for EtG and EtS, have low positive values, and deny alcohol consumption, as a further evaluation with an even more sensitive biomarker.

42.5.3 Limitations

In blood and tissues containing ethanol, the formation of PEth under certain conditions may be feasible. Without influencing the PEth levels, whole-blood samples can be stored frozen at −80 °C [31], and DBS can be stored for at least 30 days at −20 °C [32].

In vitro formation of PEth in erythrocytes has been reported after addition of ethanol. Further experimental studies in rats showed that ceramide is able to block the activity of phospholipase D and inhibits the synthesis of PEth.

42.6 Hair Analyses

Hair analysis has been established to assess ethanol intake. FAEE and ethyl glucuronide (EtG), two metabolic by-products of ethanol, are gaining attention as alcohol markers in the hair.

The time frame for the detection of alcohol consumption is longer in the hair compared to blood or urine. Due to head hair growth of 1 cm per month, depending on the hair length, evidence of alcohol consumption can be found for the respective time period. The deposit of lipophilic FAEE in the hair occurs in sebum, whereas hydrophilic EtG is incorporated through perspiration and/or from blood.

Measurement of FAEE and EtG allows differentiation between chronic excessive and moderate alcohol consumption as well as abstinence or very low levels of alcohol consumption.

In a last consensus from the Society of Hair Testing, an essential change of the consensus was accepted for the FAEEs, where the concentration of ethyl palmitate (EtPa) can be used autonomously for interpretation instead of the concentration sum (ΣFAEE) of the four esters ethyl myristate, ethyl palmitate, ethyl oleate, and ethyl stearate, as previously applied [33]. The EtPa cutoff for abstinence assessment was defined at 0.12 ng/mg for the 0–3 cm segment and at 0.15 ng/mg for the 0–6 cm segment. The cutoff for chronic excessive drinking was fixed at 0.35 ng/mg for the 0–3 cm segment and at 0.45 ng/mg for the 0–6 cm segment. The use of EtPa with these cutoffs in place of ΣFAEE for alcohol intake assessment produces only a minor loss in discrimination power, leads to no essential difference in the interpretation concerning chronic excessive alcohol consumption, and is suitable to confirm EtG results in abstinence assessment.

An EtG concentration of over 30 pg/mg hair is interpreted as definite evidence for excessive and regular alcohol consumption (>60 g EtOH per day), whereas an EtG concentration of more than 7 pg/mg is a marker of frequent alcohol use. If samples less than 3 cm or greater than 6 cm are used, the results should be interpreted with caution. The analysis of FAEEs alone is not recommended to determine abstinence from ethanol.

For abstinence assessment, EtG should be the first choice, and the analysis of FAEEs alone is not recommended to determine abstinence from ethanol. A positive FAEE result combined with an EtG below 7 pg/mg does not clearly disprove abstinence but indicates the need for further monitoring. The combined use of FAEE and EtG can be recommended to increase the validity of hair analysis [34].

In an alcohol drinking experiment, 32 women who consumed 16 g alcohol per day had EtG values of less than 7 pg in their scalp hair [27]. These divergent results may be explained by the fact that EtG values lower than 7 pg/mg do not exclude alcohol ingestion. Furthermore, scalp hair was pre-analytically cut in this study, while previous studies pulverized the specimen: The preparation pre-analytically has been reported to influence the results significantly [35].

42.6.1 Other Influencing Factors

Whereas only in one case a false-positive result for EtG in the hair after use of EtG containing shampoo has been reported, regular use of alcohol-containing hair tonic can lead to false-positive FAEE results. No such false-positive results are reported for EtG. Impaired kidney function may lead to higher EtG levels, as preliminary results indicate. BMI showed to have also an influence on EtG concentration in the hair.

False-negative results for both alcohol markers can also be caused by the use of hair cosmetics, such as alkaline hair cosmetics for FAEE [36] or oxidative treatment for EtG and hair straightening for EtG. Cleansing shampoos may also alter EtG and FAEE concentrations in hair.

The hair color and melanin content in hair play no role, in contrast to drugs and medications. In segmental investigations of hair samples, a chronological correlation to drink or abstinent phase with FAEE is not possible, but for EtG, two studies have shown this to be feasible.

Altogether, hair analysis for FAEE or EtG is currently a sensible tool to clarify past alcohol consumption, as demonstrated in many studies.

42.6.2 Practical Use

Hair analysis for FSEE or EtG is applicable in several contexts including judging driving ability and forensic psychiatry. Another clinical use of alcohol metabolite measures is the screening for alcohol use in medication- assisted treatment of opioid-dependent subjects as mentioned above

42.7 Summary

In summary, specific ethanol metabolites are available which can detect the spectrum between short-term intake of small amounts and long-term use of large amounts of alcohol (s. Table 42.1). Cutoff values and influencing factors are summarized in Tables 42.2 and 42.3. Appropriate methods of analysis and pre-analytics are crucial for a valid and reliable detection of markers. For ethyl glucuronide (EtG), the most frequently used marker, the best method for detection is chromatographic approach which is considered a standard method especially in forensic cases. A commercial test

Table 42.1 Clinically relevant options for determination of direct biomarkers, with respect to amount and duration of alcohol intake

Duration of consumption	Amount of consumption	
	>1 g/d	>40–60 g/d
<1 day	Serum, urine: EtOH, EtG, EtS	Serum and urine: EtOH, EtG, EtS; PEth in whole blood and dried blood spots (LC/MS-MS)
>1 day	Serum, urine: EtOH, EtG, EtS	Serum and urine: EtOH, EtG, EtS; PEth in whole blood and dried blood spots (LC/MS-MS)
>14 days	Serum, urine: EtOH, EtG, EtS	Serum and urine: EtOH, EtG, EtS; PEth in whole blood and dried blood spots (HPLC LC/MS-MS)
Weeks to months	Serum, urine: EtOH, EtG, EtS	Serum and urine: EtOH, EtG, EtS; PEth in whole blood and dried blood spots (HPLC LC/MS-MS), EtG and FAEEs in hair

Modified according to Thon et al. [37]
EtOH ethanol, *EtG* ethyl glucuronide, *EtS* ethyl sulfate, *PEth* phosphatidylethanol, *FAEE* fatty -acid ethyl esters

Table 42.2 Clinically relevant options for determination of direct biomarkers, with respect to amount and duration of alcohol intake

Biomarkers	Amount of consumption	Cutoff
EtG in hair	Abstinence and low intake (<10 g alc/d)	<7 pg/mg
	Social consumption (20–40 g/d)	7–30 pg/mg
	Excessive drinking (>60 g/d)	>30 pg/mg
FAEEs in hair	Repeated alcohol intake	≥200 pg/mg
	Excessive intake	≥500 pg/mg
EtG in urine	Total abstinence	0.1 mg/L
	Unintentional intake Recent alcohol use Longer back-dated alcohol intake in larger amounts	0.1 mg/l–0.5 mg/L
	Unintentional intake unlikely, but possible, active alcohol intake probable	0.5–1 mg/L
EtS in urine	Total abstinence	0.05 mg/L
PEth	>40 g/d, more than 2 weeks alcohol intake at least once with 1‰ detectable	HPLC, 0.22 μM; LC/MS-MS, 20/30 ng/ml; PEth, 16:0/18:1 or 0.05 μM

Modified according to Thon et al. [37]
EtG ethyl glucuronide, *FAEEs* fatty -acid ethyl esters in hair, *EtS* ethyl sulfate, *PEth* phosphatidylethanol

Table 42.3 Detection of direct biomarker, with respect to amount and duration of alcohol intake

Direct biomarkers	Potential influencing factor	Influence
EtG in urine	*E. coli*, dried urine spots	No
	Grade of liver disease, smoking, BMI, body water content, reduced kidney function	No
EtS in urine	*E. coli*, dried urine spots	No
PEth	Liver disease	No
	Hypertension	No
	Storage of ethanol blood samples Refrigerator temperature, −80 °C	No
EtG in hair	Hairsprays with ethanol, hair color, melanin content, age, gender, BMI	No
Direct biomarkers	**Potential influencing factor**	**Type of influence**
EtG in urine	*E. coli*, *C. sordellii*	Decrease
	Reduced kidney function	Longer detection
	Chloral hydrate	False positives
EtS in urine	Reduced kidney function	Longer detection
	Closed Bottle Test (OECD 301 D) Manometer Respiratory Test (MRT)	28 days' stable detection, depletion after 6 days
FAEEs in hair	Aggressive alkaline hairsprays	False negative
	Hairsprays with ethanol	False positives
PEth	Ethanol-containing blood samples, storage of ethanol blood samples at RT and − 20 °C	Increase
EtG in hair	Hairspray with EtG	Increase
	Reduced kidney function	Increase
	Bleaching, hairstyling products	False negative

Modified according to Thon et al. [37]
EtG ethyl glucuronide, *FAEE* fatty -acid ethyl esters, *EtS* ethyl sulfate, *PEth* phosphatidylethanol, *BMI* body – mass index, *RT* room ambient temperature, *E. coli Escherichia coli*, *C. sordellii Clostridium sordellii*

kit is available and contributed to wide distribution of the test. Of course, lab values always require critical reappraisal. However, EtG is detectable in urine using LC/MS-MS even after an ingestion of low amounts of alcohol (1 g), which also occurs in some food, drugs, and disinfectants. Individuals with the motivation to or obligation for abstinence have to be informed about these "hidden contents" to avoid involuntary intake of alcohol. For forensic purposes, the current cutoff value of 0.1 mg/L should be adapted to exclude cases of involuntary alcohol use. With respect to differences in formation and degradation, EtG and ethyl sulfate (EtS) should be analyzed together, if possible. In the absence of known influencing factors, EtG in the hair can be recommended as a marker for alcohol intake for the last 3 months. Further, guidelines for interpretations of values from international society (SOHT) are available. While positive urine values of EtG and EtS can be in accord with innocent/unintentional alcohol intake, positive values of PEth are related to previous intoxications of 0.5‰ and more. The use of "dried blood spots" is promising and may facilitate sample taking, storage, distribution, and decrease of infection risk.

42.8 Traditional Biomarkers for Alcohol Consumption

Many clinical-chemical parameters show pathological changes as evidence of the biochemical burden of ethanol metabolism. None of these conventional indicators show 100% sensitivity or specificity. Nonetheless, evidence of long-term alcohol consumption can be obtained from these state markers, especially a combination of several individual indicators. The currently used and potential alcohol biomarkers are shown in Table 42.4.

Table 42.4 Diagnostic characteristics of several conventional and potential alcohol biomarkers

Alcohol biomarker (abbreviation)	Window of assessment	Specificity/ sensitivity	Type of alcohol consumption	Application	Specific comments
Conventional alcohol biomarkers					
Ethanol (EtOH)	6 hours	High/high	Recent alcohol consumption/ alcohol intoxication	In traffic safety/ emergency department	In combination with clinical observations – monitoring alcohol habits
Gamma-glutamyl transferase (GGT)	2–8 weeks	Moderate/ moderate	Chronic, heavy	Screening/ monitoring	More specific for alcoholics ages 30–50 years
Aminotransferase ratio AST/ALT ≥ 2	Unknown	High/low	Heavy	Alcoholic hepatitis/ relapse	Less frequently used than GGT for screening heavy alcoholics
Mean corpuscular volume (MCV)	Up to several months	Moderate to high/low	Chronic	Screening/fetal alcohol effects	Show dose-dependent response to the intensity of alcohol intake
Carbohydrate-deficient transferrin (CDT)	2–3 weeks	High/ moderate	Heavy	Screening/ monitoring/ relapse	No elevation in single episodes of acute alcohol intoxication
GGT-CDT	2–3 necks	High-high	Heavy	Abstinence/ relapse	Useful for diagnostic alcohol-liver damage due to excessive and prolonged intake
Potential alcohol biomarkers and devices					
Ethyl glucuronide (EtG) and ethyl sulfate (EtS)	Several days	High/high	Recent alcohol consumption	Abstinence/ relapse	High inter-individual variations

(continued)

Table 42.4 (continued)

Alcohol biomarker (abbreviation)	Window of assessment	Specificity/ sensitivity	Type of alcohol consumption	Application	Specific comments
Phosphatidylinositol (PEth)	1–2 necks	Unknown/ high	Heavy	Screening/ relapse	Promising in differentiating alcohol – from non-alcohol-induced liver disease
Fatty acid ethyl esters (FAEEs)	24 hours (after ingestion)/99 hours (heavy drinking)	High/high	Recent heavy	Distinguishing social drinkers from heavy	Combination of FAEE and EtG in meconium – markers for fetal alcohol exposure
Whole blood-associated acetaldehyde assay (WBAA)	Unknown	High/high	Chronic/heavy	Monitoring abstinence	IgAs against acetaldehyde protein adducts – promising in differentiating alcohol – from non-alcohol- induced liver disease
Total sialic acid (TSA)	Unknown	Between GGT and ALT	Chronic, heavy	Relapse	Increased in high alcohol consumption and reduced during abstinence, especially among women
5-HTOL/5-HIAA	1 day	High/high	Recent alcohol consumption	Evaluation of treatment/ relapse	5-HTOL/5-HIAA > 20 marker of recent drinking
Transdermal devices (SCRAM, WrisTAS)	–	High/high	Record continuous alcohol consumption	By court monitoring of abstinence	Need product improvements

From Topic and Djukic [38]

42.8.1 Blood Alcohol Content Calculation

A mathematical estimation of blood alcohol content is useful when blood alcohol is not currently detectable or for prediction of alcohol level. While there are several ways to calculate it, the simplest is Widmark's equation: $Co = A/[p \times r]$, where Co is the theoretical maximum concentration of alcohol in the blood (mg/g), A is the amount of alcohol in the body (g), p is the body weight (kg), r is the correction factor corresponding to the ratio of total body water and blood water (0.6 for females and 0.7 for males).

Gender plays an important role in the total amount of water in the body. In general, men have less fatty tissue and higher percentage of water (58%) than women (49%); thus, volume of distribution (Vd) for ethanol is higher in men. According to its partition coefficient (Poct/water is 0.1), ethanol is ten times more soluble in water than in lipids. Thus, upon ingestion of the same amount of ethanol, the BAC will be higher in females than in males. The Widmark's equation has been improved subsequently by introducing individual r, based on the multiple linear regression equations:

$$\text{For females}: r\text{FI} = 0.31223 - 0.006446 \times \text{body weight}(\text{kg}) + 0.004466 \times \text{body height}(\text{cm})$$

$$\text{For males}: r\text{MI} = 0.31608 - 0.004821 \times \text{body weight}(\text{kg}) + 0.004632 \times \text{body height}(\text{cm})$$

There is no absolute accurate blood alcohol calculator because numerous factors influence the BAC, such as gender (male/female), rate of metabolism/elimination, health status, medications that might be taken, drinking frequency, amount and the type of food in the stomach and small intestine, time when food was eaten, and others [38].

42.9 Gamma-Glutamyl Transferase (γ-GT)

γ-GT is a membrane-bound glycoprotein enzyme which occurs ubiquitous in the organism but mainly in the liver, pancreas, and renal proximal tubules. γ-GT detectable in serum arises mainly from the liver so that an increase in serum enzyme activity would be a sensitive indicator for hepatobiliary diseases. Chronic alcohol consumption induces an increase in enzyme synthesis and, through direct activation of the enzyme from membrane binding, leads to increase of γ-GT in serum. The release of enzymes through liver parenchymal damage also presents a secondary mechanism in chronic alcoholic hepatitis. To exceed the normal values (4–18 U/l in women and 6–28 U/l in men) requires the chronic, daily alcohol intake over at least 4–6 weeks. A short-term, higher alcohol burden causes no such increase. Nevertheless, drinking intensity has more influence on γ-GT than drinking frequency. In absolute alcohol abstinence, normalization of the values occurs within 3 weeks to 60 days.

The sensitivity of γ-GT varies, according to age, gender, and body weight, from 35% to 85%. γ-GT increases with age in heavy alcohol drinkers as well as moderate drinkers. Contrarily, in young adults less than 30 years, even when these are alcohol dependent, the sensitivity of the markers is very low. In addition, the higher vulnerability of women to alcohol-associated liver diseases is well known. Other studies have shown that the relationship between overweight (BMI > 25) and an increase in γ-GT [39] is related. γ-GT levels can also be increased by various other causes, for example, the effects of medication and teratogens, adiposities, diabetes, cholestasis, or inflammatory liver diseases. Accordingly, the specificity of 63–85% is only satisfactory, and γ-GT, in spite of its practicability as solitary indicator of chronic alcohol misuse and current liver diseases, is deemed unsuitable [40].

42.10 Mean Corpuscular Erythrocyte Volume (MCV)

Measurements of MCV are common in standard investigations; an increase occurs in 4% of the general population and in 40–60% of patients with alcohol misuse. Koivisto et al. [41] reported definite evidence of marked dose-dependent relationship between MCV and the intensity of alcohol consumption. Increase in MCV is to be expected in long-term alcohol consumption; by contrast, the values normalize slowly during abstinence over a period of 2–4 months. Compared to γ-GT, the sensitivity of MCV in screening as evidence of alcohol misuse, at least in men, is inferior. In interpreting MCV values, other causes such as vitamin B12 or folic deficiency, nonalcoholic liver diseases, reticulocytosis, and hematologic diseases should be considered.

The mechanism responsible for increasing MCV is hitherto unclear, and direct hematotoxic damage or interaction of ethanol and its metabolites, especially acetaldehyde, with erythrocyte membrane has been suggested [42].

42.11 Carbohydrate-Deficient Transferrin (CDT)

Transferrin is the most important iron transport molecule in humans, and its synthesis and glycolization occur in hepatocytes. Depending on the iron load as well as the number and breakdown of carbohydrate chains, different isoforms can be detected. Differentiation occurs through measurements of isoelectric points (pl), whose values depend on the load of bound iron ions and number of sialic acid residues in carbohydrate chains. Abnormal isoforms with much increased pl-values over 5.65 in the liquor and serum of

alcohol-dependent patients were found and were traced back to small levels of bound sialic acid residues. In subsequent investigations, more precise differentiation in mono-, di-, and asialotransferrin was feasible, and all abnormal isoforms were subgrouped under CDT [43]. All abnormal transferrin molecules increase in chronic alcohol consumption. Measurements with HPLC showed that increased alcohol consumption leads to increased disialotransferrins, while increases in asialotransferrin occur in chronic increased alcohol consumption only. A variety of methods and respective reference levels for the detection of CDT are available. Hitherto, measurements of CDT using HPLC is the reference standard, with routine measurements of various enzyme immunoassays in use. For confirmation analyses, immune electrophoresis is employed, while direct CDT detection method using specific antibodies is still under development [44].

The underlying pathomechanism for CDT development is not exactly known. Inhibition of intracellular transmission of carbohydrates to change through toxic effects from ethanol or acetaldehyde is presumed. Ethanol's influence on the activities of membrane-bound sialine transferases and plasma sialidases in hepatocytes has been discussed, in which an imbalance in favor of sialine acid reduction enzymes occurred.

There has been no agreement in previous studies concerning the correlation between CDT concentrations in serum and the absorbed alcohol amounts. Though an increase in CDT with daily consumption of 60–80 g alcohol over 7 days has been shown, other studies have reported contradicting results. Additionally, contradicting results on the effect of moderate drinking (<40 g alcohol) are found. In alcohol-dependent patients, it is, however, sensitive enough for detecting relapses and monitoring sobriety [45].

The clinical strengths of CDT as a biomarker vary depending on gender, BMI, age, nicotine abuse, and anorexia [46]. Previous studies showed that CDT in men is a more sensitive indicator of alcohol-related diseases compared to women. CDT values in women might be increased under natural conditions but not much in increased alcohol use. Furthermore, hormonal factors appear to play a role – CDT values are definitely increased in pregnant women but reduced in postmenopausal women. Obviously in the female gender, differences in CDT serum activity depend on age as well.

Among the various conventional alcohol markers, CDT is currently considered the most useful and significant indicator [47]. Information on sensitivity and specificity varies, since no methodical standardization exists. Further, the heterogeneity of test populations concerning age, gender, alcohol consumption, duration of abstinence before serum extraction, as well as current liver diseases makes the comparison with other traditional markers difficult. In selected clinical patient groups, various test methods with specificity between 90% and 100% with high sensitivity (50–90%) have been reported.

In WHO/ISBRA study, the sensitivity of CDT with 60% in men was slightly less than that of γ-GT, and in women the sensitivity reached only 29% [6]. False-positive increased CDT values can occur in biliary cirrhotic, autoimmune hepatitis, genetically determined transferrin variants, or the autosomal recessive inherited CDG syndrome. Most patients with liver diseases have insignificantly increased CDT values so that the specificity, especially in comparison with other state markers, must be stated exceptionally high and usually reach at least 90%. Thus, CDT could be used for detection of chronic alcohol consumption and changes in drinking patterns in these patients. With a half-life of 14 days and normalization of CDT values in abstinence, evidence of drinking relapses in the post-acute phase after alcohol withdrawal treatment can be obtained.

42.12 Serum Transaminases (ASAT/ALAT)

Increases of aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) in serum are unspecific signs of hepatocellular damage. While ASAT is produced in the liver, skeleton, and cardiac muscle tissues, ALAT is a liver-specific enzyme. Thus, an increase in ALAT practically indicates liver diseases (fatty degeneration, tumors,

metastases, cirrhosis, cholangitis). By contrast, measurements of ASAT must differentiate between alcohol-sensitive, mitochondrial (m-ASAT), and cytoplasmic isoform (c-ASAT). Conclusions on an alcohol-induced liver damage can only be drawn from increased m-ASAT/c-ASAT quotients. Increased ASAT values would be found in alcohol-dependent patients from 39% to 47%. In the WHO/ISBRA study, sensitivity of ASAT between 23% and 45% (women vs. men) could be found. The toxic effects of ethanol on mitochondria lead to increased release of ASAT compared to ALAT. Thus, measurements of de-Ritis-Quotient (ASAT/ALAT) increase the alcohol specificity of both markers – a quotient over 1 and even 2 would offer strong indications for an ethyl toxic etiology.

In summary, the sensitivity and specificity of both enzymes as indicators for alcohol misuse are considered variable so that an interpretation of an increased serum activity is mainly meaningful in the context of other liver values (bilirubin, alkaline phosphatase, γ-GT).

42.13 HDL Cholesterine and Apolipoprotein

Increases in HDL cholesterol and apoprotein I/II are described in many studies as specific and sensitive indicators of chronic alcohol strain; by contrast, triglycerides and total cholesterine are nutritionally influenced. Alcohol leads to an increase in the concentrations of cholesterol and phospholipids within the HDL particles and causes a shift to bigger portions of phospholipids in richer, larger HDL_2 particles [48].

Studies showed this phenomenon to be the basic principle for the observed cardioprotective character of moderate alcohol consumption [49]. Chronic alcohol load causes an increase in HDL over 50 mg/dl, and after withdrawal and with continuing abstinence, the values normalize within 1–4 weeks. The pathogenic cause of alcohol-related HDL and apoprotein increases is postulated to be an enzyme induction as well as increased lipoprotein lipase activity.

Increased HDL levels without alcohol can occur under the influence of medication (sedatives, lovastatin), pronounced underweight, and physical strain. Still, the specificity of this marker is highly esteemed. Moreover, it proved itself to be practicable. Particularly in patients without liver damage, HDL and apoprotein I/II can be used for monitoring abstinence since changes in alcohol consumption would be accurately reflected.

42.14 Cholesteryl Ester Transfer Protein (CETP)

Cholesteryl ester transfer protein is a glycoprotein synthesized in the liver and catalyzed out of HDL particles through lipid diffusion into LDL particles. Through alcohol consumption, the plasma concentration and activity of CETP are reduced, thereby increasing HDL concentration. Moderate drinking, by contrast, hardly influences CETP activity. The sensitivity and specificity of CETP as an alcohol marker can be compared to those of MCV, γ-GT, ASAT, and ALAT. Nonetheless, the use of CETP as an indicator for alcohol misuse is limited by the complex measurement method and by the influence of drugs and various diseases.

42.15 β-Hexosaminidase

β-Hexosaminidase is a lysosomal liver enzyme detected in serum or urine using spectrometric methods. Higher serum activity of this glycoprotein was reported in alcohol-dependent patients. A daily consumption of 60 g alcohol leads to significant serum increases; even short-term alcohol load is reflected in alcohol patients by its low half-life and resulting limited normalization in values (<6, 2 U/l) 2–4 days later. The pathological mechanism in rats is the reduction in biliary elimination of the enzyme in chronic ethanol intake. The specificity of β-hexosaminidase in serum is stated to be 91–98%, and the sensitivity is 69–94%. β-Hexosaminidase activity reflects recent alcohol consumption, while β-hexosaminidase in urine remains increased for longer periods after alcohol consumption (Fig. 42.1).

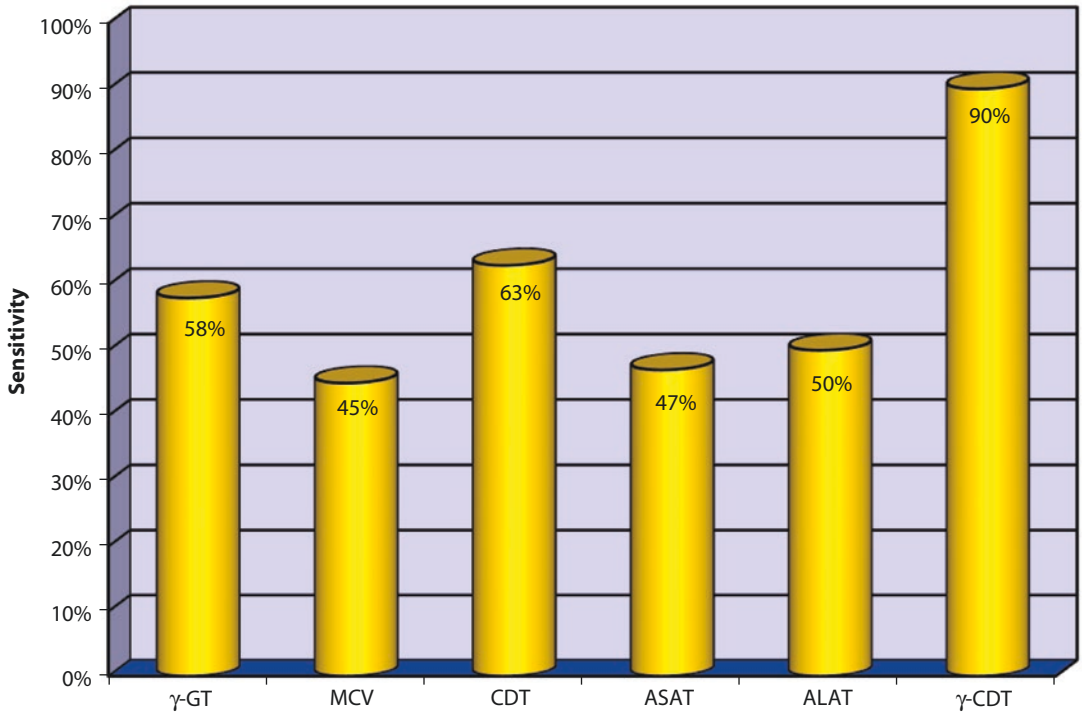

Fig. 42.1 Comparison of sensitivities of conventional markers with γ-CDT. (Modified from Niemelä [50]) [15]

42.16 Methanol (MeOH)

Methanol is a monovalent alcohol produced endogenously; under physiological conditions, the concentration in serum is between 0.5 and 1.0 mg/l. Methanol can be ingested exogenously through alcoholic drinks, fruit juice, and pectin-containing fruits (e.g., bananas or apples). The metabolism of methanol occurs in the liver through alcohol dehydrogenase (ADH), which shows a manifold increased affinity to ethanol compared to methanol even without alcohol ingestion. That being so, in the presence of ethanol in concentrations over 0.2–0.5%, a competitive inhibition of methanol breakdown occurs, which, in continuing ethanol availability, leads to accumulation of endogenous methanol. Should the ingested alcohol also contains methanol (e.g., fruit-flavored gin, whisky), the blood levels would be potentiated even more by endogenous accumulation. The methanol levels normalize itself in alcohol abstinence within several hours to several days. Early evidence of increased blood methanol levels after longer drinking periods was reported in the 1970s, among others. In numerous studies, a coincidence between increased methanol levels and blood alcohol levels has been found. Consequently, methanol values >10 mg/l, which were not caused by normal and short term, even high alcohol load over 1.5–2.0%, were estimated and considered as an indicator for recent alcohol misuse or longer alcohol consumption phase. Despite its high specificity, methanol is only suitable as a short-term state marker because it is rapidly normalized. Its significance lies primarily in screening alcohol misuse in clinical as well as forensic cases.

42.17 Acetone and Isopropanol

Physiologic levels of isopropanol in blood are up to 0.1 mg/l and acetone up to 7 mg/l. Both substances are not found in alcoholic drinks. Isopropanol and acetone are in reciprocal biotransformation process, meaning isopropanol is

reduced to acetone and formed, through oxidehydration, from acetone. Both processes occur via alcohol dehydrogenase. Alcohol load causes an increase in isopropanol in blood; conversely during withdrawal, acetone is increased. Higher isopropanol and acetone levels occur mainly in alcohol-dependent patients with concurrent eating disorders or reduced nutritional intake. It is established practice to pool both substances in serum concentration, and a level of 9 mg/l has been recommended. Still, isopropanol and acetone appear less convincing than methanol as alcohol markers because increased acetone levels also result from metabolic disorders such as ketosis in hunger, diabetes, cooling, and heavy physical strain (Fig. 42.2).

42.18 Combination of Individual State Markers

Since individual conventional alcohol markers were found to be insufficiently sensitive and/or specific for the recognition of alcohol misuse, several important parameters in varying combinations were investigated. The better known combinations comprised of CDT, γ-GT, MCV, and ASAT.

42.19 Gamma-Glutamyl Transferase and Carbohydrate-Deficient Transferrin

Some studies showed that the combined use of γ-GT and CDT resulted in higher sensitivity and specificity compared to use of either one alone. Sillanaukee et al. [52] reported a sensitivity of 75% and specificity of 93% for γ-CDT from 257 alcohol-dependent patients and 362 occasional drinkers. γ-CDT is estimated using the formula **[γ-CDT = 0.8 ln(γ-GT) + 1.3 ln (CDT)]**. Compared to CDT and γ-GT alone, ASAT, ALAT, or MCV showed the logarithmic transformation from γ-GT and CDT to have the best predictive value to differentiate between alcohol-dependent patients and occasional drinkers. Values for γ-CDT correlate to current amounts of consumption, regardless of whether a heavy alcohol-dependent individual or an occasional drinker was tested. γ-CDT can thus be used to monitor abstinence, though in continuing abstinence the values normalize within 2–3 weeks. Considering the cost efficiency and simple application, γ-CDT appears to be a suitable indicator in clinical routine work.

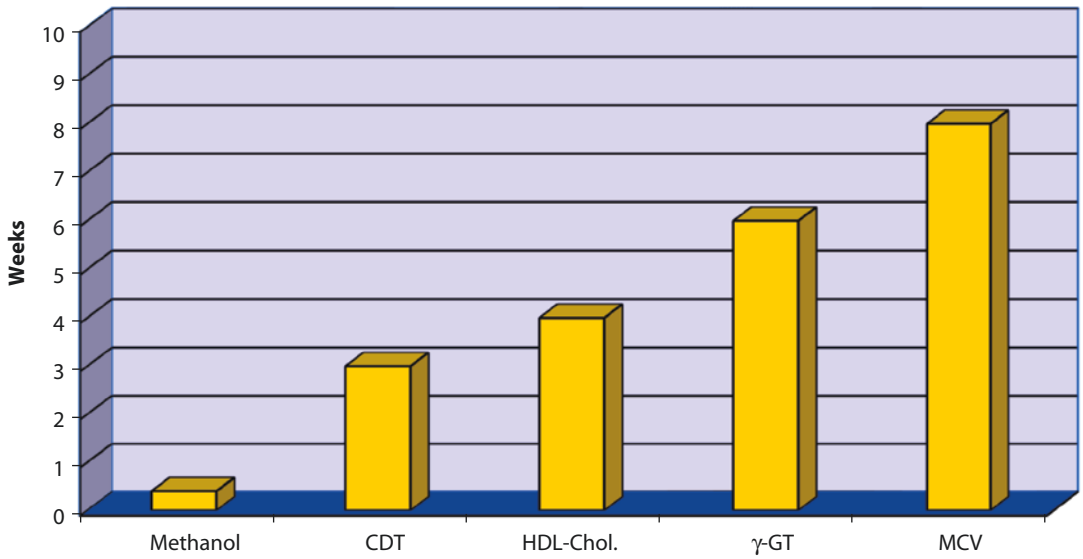

Fig. 42.2 Depiction of alcohol markers in appropriate time lines. (Modified from Gilg [51])

42.20 Alc Index

By combining methanol, acetone/isopropanol, γ-GT, and CDT in a logistic regression formula, Brinkmann et al. [53] developed the so-called Alc index to differentiate between alcohol-dependent patients and nondrinkers. The basic principle for the investigations was the hypothesis that each of these alcohol markers shows overlap in values in the collective with none or low alcohol consumption and alcoholics. From the results, an Alc index of 1.7 as cutoff was defined with a specificity of 100% and a sensitivity of 90% to differentiate between alcohol-dependent and nonalcohol-dependent individuals. The advantage of this index is the single cutoff point instead of four for individual markers, through which it can prevent false conclusions with raised values of an isolated marker.

42.21 Early Detection of Alcohol Consumption (EDAC) Test

EDAC uses results from a series of routine lab parameters to identify heavy drinkers and light drinkers in study groups. Already in the 1980s, attempts have been made, through multivariate statistical analysis with blood samples from conspicuous patients with alcohol, to differentiate between light alcohol misuse and heavy alcohol dependence. The multiple chemical and clinical parameters extracted should reflect alcohol's influence on various organs and organ systems. These studies were subsequently abandoned because of impracticable, partly costly statistical analysis. Harasymiw et al. [54] developed EDAC test to be an established procedure, in which a form of "mathematical fingerprint" for each tested patient could be created from 10 out of 30 routine lab values through a linear discrimination analysis. The fingerprint of an individual could possibly be that from a heavy alcoholic and presented as P-positive, representing the degree of concordance to the stereotyped alcoholic lab profile. In general, a P-positive value over 50% showed current heavy alcohol consumption, whereas values below or equal to 50% showed evidence of light alcohol misuse. The EDAC test was successfully used as screening for alcohol misuse and to identify heavy or risky alcohol consumption in various studies on different study populations. A higher sensitivity of 34–65% (women/men) for EDAC test compared to 23–30% for γ-GT in a population of 1605 heavy drinkers or probands with risky alcohol consumption has been reported. The specificity is 89% (men) and 98% (women). Sensitivity and specificity over 80% each was reported in the identification of alcohol misuse in heavy male and female drinkers. Considering these results, EDAC test in primary care can establish itself as a suitable procedure for use in routine blood tests, its cost efficiency through freely optional lab values, as well as the availability of an electronic version with automatic statistical analysis from certain providers.

42.22 GGT-ALT Combination

Another combination of enzymes, GGT-ALT (alkaline phosphatase), can also be useful for clinical diagnostic validation of liver damage related to excessive and prolonged intake of alcohol. If the ratio of GGT-ALT exceeds the value 1.4, there is a probability of 78% that the liver impairment is due to alcoholism. This particular combination shown was not a biomarker when used for monitoring the treatment of alcoholics with disulfiram (Fig. 42.3).

Although the suspicion of alcohol abuse behind hepatotoxicity may be supported by several lines of clinical and biochemical data, the specific role of alcohol in many cases is difficult to distinguish in individuals who deny alcohol use. Clinical symptoms related to heavy drinking may originate from virtually any tissue. Unexpected abnormalities in liver enzymes or blood cell counts in health screening programs may also reveal alcohol abuse.

Subsequently, efforts should be focused on objective confirmation of alcohol use and to rule out other etiologies. Nonalcoholic fatty liver disease (NAFLD) is the most common nonalcoholic

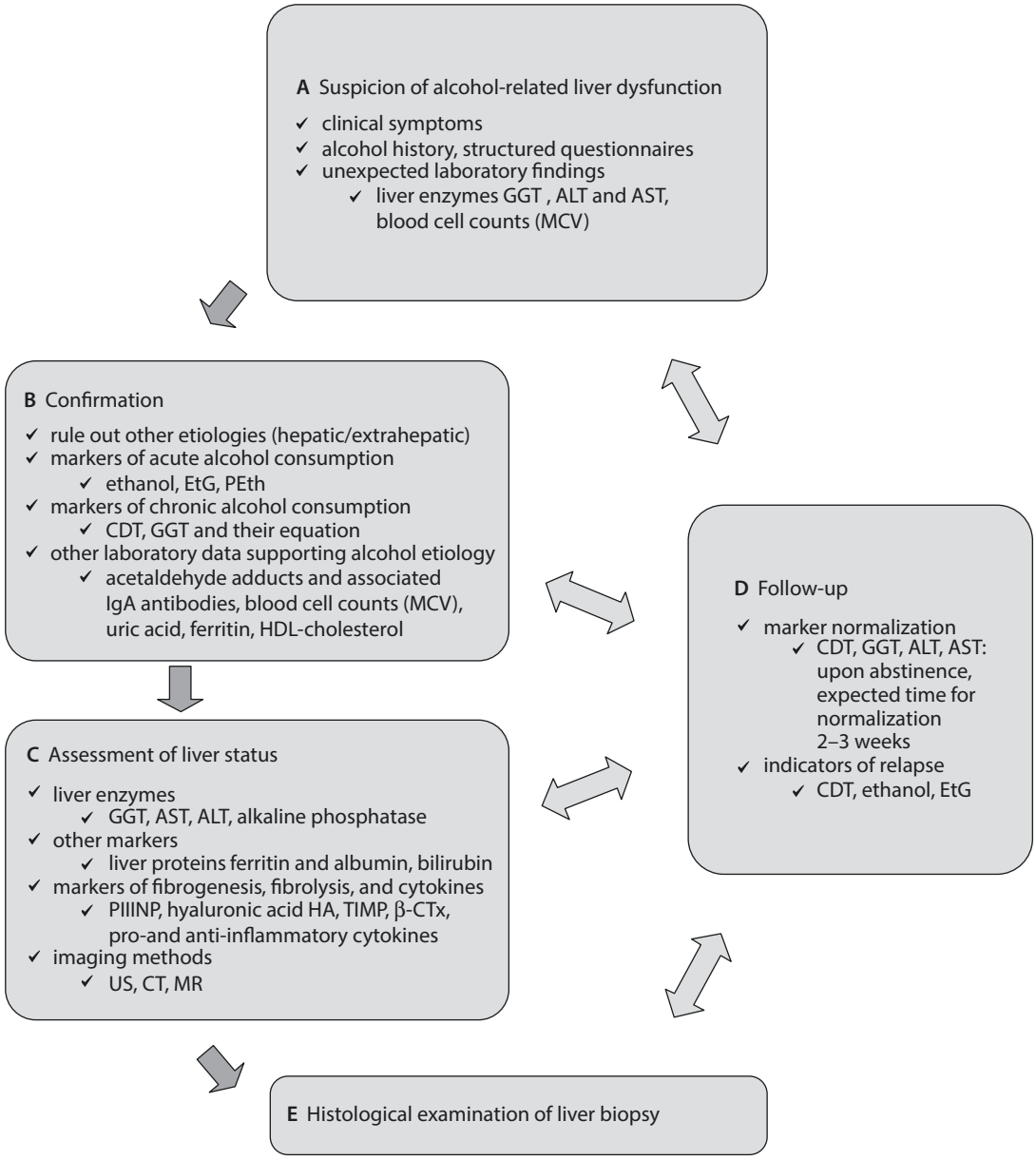

Fig. 42.3 Schematic representation of the clinical assessment of liver dysfunction in alcohol consumers. (Niemela and Alatalo [55])

etiology behind liver dysfunction, and the workup should consist of evaluating metabolic comorbidities with measurements of body mass index, waist circumference, and oral glucose tolerance. Specific tests are available to rule out viral hepatitis and several genetic diseases, such as hemochromatosis. In alcohol consumers, ethanol may be present even at the time of the clinic visit. Measurements of ethanol metabolites or other laboratory parameters sensitive to ethanol may provide confirmatory data. Liver enzymes give information on the nature of the liver pathology. An isolated abnormality in GGT is usually reversible and related to increased oxidative stress burden. Increased ALT is commonly a result of fat deposition in the liver and can be reversible.

Elevated ferritin and albumin may occur in early phases of liver disease, whereas in patients with advanced alcoholic liver disease (ALD), the rates of albumin synthesis decrease and correlate with poor prognosis. ALD status is also associated with both the collagen and cytokine markers. Markers of collagen synthesis and degradation as well as pro- and anti-inflammatory cytokines may follow inverse kinetics, which may help to differentiate alcoholics at risk for cirrhosis. US (ultrasonography), CT, computed tomography, MRI, and proton magnetic resonance spectroscopy are commonly suggested. Follow-up of laboratory values is an integral part of the comprehensive assessment and treatment of patients with signs of liver dysfunction. If excess alcohol consumption (or obesity) is suspected, normalization during abstinence (or weight loss) is confirmatory. If initial GGT levels return to normal after abstention, and the patient is likely to have recovered from liver disease. Liver enzyme activities repeatedly above twice the upper reference limit are used as decision-making point for liver biopsy to rule out severe liver diseases and to distinguish patients needing the closest monitoring. Follow-up by markers of ethanol consumption, such as CDT, can be used to assess the degree of alcohol dependence and to detect relapses, which increase the probability of subsequent severe liver problems. Current clinical gold standard for the diagnosis and grading of hepatic disease is liver biopsy. It is, however, an invasive procedure with sampling variability and therefore is not suitable for screening or repeated measurements.

42.23 Conclusion

Biomarkers, as additions to self-reports, are important in the diagnosis and therapy of alcohol-related disorders. The traditional biomarkers have varying other limitations besides practicability and cost efficiency.

In summary, especially regarding traditional biomarkers, a combination of various lab parameters (e.g., CDT and γ-GT) allows sufficient inference on regular and even longer-term (days, weeks) alcohol consumption The diagnostic sensitivity of individual parameters, such as ASAT or ALAT, is low, and the specificity is moderately high, with the exception of CDT which shows moderate sensitivity and high specificity to differentiate between alcohol-dependent individuals and control persons. The strengths of these traditional markers lie in their practicability and, except for CDT, cost efficiency in clinical routine. Normalization of this marker occurs only after weeks or months of abstinence so that inference of current or short-term recent alcohol consumption can be made.

In comparison, direct ethanol metabolites are highly sensitive and specific, covering the complimentary period between consumption and detection, and are routinely used. Thus, they open new perspectives in the prevention, interdisciplinary cooperation, diagnosis, and therapy of alcohol-related disorders.

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Clinical Screening for Illegal Drug Use, Prescription Drug Misuse and Tobacco Use

43

Sawitri Assanangkornchai and J. Guy Edwards

Contents

Abstract

Screening aims at detecting substance use (ideally at an early stage) with a view of providing subsequent treatment if required. It is most productively employed in populations in whom there is a high prevalence of use, such as general and emergency medical patients and those attending clinics for pain or sexually transmitted disorders. It is of less value in well-staffed facilities that already routinely inquire about substance use during comprehensive clinical assessments. Screening may also be helpful in people who have come into conflict with the law.

Numerous screening instruments have been designed, but few have satisfactory psychometric properties, and none has been

S. Assanangkornchai (✉)
Epidemiology Unit, Faculty of Medicine,
Prince of Songkla University, Songkhla, Thailand
e-mail: savitree.a@psu.ac.th

J. G. Edwards
Formerly of Southampton University Hospitals,
Southampton, UK

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shown to produce a better long-term outcome in the real world of clinical psychiatry than asking brief questions about substance use followed by referral for specialist treatment and rehabilitation when required.

Examples of the more widely used instruments are the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), CAGE-AID (mnemonic for items Cut down, Annoyed, Guilty, Eye-opener, -Adapted to Include Drugs), Drug Abuse Screening Test, and Fagerström Test for Nicotine Dependence. The choice of an instrument should depend on its psychometric properties, the population being screened, availability of staff to use it properly, and practicality of introducing it into the facility.

Ethical aspects of the use of the instruments are important. Outside purely clinical or sociological research screening is likely to have limited value unless follow-on treatment is available and offered to the substance misuser, and he/she is encouraged to accept it and adhere to it. The best test of the real value of screening will be a clear demonstration that it prevents longer-term medical and psychosocial consequences of substance misuse.

43.1 Introduction

Screening for substance misuse and use disorders aims at helping to identify people who have suffered the consequences of using one or more substances or are at risk of future harm if they continue to use the substance(s). Ideally this should be at an early stage and should be followed by treatment if indicated. Included among the WHO's recommended indications for screening in general are the seriousness of the effect the medical condition has on the health and well-being of the individual and the community and the availability of a suitable, reasonably priced screening test and effective treatment for patients screened positive. It is accepted that early recognition of the disorder followed by intervention leads to a more favorable outcome. Based on these indications, screening for misuse of psychoactive drugs is clearly indicated [5].

Screening instruments for drug misuse have been designed for use in the community and healthcare facilities and to help in medicolegal assessments. Cross-sectional and longitudinal screening for drug use is of value in research into medical treatment and academic sociological research.

43.2 Screening in Different Settings

43.2.1 Healthcare Facilities

Screening may be undertaken in primary care; general and emergency medical, psychiatric, and other specialized facilities (e.g., HIV/AIDS clinics or obstetric units); and community hostels. Some instruments are self-administered, whereas others are administered by staff of various disciplines. Studies have shown benefits of screening for drug use in healthcare settings using the Screening, Brief Interventions, Referral for Treatment (SBIRT). This is employed in an integrated, public health approach to the management of people at risk of adverse consequences of alcohol and other drug use and probable drug use disorders (DUD) [6]. Various factors militate against the implementation of SBIRT, the main ones being underfunding, understaffing, and competing priorities.

43.2.1.1 Primary Care

Primary care deals with a wide range of people and an equally wide range of lifestyles and disorders, including substance use disorders. Its workers are usually seen as trustworthy, and it provides an excellent opportunity for screening for drug misuse as a routine part of healthcare. Patients with problems related to drug misuse are likely to have frequent consultations. Screening in primary care may identify nondependent individuals who use drugs in a harmful way and respond well to intervention. Drug misuse may worsen concomitant health problems, so screening pro-

vides an opportunity to educate patients about this risk. We therefore endorse WHO recommendations on screening in general practice, with consideration given to the use of the Alcohol, Smoking, Substance Involvement Screening Test (ASSIST) or one of its modified versions [59].

However, the workload in primary care is usually stretched to capacity, so screening may only be carried out with great difficulty (or not at all) without extra resources. An example of this is seen in the UK where the current government underfunds the National Health Service (NHS) to such a degree that clinics typically have to ration time to only 10 minutes per symptom or problem per appointment. And that harsh rationing even applies to elderly patients with multiple pathologies.

If that is the situation in the fifth richest country in the world, it is not difficult to imagine the situation in the most deprived, poorest countries where even 10 minutes might be considered a luxury.

43.2.1.2 Secondary Care

General Medicine

There is a high prevalence of substance use among general medical patients. Hospitals are therefore important places in which to screen patients, hoping that any substance misusers identified will accept treatment. In hospitals there is more time for screening than in most other medical settings and also more time to educate the patient about the relationship between substances misused and his/her medical condition [41].

Emergency Medicine

Drug misusers often attend accident and emergency (A&E) departments with substance-related medical or surgical problems, notably toxic or withdrawal states, trauma due to accidents, deliberate self-injury, or injury caused by others. Thus, emergency departments too are appropriate facilities to screen, especially for the benefit of people who have less access to alternative healthcare. Screening instruments that rapidly identify patients who require further diagnostic evaluation and/or brief intervention are important. A systematic review identified 11 instruments that have been used in youngsters under 21 attending A&E and recommended asking just one question to detect cannabis use disorder – "In the past year, how often have you used cannabis?" – with the response categories, "Once or less" or "Two or more times" (sensitivity, 0.96; specificity, 0.86) [43].

To illustrate the problems faced by A&E departments, let us again consider the situation of the British NHS. Just as the government's gross underfunding has an adverse effect on patient care in other key services like general practice, so it affects overworked A&E departments. As a result, severely ill patients often have to wait for hours in ambulances and/or lay on trollies in corridors waiting to be assessed, and some patients needing admission may have a further wait for an inpatient bed to be found for them. So it is not difficult to understand why A&E staff, however much they would like to help in screening for drugs, may simply not have time to do so.

Services for Youngsters

Early to late adolescence is a critical risk period for starting to use substances, which peaks between the ages of 18 and 25 [58]. The American Academy of Pediatrics [1] therefore recommends screening of every pediatric patient aged 12 or over, whether or not they are reported as having used drugs.

The screening can be undertaken in healthcare facilities, schools, child welfare facilities, and the juvenile justice system. It should be carried out with a valid, sensitive instrument, and, when the results suggest there is cause for concern, youngster should be referred for a comprehensive clinical assessment. At all stages of the process, care should be taken to ensure that no vulnerable young person is unjustifiably labeled as a drug misuser.

The easy availability of cannabis, coupled with the erroneous idea that it rarely causes harm, makes this drug one of the most common substances initiated in adolescence [58]. So screening adolescents for its use is particularly important.

Validated screening tools available for substance use disorder (SUD) among adolescents aged 12–17 in primary care are the Brief Screener for Alcohol, Tobacco and other Drugs (BSTAD) and Screening to Brief Intervention (S2BI) [42].

Services for the Elderly

During recent years, there has been mounting concern over substance misuse in the elderly. There are many explanations for this. They include the 1946–1964 baby boom effect, with children born during this time reaching adolescence at a time of escalating substance use worldwide, and people then continuing to misuse substances throughout midlife until old age. During this period, there was also an increase in life expectancy. Increasing age was accompanied by multiple pathology, increased misuse of over-the-counter and illegal drugs, and increased prescription of drugs with addiction potential, notably benzodiazepines and opioids [58].

In addition to these trends, there has been a relaxation of enforcement of laws on cannabis possession (with some countries and states legalizing it) and latterly a relaxation of legislation of the use of cannabis for therapeutic purposes.

For these reasons, older adults should be sensitively but routinely screened for alcohol and other drug use, despite difficulties arising from similarities between the symptoms of drug misuse and those of some of the common illnesses of later life and lack of a specific screening instrument for the elderly.

Pain Clinics

Pain can be associated with drug misuse in several ways: there may be an underlying condition contributing to both the severity of the pain and the drug misuse (e.g., a depressive disorder); patients may become dependent on their prescribed analgesics (therapeutic dependence); and substance misusers with pain of organic origin, or with exaggerated or simulated pain, may try to manipulate their doctors into prescribing more addictive substances than are clinically needed – for themselves and/or to give or sell to other substance misusers. Whatever the relationship, screening patients attending pain clinics for the inappropriate use of prescribed or illegal drugs is important. During recent years, there has been a dramatic increase in the use of opioids for treating pain and a corresponding escalation in the number of deaths from overdoses of opioids at great human and economic cost [58].

Attempts to understand and tackle these increases are hampered by difficulty in diagnosing dependence in patients prescribed opioids [24]. If it is so difficult to make a valid diagnosis, it is not surprising that it is also difficult to create a valid screening instrument for opioid dependence, and we have to place much reliance on the clinical assessment.

The US National Institute of Drug Abuse (NIDA) recommends supplementing this by screening patients for opioid misuse on their initial clinic visit and prior to prescribing any opioids for pain**,** using the Opioid Risk Tool (ORT) [42, 60].

Psychiatric Units

There is evidence to suggest that the prevalence of tobacco and other substance misuse in patients with some disorders is higher than in others, but substance misuse and psychiatric comorbidity in general occurs so often that it is essential that a history of misuse is taken routinely in all psychiatric patients. In fact, failure to do so in some patients can be a serious omission, sometimes even bordering on negligence. Tiet et al. [56] in their review concluded that there are no currently available instruments that have particular advantages in psychiatric patients, while the lengthier, more complicated ones can be confusing for those with severe illnesses – particularly when administered in addition to a thorough psychiatric assessment.

Antenatal Care

Universal screening of pregnant women for substance misuse has been recommended [62]. It should be performed as early as possible in pregnancy and at every subsequent antenatal visit so that clinicians are aware of their patient's substance use, can make better informed decisions about drug treatment and prenatal care, and can minimize the time the fetus is exposed to the drug(s).

Screening during pregnancy is especially important in those with a previous history of drug misuse, prenatal and/or birth complications, delays in accessing prenatal care, or frequently missing prenatal appointments. Some screening instruments have been specifically designed for pregnant women, e.g., 4P's Plus [18], the Substance Use Risk Profile-Pregnancy (SURP-P) scale [63], and Wayne Indirect Drug Use Screener (WIDUS) [45].

43.2.2 Medicolegal Practice

43.2.2.1 Criminal Justice System

There is a high prevalence of substance misuse also in people who come into conflict with the law, especially those whose crimes have been carried out to acquire money for drugs. So here too there is fertile ground for screening – by personnel within the criminal justice system or by colleagues working in associated medical services, like prison medical officers or staff working in court diversion schemes. An aim of screening, in addition to providing treatment for those in immediate need, is to help interrupt the cycle of addiction and drug-related crime, with benefits to society as well as to the drug misuser.

Although drug-using offenders are mostly abstinent while in custody or prison, when released many resume their previous patterns of drug and alcohol use, placing them at risk of rearrest and increased health problems, including HIV. Thus, there is need for intervention to help reduce risky behaviors and encourage treatment.

During detention, people are at a "teachable moment" for screening and intervention. They have just been arrested and may want to avoid further conflict with the law. Initially, they may be distressed or simply just want "something to do" by way of distraction. That in itself does not mean the subject is well motivated for treatment, but in this teachable moment better motivation could follow [47].

Screening should begin with simple questions regarding substance misuse asked by the arresting police officer. Following this, there are several other opportunities for screening as the accused moves through the justice system: in the police station and prison and during pretrial investigations, meetings between prosecuting and defense council, and social assessments conducted by probation officers. The UNCOPE is a valid, brief six-item screen used for identifying substance use disorders among prisoners [48].

43.3 Some General Considerations

43.3.1 Ethics

There are many ethical as well as legal and social issues to be considered when deciding whether and how to screen patients. Screening is generally accepted as being harmless so long as the patient is fully informed of its purpose, permission is given, and any appropriate follow-up treatment required is provided.

Even when using a simple screening instrument, it is important that we remain aware of the concerns and sensitivities of our patients/clients, concerns such as embarrassment at succumbing to their "weakness" in taking drugs, believing there is no point in screening as there is no "cure" for their "addiction," or fear of the legal and social consequences of drug use, including stigmatization. As in all good medical practice, we should also ensure that honesty and transparency are central to our dealings with patients.

We can go some way toward allaying patient's anxieties by emphasizing that the decision to reveal information in response to questions asked by an instrument is theirs and theirs alone and assuring them that anything revealed will be treated in strict confidence and not disclosed to others without their permission. Doing this is particularly important in medicolegal work (whether in civil or criminal cases), especially when dealing with delinquent youngsters, to help gain their trust, confidence, and cooperation.

It should also be made clear to the patient that screening instruments do not possess "magical" properties; they simply comprise a set of questions that are asked regularly in a clinical assessment and contain no questions that attempt to

"catch them out" – which we have no right to ask. Any attempt to do so would be dishonest and, like failing to observe the fundamental principles of confidentiality, a breach of professional ethics.

43.3.2 Psychometric Properties

It is important to confirm that all instruments were properly constructed to begin with, properly evaluated subsequently, and then properly administered to the right person or population in the right way. Even when these principles have been conscientiously adhered to, there remains the glaring uncertainty as to whether the instrument measures what it sets out to measure. And, of course, what a person says he does is not necessarily the same as what he actually does.

43.3.3 Main Aims of Screening

While it is of interest academically to elicit data on all substance use, as clinicians we are less interested in people who occasionally take substances "recreationally," especially if conforming with the behavior of their peers or take them only in certain situations, like clubs or raves. Similarly, we are less interested in those who take substances for clearly defined, short periods, as during their university days, or for specific purposes like attempting to increase their sexual excitement.

We are prepared to advise all people of the dangers of such sporadic or short periods of drug-taking, but our main concern is for those who take drugs for longer periods. This is especially the case when they are dependent on one or more substance, have already experienced adverse medical or psychosocial consequences**,** or are exposed to the risk of these problems in the future.

Several familiar words and terms are used in the field of substance use, and there are debates on what is normal as opposed to abnormal use; differences between use, misuse, and abuse; when psychological and/or physical dependence begins; the difference between these conditions; and the question, "What is a disorder?" These are of theoretical and practical interest but matter less at the screening stage than later in assessment. The main aim at this stage is to identify people who have or are at risk of substance-related problems and may therefore benefit from advice and/or intervention regardless of what provisional labels are applied to them.

Having done the screening, the clinician, aided by the data elicited by the screening instrument, may then complete the assessment, sharpen up on the diagnosis, and provide the appropriate intervention.

43.4 Screening Instruments for Substance Use

There are available screening instruments for single or multiple substance use, problems caused by the substances, and comorbidity (Table 43.1). Some of these have been created for particular patient groups. We summarize below their main characteristics and uses of the most commonly used instruments.

43.4.1 Instruments Inquiring about the Use of One or More Drugs

ASSIST The ASSIST has high construct and concurrent validity [28] and is currently the most extensively studied and widely used instrument. It was developed by a group of WHO researchers to help detect substance use and related problems in primary and general medical care and assess the level of risk for each substance identified. It seeks information on the use of all types of psychoactive substances, including tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, and opioids. It asks if any of these have ever been used and, if so, the frequency of use during the past 3 months; if the respondents have had a strong desire or urge to use the substance; the frequency of any problems they have had; if the substance has interfered with their responsibilities; if anyone

Table 43.1 Screening instruments for drug use and drug use disorders

Instrument	Full name	Reference	Population studied	Time frame	No. of items	Administered by	Approx. time required	Responses/scores
(a) Instruments inquiring about one or more drugs								
ASSIST	Alcohol, smoking and substance involvement screening test	[61]	Adults	Lifetime Past 3 months	8 items	Clinician interviewed, computer administered, self-administered	10 min for administration, 5 min for scoring	0–3: low risk – no intervention (0–10 for alcohol) 4–26: moderate risk – brief intervention (11–26 for alcohol) 27+: high risk – more intensive intervention
DHQ PDHQ	Drug history questionnaire Psychoactive drug history questionnaire	[54]	Adults	Lifetime Past 6 months	5 items	Self-administered	5–10 min	No specific cutoff
S2BI	Screening to brief intervention	[36]	Adolescents 12–17 years	Past 12 months	8 items	Computerized self-administered	2 min	Answer “use” to each drug type
BSTAD	Brief screener for alcohol, tobacco, and other drugs	[31]	Adolescents 12–17 years	Past 12 months	3 + 2 items	Computerized self-administered	2 min	Answer “use” to individual drug and then continue to more drugs
SUBS	Substance use brief screen	[39]	Adult primary care patients	Past 12 months	4 items	Computerized self-administered	5–10 min	Answer “use 1–2 days in the past 12 months” to individual drug
TAPS	Tobacco, alcohol, prescription medication, and other substance use	[38, 40]	Adult primary care patients	Past 12 months and 3 months	4 + 25 items	Computerized self-administered and clinician interviewed	5–10 min	TAPS-1: Positive = use that substance and then continue to TABS-2 items specific to that substance class

(continued)

Table 43.1 (continued)

Instrument	Full name	Reference	Population studied	Time frame	No. of items	Administered by	Approx. time required	Responses/scores
CAGE-AID	Cut down, annoyed, guilty, eye-opener-adapted to include drugs	[13]	Adolescent; patients with comorbidity; adults	Lifetime	4 items	Self-administered	5 min	Range: 0–4 Cutoff score 1 or more for drug dependence
CRAFFT RAFFT	Car, relax, alone, forget, friends, trouble	[32]	Adolescents American Indian/native Alaskans	Lifetime past year	6 items	Clinician-interviewed, self-administered, computerized	5 min	Range: 0–6 Cutoff score of >2 for risky use
DAST	Drug abuse screening test. Adolescent version (DAST-A) available	[53]	Adults College students; pregnant women	Lifetime	10, 20, 28 items	Self-administered	5–10 min	Range: 0–10, 20, 28 DAST-28: Cutoff 6 DAST-20: Cutoff 6 DAST-10: Cutoff 2
DAP quick screen DAP-4	Drug and alcohol problem quick screen	[51]	Adolescents	Lifetime	30 items and 4 items	Self-administered	<10 minutes	Range: 0–30 Score of >6 considered high risk for "red flag" behaviors
DUDIT	Drug use disorder identification test	[10]	Adults	Lifetime past year	11 items	Self-administered	5–10 min	Range: 0–44 Cutoff score of 25 suggestive of substance dependence Cutoff score of 8 or less severe drug abuse
SACS	Substances and choice scale	[19]	Adolescents	Past month	10 items	Self-administered	5–10 min	Each item scores 0, 1, 2 for not true, somewhat true, certainly true Range:0–20 Cutoff: 2

SSI-SA	Simple screening instrument for substance abuse	[17]	Adults; law-enforced treatment programs for patients with comorbidity; adolescent medical patients	Lifetime	16 items	Clinician- interviewed, Self-administered	10 min	0–1: No/low risk 2–3: Minimal risk 4+: Moderate/high risk
TICS	Two item conjoint screen for alcohol and other drug problems	[12]	Adults	Past year	2 items	Self-administered	<5 min	Cutoff: 1
UNICOPE	Use, neglected, cut down, objection, preoccupied, emotional discomfort	[27]	Adults	Lifetime Past year	6 items	Interviewer administered	5–10 min	Cutoff: 2
(b) Instruments specific to one drug								
CAST	Cannabis abuse screening test	[35]	Adolescents	Lifetime	6 items	Self-administered	< 5 min	Range: 0–6 Score > 4: Problematic cannabis use
CUDIT CUDIT-R	Cannabis use disorders identification test	[2]	Adults; adolescents	Past 6 months Current	10 items 5-point Likert scale	Self-administered	5–10 min	Range: 0–40 Cutoff:8
CUPIT	Cannabis use problems identification test	[8]	Adolescents; adults	Lifetime Past 12 months	16 items	Self- administered	5 min	Range: 0–82 Cutoff:12
MSI	Marijuana screening inventory	[3]	Adults	Lifetime Past year	31 items	Self- administered	5–10 min	Range: 0–31 Cutoff:3

(continued)

Table 43.1 (continued)

Instrument	Full name	Reference	Population studied	Time frame	No. of items	Administered by	Approx. time required	Responses/scores
PUM	Problematic use of marijuana	[44]	General adult population	Lifetime	8 items	Self- administered		Range: 0–8 Cutoff:2
CDS-12 CDS-5	Cigarette dependence scale	[23]	Adults adolescents	Lifetime Current	12 & 5 items	Self- administered	10 min	Range: CDS-12: 12–60; CDS-5: 5–25
FTND FTQ m-FTND	Fagerstrom test for nicotine dependence	[26]	Adults adolescents college students	Lifetime	6 items	Clinician-interviewed; self-administered	<5 min	Range: 0–2 cutoff: 6
TDS	Tobacco dependence screener	[30]	Adults; smokers	Lifetime	10 items	Self- administered	5 min	Range: 0–10 Cutoff:
COMM	Current opioid misuse measure (for opioid medication misuse)	[15]	Adult patients with chronic non-cancer pain	Current past 30 days	17 items	Self- administered	5–10 min	Cutoff: 9
ORT	Opioid risk tool	[60]	Adult patients prescribed opioids for chronic pain	Lifetime	5 items	Patient-completed (PC-ORT) clinician-completed (CC-ORT)	5 min	Range: 0–16 Cutoff: 0–3 low risk, 4–7 moderate risk > 8 high risk
SOAPP	Screener and opioid assessment for patients with pain	[14]	Adult patients taking opioids for chronic pain	Lifetime	5, 14, or 24 items	Self-administered	5–10 min	Cutoff: >7

PDUQ	Prescription drug use questionnaire, -patient version	[21, 22]	Patients with chronic non-malignant pain and on opioid therapy	Current	42 & 31 items	Clinician-interviewed (PDUQ), self-administered (PDUQp)	20 min	Cutoff: 10
(c) Instruments inquiring about multiple problems, including dual diagnosis								
CODSI-MD CODSI-SMD	Co-occurring disorder screening instrument	[50]	Offenders	Past 12 months	6-item version (CODSI-MD) screens for any mental disorder 3-item version (CODSI-SMD) screens for severe mental disorder	Self-administered	5–10 min	CODSI-MD Range:0–6 Cutoff: >3 CODSI-SMD Range: 0–3 Cutoff: >2
DUSI[a]	Drug use screening inventory-revised	[55]	Adults; adolescents	Current status	159 items	Self-administered computer-based available	20–40 min	Range: 0–100% No cutoff specified in documents
PL	DrugCheck problem list	[29]	Adolescents, adults, co-occurring clients	Past 3 months	12 item	Clinician-interviewed	5–10 min	Range:0–12 Cutoff: >2
POSIT	Problem-oriented screening instrument for teenagers	[16]	Adolescents	Lifetime	139 items, 10 problem areas	Self-administered	20–30 min	Cutoff scores indicating low, medium, or high risk for each of the ten problem areas

[a]Fee required for use; other instruments free in public domain

has expressed concern about their substance use; if they have tried to decrease or discontinue use; and if they have ever used any substance by injection. Linked with brief intervention, the ASSIST can help a person explore options for addressing their substance use [59].

There are modified forms of the ASSIST – the NM-ASSIST (NIDA-modified ASSIST) [42]; ASSIST-Lite (ultrarapid ASSIST) [4]; ASSIST-Y for use in children and adolescents aged 10–17 years [59]; "ASSIST on ICE," which is the instructional video and manual of the ASSIST and brief intervention specific for methamphetamine use [25]; and the ASSIST Checkup, which is a free downloadable app for use on a mobile device and gives instant feedback and tips on how to cut back or stop substance use. It also provides information on where to seek help. Electronic versions of the ASSIST (eASSIST) and ASSIST-Lite (eASSIST-Lite) are also available. The ASSIST and its modified forms have been translated into several languages, including Arabic, Chinese, French, German, Spanish, and Thai [59].

In addition to the clinician interview version, self-report, paper-based [7], and computer-based (ASSISTc) [20] formats of the ASSIST were developed for use in university students and a self-administered audio computer-assisted, self-interview (ACASI-ASSIST) format for primary care [38, 40]. Both formats are comparable to the clinician interview format but have the apparent advantages of not requiring an interviewer, facilitating screening and assessment in college students and busy healthcare settings, and reducing costs.

Substance Use Brief Screen & Tobacco, Alcohol, Prescription medication and other Substance use (SUBS & TAPS) Based on the NM-ASSIST, the Substance Use Brief Screen (SUBS), a four-item computerized, self-administered screening instrument [39], and the Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) tool, a two-step screening and brief assessment instrument, were developed [38, 40]. They both seek information on the frequency of use of tobacco, four or more alcoholic drinks per day, illicit drugs including cannabis, and the inappropriate use of prescription drugs during the past 12 months. The TAPS consists of two parts: a four-item screen (TAPS-1) and a substance-specific assessment of risk tool (TAPS-2) for individuals who screen positive on TAPS-1. Both instruments performed well in primary care, and they have the advantages of being brief and self-administered**,** using a tablet computer or online tool [52].

Examples of instruments that inquire about any drug use and their adverse effects are CAGE-AID [13] and CRAFFT/RAFFT [32]. The CAGE Adapted to Include Drugs (*CAGE-AID*) is a modification of CAGE – a mnemonic based on Cut down, Annoyed, Guilty, Eye-opener – which has been used in screening for alcohol misuse since the mid-1970s [37].

CRAFFT is a mnemonic, based on its individual items: Car, Relax, Alone, Forget, Friends, Trouble [32]. It is the most well-studied instrument for screening for alcohol and drug use and related problems in adolescents and adults. Its six items are preceded by three preliminary questions that ask about the use of alcohol, cannabis, and other drugs. It asks about specific lifetime events and behaviors, irrespective of when they occurred.

The instrument was found to be suitable for distinguishing between alcohol and other substance use, problem use, abuse, and dependence. Although the CRAFFT was designed for clinical use, it is also suitable for large-scale surveys in other settings and provides a measure of severity but not frequency of use in adolescents [11].

Drug Abuse Screening Test (DAST) The DAST-28 is a research instrument used to screen and assess the effectiveness of treatment [53]. It provides a measure of the severity of drug-related and other problems experienced during the respondent's lifetime. It has been found most useful in people who do not seek treatment. The DAST cannot distinguish between active or inactive drug use or abstinence and low-risk use, abuse, or dependence.

Alternative versions of the DAST-28 have been developed – the DAST-20, DAST-10, and DAST-A (for adolescents). DAST has moderate to high reliability and validity, depending on the group studied [64]. Most recently, a two-item brief DAST (DAST-2) has been developed. The questions asked are "How many days in the past 12 months have you felt bad or guilty about your drug use?" and "How many days in the past 12 months have you used drugs other than those required for medical reasons?" A response of 1 or more days to each question was considered to meet the DAST criteria for drug use disorder (DUD) and negative consequences of drug use [57].

Screening questionnaires of this type are not only quick to administer, but they also have the advantage that people who use multiple substances may be more likely to respond positively to a question about drugs in general than to questions about specific drugs. However, they have some disadvantages. For example, they may not detect specific substances, and someone who uses only alcohol may not respond positively to a question that refers to "drugs."

43.4.2 Instruments that Ask about the Use of Single Drugs

Apart from instruments used to screen for alcohol, there are also instruments that screen for individual drugs.

43.4.2.1 Cannabis

Short instruments designed specifically for cannabis screening that have satisfactory psychometric properties and have been used in various populations include the Cannabis Abuse Screening Test (CAST) [35], Cannabis Use Disorders Identification Test (CUDIT) [2], and Problematic Use of Marijuana (PUM) [46].

43.4.2.2 Opioids

Because of the widespread increase in prescription of opioids, several instruments have been developed to detect prescription opioid misuse in various clinical settings, including A&E departments, pain clinics, and pharmacies. Examples of these include the Prescription Drug Use Questionnaire (PDUQ) [21], Opioid Risk Tool (ORT) [60], and Current Opioid Misuse Measure (COMM) [15].

The Opioid Risk Tool (ORT) is a brief, self-report, screening tool designed for use in adults in primary care to assess the risk of opioid abuse among individuals prescribed these drugs for chronic pain. It can be administered and scored in less than 1 minute and has been validated in men and women treated for pain [60].

Prescription Drug Use Questionnaire (PDUQ) The 42-item Prescription Drug Use Questionnaire (PDUQ), clinician interview version [21], and its 31-item self-report patient version (PDUQp) [22] have been validated to detect "problematic opioid medication use" in patients with chronic pain. It has domains of pain, opioid use patterns, social/family factors, and substance use history and can be self-administered in a busy clinical setting. The PDUQp has been shown to perform well in screening for prescription opioid misuse and use disorder among older adults in emergency setting [9].

43.4.2.3 Nicotine

The Fagerström Test for Nicotine (or Cigarette) Dependence (FTND) is a revision of the Fagerström Tolerance Questionnaire (FTQ) [26] and is the instrument most widely used to screen for nicotine use. The FTND was designed to provide an ordinal measure of nicotine dependence. It contains six items that seek information on the number of cigarettes smoked, compulsion to smoke, and dependence. It provides a rating of severity that can be used to help plan treatment and assess the prognosis. Its brevity and ease of scoring make it an efficient way of obtaining clinically meaningful information. It can be incorporated into general health and lifestyle screening questionnaires in clinical and nonclinical settings.

A modified version of the scale (modified Fagerström Tolerance Questionnaire, mFTQ) has been adapted for use in adolescents, which shows acceptable internal consistency and validity across countries [49].

Other available instruments are the Tobacco Dependence Screener (TDS) [30] and Cigarette Dependence Scale (CDS) [23].

43.4.3 Instruments that Inquire about Multiple Drug-Related Problems and Comorbidity

These instruments help identify drug-related problems in mental and physical health, relationships, and adjustment at school or work. They may locate areas in need of further assessment and suggest services required. Examples include the Drug Use Screening Inventory-Revised (DUSI-R) [55], Problem-Oriented Screening Instrument for Teenagers (POSIT) [16], Co-occurring Disorder Screening Instrument (CODSI) [50], and DrugCheck Problem List (PL) [29].

Problem-Oriented Screening Instrument for Teenagers (POSIT) The POSIT is a self-administered 139-item questionnaire, with fixed "yes/no" responses, designed for use in adolescents aged 12 to 19 [16]. It identifies problems in ten domains that require further assessment and might need intervention – substance use/abuse, mental and physical health, family and peer relations, vocation, and special education. The instrument can be used by school personnel, juvenile and family court personnel, medical and mental healthcare staff, and staff working in substance use disorder treatment programs. The POSIT has been found to have strong internal consistency in several of its subscales and good test-retest reliability and overall validity ([33], [34]).

43.5 Conclusion

Because of the high and increasing prevalence of substance use disorders and its consequences, screening for substance use is important in medical, psychiatric, and forensic services. There is a higher prevalence of use in some groups than others, such as those attending A&E departments and pain clinics and those who come into conflict with the law.

Numerous screening instruments have been designed and validated. Factors that determine the choice of an instrument are not only its psychometric properties but also the practicality of employing it. The enormous pressures of working in a busy clinical unit often preclude screening without special assistance.

Screening is only the first step on a very long journey toward providing a successful treatment and rehabilitation outcome. It is of limited value without the provision of treatment opportunities and encouraging substance users to accept and then adhere to any treatment offered. Finally, it is important to determine the success rate of screening in terms of discontinuation or at least decreased use of substances compared with standard practice and to assess what effect it has in reducing complications.

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Drug Testing in Addiction Medicine

44

Christopher Tremonti and Paul S. Haber

Contents

C. Tremonti (✉)
Sydney Local Health District,
Camperdown, NSW, Australia
e-mail: chris.tremonti@health.nsw.gov.au

P. S. Haber (✉)
Drug Health Services, Sydney Local Health District,
The University of Sydney Central Clinical School,
Sydney, NSW, Australia
e-mail: paul.haber@sydney.edu.au

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Abstract

Drug testing in addiction medicine is typically carried out via either immunoassay, such as in urine drug screens, or gas chromatography mass spectrometry (GCMS). Immunoassays are prone to false positives, and where there is conjecture, should be confirmed with GCMS. Guidelines, such as AS/NZS 4308:2008 in Australia, currently dictate the levels at which a test is considered positive in order to avoid false positives caused by such situations as passive cannabis inhalation or poppy seed ingestion. Most tests typically utilize urine, though other matrixes can be tested including saliva, blood, and hair. Amphetamine immunoassays in particular are prone to a high number of false positives due to their cross-reactivity with other medications. Cocaine, on the other hand, is typically fairly specific for its metabolite benzoylecgonine. Urine drug screens usually screen for non-synthetic opioids only: morphine, codeine, and heroin. While 6-monoacetylmorphine is pathognomonic for heroin use, this is often not present, and it can be challenging to determine the true source when opioids are detected in urine. Methadone metabolite EDDP can be tested via immunoassay; however, buprenorphine requires being sent to a laboratory that can perform GCMS. Chronic cannabis use can result in a positive immunoassay for weeks following cessation of use. Benzodiazepines have a complex metabolic pathway, and as such it is normal for patients on diazepam to test positive for temazepam or oxazepam. The increasing use of synthetic cannabis and cathinones presents a challenge for diagnostic testing, as there are vast numbers of new products entering the market regularly and diagnostics cannot maintain pace with production.

Keywords

Urine drug screen · Gas chromatography mass spectrometry (GCMS) · Illicit drugs · Immunoassay · Opioids · Benzodiazepines

Drug testing involves the analysis of urine or other bodily fluids for the presence of prescription drugs, illicit substances, and/or their metabolites. Drug testing is done in several contexts: clinical toxicology in emergency departments and clinics including addiction treatment, workplace drug testing, postmortem toxicology forensic toxicology including drug-facilitated sexual assault, and sports toxicology. Each setting adopts different approaches and technologies to detect the relevant drugs of abuse. This chapter primarily focuses on clinical issues relevant to addiction specialists. Testing for alcohol and its metabolites is considered in Chap. 10. Therapeutic drug monitoring is not considered here, with the exception of methadone blood levels to monitor agonist treatment.

44.1 Introduction

Self-report generally provides valid information concerning drug use, but valid and independent information about substance exposure is often very valuable. Laboratory methods may be employed to determine the substances used, the timing, and the amount of use. A range of bodily fluids or tissues can be assayed for the presence of drugs of abuse, including urine, blood, oral fluid, sweat, meconium, vitreous humor, and hair. Each has its own advantages and disadvantages. With some exceptions, the results are qualitative rather than quantitative and provide only limited specificity concerning time of use.

Urine is the most commonly used matrix as it tends to offer a longer detection window compared to blood and oral fluid and can be obtained

via relatively noninvasive means. The convenience of urine, however, is weighed against the risk of adulteration or substitution by the patient.

At this point, it is worth noting the medicolegal status of the tests done in addiction medicine. There are standards, such as AS/NZS 4308:2008 in Australia, that specify how samples need to be collected and tested in order to satisfy regulatory requirements for medicolegal testing (Table 44.1). Most hospital laboratories do not document chain of custody of sample nor adhere to the rigorous practice demanded for medicolegal testing. Thus, testing that is done for "clinical purposes" may not satisfy the regulatory requirements applied to medicolegal testing, depending on local policy. It is important to understand the testing procedures in the local setting and to discuss this with patients when doing drug testing.

Nonetheless, there are steps the addiction specialist can take to ensure a more reliable test. Collection should be done in an area without access to water and ideally where a dye has been added to cistern water. The temperature of the urine should be tested immediately after collection to determine that the sample has been freshly voided. The creatinine concentration, the pH, and the presence of oxidizing agents should also be tested to determine dilution or adulteration that can interfere with drug detection.

Table 44.1 Overview of standards for drug testing (Australian AS/NZS 4308:2008)

Collection site	Privacy Security and access Chain of custody
Integrity and identify of specimen	Precautions to prevent dilution Collection procedure Preparation for dispatch Transportation to laboratory
Laboratory requirements	Security Specimen reception Specimen integrity testing (measure creatinine) Specimen storage
Testing procedures	Use of immunoassay Personnel Quality control Cutoff levels (see Table 44.2) Confirmatory testing Reporting Record keeping

It is also worth noting that no single assay technology or assay strategy will detect all drugs of possible interest. Should a patient present appearing intoxicated, there is no specific test that will reliably identify the substance that has caused the reduction in consciousness. Comprehensive broad-spectrum analyses for all intoxicating drugs are labor intensive, and so most clinical laboratories that perform drug testing adopt a limited testing strategy to satisfy specific clinical situations and with varying degrees of success.

44.2 Drug Screening and Limitations of Testing

There are some important principles that apply to the use of drug testing in addiction medicine, namely, the concept of *screening tests*, *confirmatory tests*, *false positives*, and *false negatives*.

The most common test undertaken in addiction medicine, the urine drug screen, is an excellent example of a screening test, used to identify the most commonly abused substances. Most drug-screening tests use immunoassay technology, which use antibodies to detect the metabolites of drugs [1]. Because of cross-reactivity with other drugs, and because the cutoffs for screening tests are usually set very low in order to not miss positive results, there is a low specificity and high sensitivity. This will result in a higher number of false positives.

Most confirmatory testing for drugs, including those of dependence, is done via specific chromatography, typically gas chromatography mass spectrometry (GCMS) [2]. These tests are much more complicated and typically require being sent to a specific lab with specific conditions under which the tests are performed in accordance with relevant standards [3]. As these tests are more specific, they do not produce as many false positives. If there is discordance between the clinical situation and the result of a screening test, the sample should be sent for confirmatory testing with GCMS. The key practice point is that an aliquot from the *same sample* must be sent because drug(s) present in the first sample may no longer be present in a sample obtained days or

weeks later. Consequently, results must be reviewed and supplementary tests correctly ordered before the sample is discarded. This requires effective collaboration between clinical services and laboratories.

On top of this, it is important to appreciate that all laboratory testing, screening, or confirmatory, has cutoff values in order to avoid false positives. Part of the reason for this is that testing often occurs in the workplace, and a false-positive result can have significant consequences for an employee. A commonly used example is of poppy seeds causing positive opioid results [4, 5]. As such, the levels at which a test is deemed positive has been set for each illicit substance, be that opioid, amphetamine, or cannabis, by the particular standards of each country, such as AS/NZS 4308:2008 in Australia and New Zealand [3]. A negative result does not mean that the drug is absent, rather that the concentration in the matrix is less than the threshold concentration and, even if positive, considered unlikely to be of practical importance (a potential false negative). Cutoffs for immunoassay testing of common drugs of abuse according to AS/NZS 4308:2008 are shown below (Table 44.2).

As such we can see that all testing needs to serve the clinical context. A positive urinary drug screen should be sent for confirmation to ensure it is not a false positive particularly if significant action may follow from a positive result. On the other hand, when there is a high clinical suspicion for drug misuse, but a negative urinary drug screen, the sample should be sent for GCMS testing specific for the agent of concern.

This chapter will provide common false positives for each drug of abuse, but it is worth noting that circumstances can be highly variable. The strongest evidence of a legitimate false positive would be to have a patient produce a negative urine drug test, witness them take the suspected interfering drug, and send their urine for testing that shows positive immunoassay and negative GCMS. The weakest would be a case of a person denying use of an illicit substances and claiming use of an interfering substance [6].

Table 44.2 Cutoff levels for drug detection. (Reproduced from Australian Standard AS/NZS 4308:2008)

Class of drug	Cutoff level (ug/L)
Amphetamine type substances	300
Benzodiazepines	200
Cannabis metabolites	50
Cocaine metabolites	300
Opiates	300

There are other limitations on testing. Designer drugs, such as synthetic cannabis or cathinones ("bath salts"), are so new that specific assays are not available to test for these. Urinary drug screens are limited by time and as such cannot assess patterns of use and burden of dependence [7]. Furthermore, there are literature reports of passive inhalation of particular substances of abuse yielding a positive result [1].

44.3 Clinical Role of Drug Testing in Addiction Practice

The main role for drug testing is to detect the use of drugs not reported by the patient. Drug tests are no substitute for a good clinical history. There have been studies questioning the validity of self-reporting as a screening tool [8–10]. However it is worth noting that even within these studies, the sensitivity and negative predictive value of self-reporting remain quite high [8]. Furthermore, it appears that in patients seeking treatment – the very patients we work with in addiction medicine practice – the sensitivity and negative predictive value of self-reporting increase [11, 12]. Some papers also show that the bigger shortfall in self-reporting is *overstating* use, rather than understating [7, 13], and this may be because patients feel they need to overstate their dependence issue in order to receive treatment. Interestingly, Digiusto et al. looked at the urinary drug screens and self-reporting of 341 patients attempting to enter methadone treatment and found that while most drug use was overreported, especially in patients who had been treated before, the major drug underreported was methadone itself. This suggests patients are desperate for treatment, but may have already started medicating themselves illicitly, and fear the consequences of this being detected by the clinical team [13]. In short, uri-

nary drug screens should be an adjunct to clinical history but not a substitute. Typically, the patient will be more likely to report drug use if there is a strong therapeutic relationship and if there are no adverse consequences of reporting recent use. In this setting, self-report will provide details of quantity and frequency that laboratory testing is unable to match, such that self-reports are more useful than laboratory data. For the patient who does not appear intoxicated and who reports no recent drug use, periodic urine drug screening can be worthwhile. Indeed, the main clinical use of a positive urine drug test is to encourage more forthright and detailed self-reporting in this context.

In the addiction setting, there are a number of situations where drug testing can be useful, such as monitoring the use of prescribed benzodiazepines, ensuring that takeaway doses are being used by the patient and not diverted, and when there is concern around concomitant use of sedatives, in particular opioids and benzodiazepines. Even in these situations, an honest, nonjudgmental conversation about what substances the patient is using will supplant urine drug testing. For example, if a patient on a methadone program admits to using heroin, there is little benefit in testing for heroin on a urine drug screen particularly as most tests cannot detect heroin. Again, we emphasize the importance of clinical acumen and good rapport with a patient more than relying on regimented testing.

44.4 Dealing with a Positive Test Result

Discussing a positive test result with a patient can be confronting. It is therefore important to explain to patients in a clear and nonjudgmental manner prior to testing the reasons for performing drug screening. This will alleviate many of the anxieties around a positive result. Should a patient return an unexpected positive specimen, the clinician should undertake the following steps [14]:

- Review the patient's medications for possible false positives.
- Confirm the result with GCMS on the same sample if clinically indicated.
- Present the result to the patient in a clear and nonjudgmental manner.

Test results should only be interpreted by a suitably skilled clinician with knowledge of the patient and the testing process. The authors have experience of community workers removing children from their mothers because of false-positive urine tests as just one example.

44.5 Testing in the Emergency Department

The question of whether to use urine drug screens on patients in the emergency department is a vexed one. Some authors have suggested utilizing the UDS in order to diagnose substance abuse disorders and provide primary care [14]. However, there is no clear evidence to suggest this is useful. A literature review from Tenenbein of over 6000 patients presenting to the emergency department concluded that A UDS was unlikely to significantly impact upon management of the patient in the emergency department [15]. While this review focused primarily on immediate management outcomes, such as time in the emergency department, and procedures the patient received, others have suggested limited utility beyond this time frame. Riccoboni retrospectively reviewed over 200 psychiatric admissions, comparing those that had UDS to those who did not, and found it made little difference in management of their psychiatric illness [16]. This is supported by other studies in psychiatric patients that emphasize the urine drug screen should not trump good clinical history [17, 18]. The authors would suggest that urine drug testing in the emergency department should be performed in order to confirm a suspected diagnosis related to substance abuse when the patient's history does not corroborate. Furthermore, the information should only be presented to the patient when confirmed via GCMS and as a means of helping the patient seek appropriate treatment of a potential substance dependence.

44.6 Point-of-Care Testing

There are a variety of new point-of-care tests entering the market, including dipsticks, breath tests, cassettes, and urine drug cups, which integrate the testing strip with the collection cup [14, 19].

Point-of-care devices have the benefit of fast results and appear to have low rates of false positives and false negatives [14]. However, it is worth looking at devices that have been externally validated in studies and noting the cutoffs used by the particular test. Ultimately, they cannot replace GCMS for performance.

44.7 Saliva/Oral Fluid/Mobile Drug Testing

Mobile drug testing is now being utilized in the USA, Europe, and Australia for the detection of cannabis, cocaine, and MDMA in drivers [20–22]. These have many of the same advantages and disadvantages with other point-of-care tests listed above [2]. Saliva typically remains positive for 12–24 hours after drug use, though potentially longer in chronic users [22]. It is also worth noting a few idiosyncrasies to the testing of saliva. Cannabis has been shown to be more difficult to detect [22, 23], while drug deposits in the mouth can cause increased levels in quantitative testing when done in the immediate period after use [24].

Despite these shortcomings, saliva testing has the advantage of limited opportunity for adulteration [2, 22].

44.8 Detection Times

An often-asked question is how long a test will remain positive for, to which there is no hard and fast answer. One can expect a test to remain positive for around five half-lives of the drug, as this is the time taken to excrete around 97% of the drug. However, duration of positivity is determined by many pharmacological factors, including body weight and composition, half-life of the drug, dose, duration of use, volume of distribution, bioavailability of the drug, and the half-lives of metabolites [1, 2, 25]. Nonetheless, this chapter will attempt to provide a guide for each substance of abuse around how long a test will remain positive.

44.9 Drug Testing Technologies

44.9.1 Immunoassay

Most clinical laboratories use immunoassay on high-capacity automated analyzers as first-line screening. All immunoassays are based on an antibody directed against either the drug of interest or a metabolite of the drug of interest. An example would be the immunoassay screen for cocaine, which has an antibody against benzoylecgonine.

Cloned enzyme donor immunoassay is the most commonly used assay in Australasian laboratories. The process involves mixing the patient's sample with an assay kit. The kit will contain an antibody against the metabolite of the drug being tested for and also the antigen of the drug being tested for tagged with an enzyme, such as glucose-6-phosphate dehydrogenase [26]. This enzyme converts NAD to NADH. If there is no drug present in the patient's simple, then the antibody from the kit will bind the antigen from the kit, and no enzymatic reaction will occur. However, if there is drug present in the patient's sample, then these metabolites will bind the antibody of the kit, leaving the antigen from the kit free and thus able to complete its reaction. The product of the reaction, in this case NADH, can then be tested for.

Because of cross-reaction of different substances for the antibody in the assay kit, one can easily see how false positives and false negatives can occur frequently. This is a major limitation of immunoassays in drug testing.

44.9.2 Chromatography and Mass Spectrometry

Chromatography is a process whereby individual components of a complex mixture are physically separated and identified. There are three tech-

niques that can be used to separate and identify drugs in a body fluid such as urine: thin-layer chromatography (TLC), gas chromatography (GC), and liquid chromatography (LC). All these techniques involve a stationary phase and a mobile phase. For example, in GC the stationary phase is a polymer that coats the inner wall of a silica capillary tube. The mobile phase is an inert gas, such as helium. As in all forms of chromatography, the separation is achieved by allowing the drug to bind to the stationary phase and passing the mobile phase through so as to progressively remove the drug.

The identification of the drug eluted into the mobile phase uses a variety of techniques and requires comparison of the test sample with known pure standards. In TLC, drugs are detected by direct visualization, requiring the interpreter of the test to have knowledge of the various patterns that may be formed. GC and LC, however, use instrumental techniques of analysis, and while there are several different detectors that can be used to distinguish the presence of a drug, the preferred detectors in drug analysis are mass spectrometers.

Mass spectrometry involves the formation of charged ion(s) from the drug molecule. These charged ions can be sorted in the mass spectrometer and the mass of each ion determined. Different drugs give rise to a distinctive ion "fingerprint."

44.10 Detecting Specific Drug Classes

It is worth looking at each drug individually, focusing on the metabolism of the drug and the metabolites being test, the expected duration the test will remain positive, common cross-reactions, and, for certain drugs, whether passive inhalation can cause positive results.

44.10.1 Amphetamines

It is important to appreciate that the term "amphetamine" refers specifically to 1-phenylpropan-2-amine. There are, however, many other compounds structurally related to amphetamine that are often categorized under the broad umbrella of "amphetamines": methamphetamine ("crystal meth" or "ice"), methylenedioxyamphetamine (MDA), and methylenedioxymethylamphetamine (MDMA or "ecstasy"). The different assays used in urinary drug screens vary in reactivity for the various types of amphetamine.

Amphetamines are typically detectable in urine for around 48 hours after administration of the drug, though this can vary [27]. Amphetamines are typically basic, and consequently the rate of renal excretion of the unchanged drug is dependent on urine pH. Acidic urine gives amphetamine a charge that promotes excretion because the ionized form of amphetamine is poorly reabsorbed across the distal convoluted tubule of the kidney. Therefore by acidifying urine, such as with high doses of vitamin C, one can theoretically excrete amphetamine quicker. The half-life of amphetamines can be as short as 4 hours with acidic urine, as opposed to 12 hours with uncontrolled urinary pH, theoretically dropping the excretion time to less than 24 hours.

While there have been some concerns around immunoassay detection of amphetamines at low doses [28], GCMS is around 90% sensitive for detection even in doses as low as 10 mg [27]. It would not be unusual for a patient abusing amphetamines to be using far higher doses [25]. At the same time, patients that use medicinal amphetamines, particularly lisdexamfetamine for ADHD, would be expected to test positive as this is a prodrug converted in vivo to amphetamine.

As already mentioned, amphetamines have a vast number of cross-reactivities. This stems largely from the simplicity of the molecule, making it difficult to develop specific antibodies, and the high number of structurally similar sympathomimetics [6]. The most common source of a false-positive test is cold medicines such as pseudoephedrine. Promethazine [29], labetalol [30], ofloxacin [31], and bupropion [32] have all been shown to cause false-positive results for methamphetamines.

Furthermore methamphetamine is a chiral molecule. Typically, the illicit form is dextrorotary (d-form) or a racemic mixture of levorotary (l-form) and d-form. L-form methamphetamine

is also a metabolite of selegiline and Vicks VapoRub and thus these can cause false positives [33].

There is no evidence that passive inhalation of methamphetamines can cause false-positive urine drug tests [34].

Designer amphetamines and synthetic cathinones, such as mephedrone or methcathinone, present a new challenge for drug testing, due to the number of different chemical structures that exist among these drugs [35]. Furthermore, new designer drugs are being introduced into the market regularly, making it difficult to produce immunoassays for each drug. Nonetheless, there is at least one immunoassay on the market, validated for mephedrone, methcathinone, methylenedioxypyrovalerone (MDPV), and 3′,4′-methylenedioxy-α-pyrrolidinobutiophenone (MDPBP) [36]. Many other established cathinones can also be detected via GCMS [35].

44.10.2 Benzodiazepines

Benzodiazepines have a variety of metabolic pathways, which can complicate testing.

There is almost no excretion of unconjugated parent benzodiazepines, and only three are excreted following glucuronidation alone: oxazepam, temazepam, and lorazepam. However, these three drugs show the complexity of testing for benzodiazepines, as the immunoassays will not detect their glucuronide conjugates unless the urine was treated with β-glucuronidase before testing, a practice not commonly done.

The metabolism of diazepam also warrants specific discussion. Diazepam can be demethylated to form nordiazepam or hydroxylated to form temazepam. Both these metabolites can form oxazepam. When taken orally, temazepam itself is demethylated to oxazepam. As such, benzodiazepine assays typically look for oxazepam and nordiazepam, as they are common metabolites in benzodiazepine metabolism. However, they may miss other commonly abused benzodiazepines, such as alprazolam, whose main metabolites are α-hydroxyalprazolam and 4-hydroxyalprazolam [37]. Clonazepam is converted to 7-aminoclonazepam, and flunitrazepam, metabolized to 7-aminoflunitrazepam. Lorazepam is excreted as an inactive glucuronide (Fig. 44.1).

Given the above, if monitoring use of prescribed benzodiazepines in an addiction setting, a simple immunoassay will not suffice, and the urine should be sent for formal GCMS.

Interpretation of results is a key issue. A patient may be prescribed diazepam, and urine testing may reveal diazepam, nordiazepam, oxazepam, and temazepam. This result reflects normal drug metabolism and does not signify nonprescribed use of the latter two drugs.

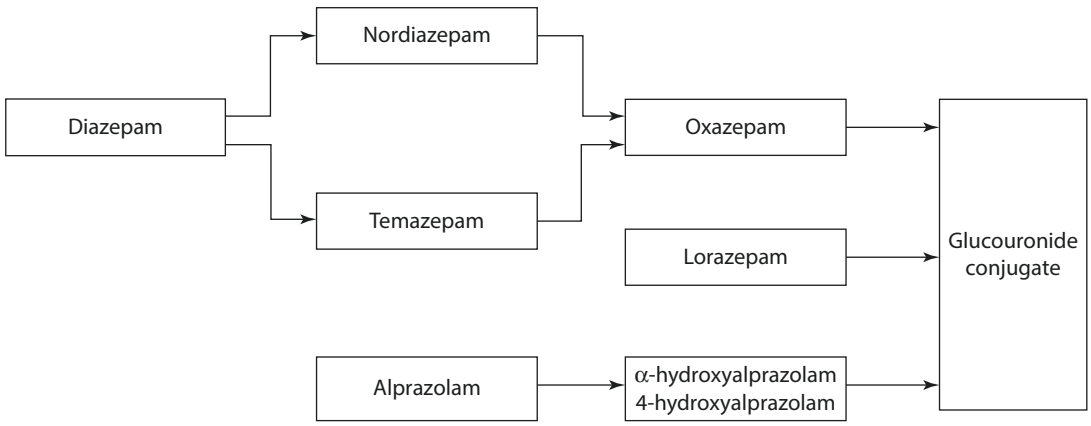

Fig. 44.1 Interconversion of commonly used benzodiazepines. (Adapted from Moeller 2016)

Detection times for benzodiazepines vary depending on duration of action. Diazepam, a long-acting benzodiazepine, can be detected for up to a week even after a single dose [26], while the metabolite nordiazepam can be detected for up to 3 weeks [38]. Short-acting benzodiazepines, such as alprazolam, temazepam, and oxazepam, may only be detectable for around 24 hours, while intermediate acting benzodiazepines, such as lorazepam, can be detected for up to 12 days [14]. Having said this, chronic use of benzodiazepines can result in a positive test for up to a month following cessation [14]. Flunitrazepam has received a lot of attention due to reports of it being used in cases of date-rape and is detectable after acute dosing for at least 48 hours using GCMS [39].

There is strong evidence that efavirenz [40], an antiviral used for HIV, and sertraline [41] both cause false positives in urine drug testing for benzodiazepines, while there has been a case report of oxaprozin, a nonsteroidal anti-inflammatory, causing a false positive [42].

44.10.3 Cannabis

Tetrahydrocannabinol (THC), the main psychoactive component of the hemp plant cannabis sativa, undergoes a complex metabolism to carboxy-THC. Carboxy-THC is not psychoactive and is extensively conjugated with glucuronic acid before excretion into urine.

The current cutoff concentration for immunoassay of cannabis metabolites has been set at 50 μg/L in the Australasian standard AS/NZS 4308:2008 because of concerns around passive smoking. There have been several studies that have looked at passive smoking, and the consensus is that passive smoking is unlikely to result in a urinary concentration of cannabis metabolites that exceeds 50 μg/L.

Carboxy-THC has an elimination half-life of around 6 days. However, THC is lipophilic and has a high volume of distribution, meaning chronic users of cannabis establish a significant reservoir of carboxy-THC in adipose tissue. The time taken for carboxy-THC to fall back to below the cutoff concentration in urine therefore depends on the amount of THC stored in tissue lipids, which in itself depends on duration and amount of exposure.

Following a single occasion of cannabis use, GCMS will typically be positive for 72 hours. Moderate users of cannabis, using four times per week, will typically have a negative test in 5–7 days after stopping the drug. Daily users will typically test positive for about 12 days post ceasing use, but chronic users may have a positive test for more than 30 days [43].

Given the extended duration of detection of carboxy-THC in the urine of long-term heavy users of the drug, it can make ongoing detection post cessation challenging. One approach is to determine a carboxy-THC: creatinine ratio for urine samples collected at different times. A comparison of these two ratios allows for assessment of continued use.

Detection of synthetic cannabinoids is difficult for many reasons. Typically, they are highly potent, so only a small dose is required, and metabolized quickly [44, 45]. Furthermore, there are over 800 different types of synthetic cannabinoids, making it difficult to produce immunoassays to detect all types and to keep up with the new drugs being introduced into the illicit market [44]. Despite the challenges, there are some immunoassay kits available for detection of synthetic cannabinoids, including DrugCheck K2/Spice Test, DrugSmart Cassette, and RapiCard InstaTest [45].

Clinicians should also be aware that dronabinol, a synthetic form of THC approved for use in spasticity in multiple sclerosis, will test positive on urine drug screens, though nabilone, approved in some countries for use in nausea during chemotherapy, will not [46, 47]. While both are synthetic cannabinoids, nabilone is a synthetic derivative [48] and has enough difference in structure to test negative.

Proton pump inhibitors have been shown to cause false positives both in case reports and formalized testing [49, 50]. The urinary metabolite of Efavirenz, 8-ether-glucoronide, cross-reacts

with cannabinoid immunoassays [51, 52]. Naproxen and ibuprofen also have a small possibility of false-positive results on immunoassay, and as such, confirmatory testing with GCMS is warranted should this occur [53]. Certain baby wash products can also produce a false positive on immunoassay, which is important in the setting of neonatal drug testing [54].

44.10.4 Opioids

An understanding of opioid metabolism is critical when interpreting urine drug tests. It is important to note that morphine, codeine, and heroin (diacetylmorphine) are the only fully natural opioids, and most immunoassays are directed at these three substances and their metabolites. Synthetic opioids, such as fentanyl, methadone, buprenorphine, pethidine, oxycodone, and oxymorphone, are structurally different enough to natural opioids that they will not be detected by these immunoassays and require either specific assays directed at their metabolites or GCMS [14]. Thus, a patient using illicit fentanyl or prescribed buprenorphine will typically have a negative urine drug screen, and further testing is required in order to show use of synthetic opioids.

44.10.5 Morphine, Codeine, and Heroin

Heroin is rapidly metabolized to both 3-monoacetylmorphine, which is inactive, and 6-monoacetylmorphine (6-MAM), which is rapidly deacetylated to morphine, and has a half-life of about 5 minutes. 6-Acetylcodeine is an impurity often found in illicit heroin, and this can be metabolized to codeine also [55, 56].

Morphine is mostly metabolized to 3-glucuronide and 6-glucuronide, though it has a number of minor metabolic pathways, including to form normorphine and hydromorphone [55, 57].

Codeine is O-demethylated to yield morphine via the actions of CYP2D6 in the liver. However, a large portion of codeine is excreted as codeine 6-glucouronide, while it may also be metabolized to norcodeine and hydrocodone [55, 57, 58] (Fig. 44.2).

Urine immunoassay will not distinguish between codeine, morphine, and heroin. If there is conjecture over which opioid the patient took, the sample needs to be sent for GCMS. Detection of 6-MAM is pathognomonic for heroin use; however, it is usually only detectable for a few hours because of its short half-life (20 minutes) [6–8]. This will often leave the clinician with a

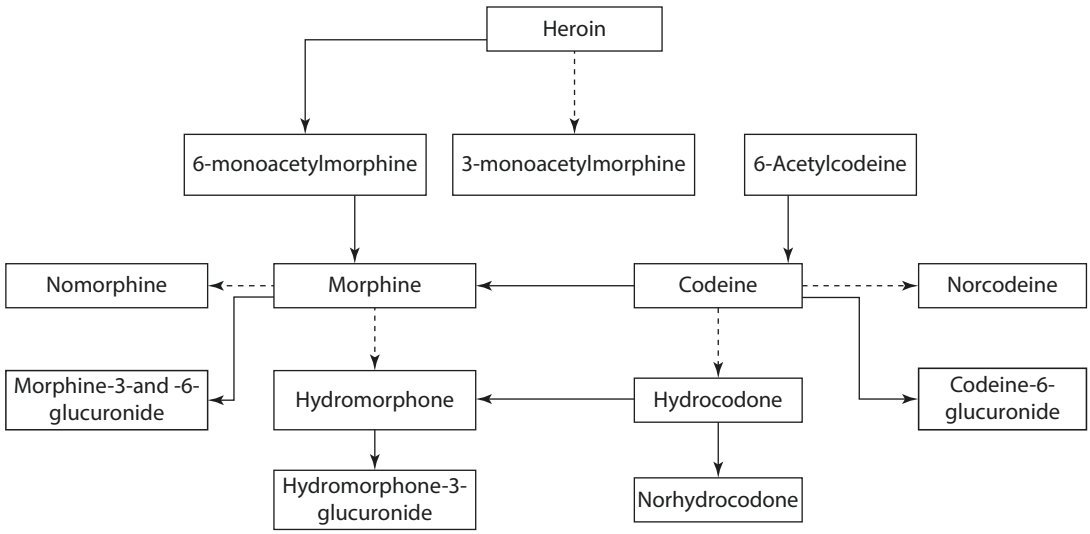

Fig. 44.2 Interconversion of commonly used opioids. (Adapted from French [55])

test that is positive for morphine, codeine, or both, which presents an interesting challenge. Codeine may arise from prescribed analgesics or, as mentioned above, from an impurity in heroin. Morphine may also be derived from codeine, from a prescription for the medication, or from heroin. Furthermore the patient may have used multiple opioids, further complicating the picture [59]. The codeine/morphine ratio may help in this situation. Several studies in both urine and blood have shown that when patients have used heroin, confirmed by the presence of 6-MAM, morphine levels will be greater than codeine [56, 59, 60]. Furthermore, when healthy volunteers take codeine alone, the level of morphine metabolites in urine will typically be lower than codeine, even though codeine is metabolized in part to morphine [59, 61, 62]. This has even been observed in the blood of rapid codeine metabolizers [63]. The following has therefore been suggested: A urine morphine/codeine ratio greater than 2 and total morphine >200 ng/ml suggests morphine or heroin use, while a morphine/codeine ratio less than 2 and total morphine <200 ng/ml suggests codeine use alone [60, 64] (Table 44.3).

Furthermore, current Australian guidelines dictated by AS/NZS 4308:2008 prescribes an opioid cutoff of 300 μg/L for immunoassay screening. This can still result in false positives caused by the ingestion of poppy seeds. In the USA, the Substance Abuse and Mental Health Services Administration (SAMHSA) changed this cutoff to >2000 μg/L in order to exclude poppy seeds as a potential cause of a positive opiate immunoassay. This cutoff, however, may miss true positives.

Several non-opiate drugs may cause false positive tests including the quinolone antibiotic gatifloxacin [65], ofloxacin [66], rifampin, and rifampicin [67, 68].

Table 44.3 Urine findings after use of morphine or codeine. (Adapted from Stefanidou [64])

Morphine/codeine ratio	Total morphine	Suggests
>2	>200 ng/ml	Morphine or heroin use
<2	<200 ng/ml	Codeine use

44.10.6 Methadone

Methadone immunoassays can test for either methadone itself or the inactive metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP) [1]. The latter is preferred for testing as patients can spike their urine with methadone in order to avoid detection of diversion of methadone doses. Methadone typically remains positive in urine for around 2–4 days, though it can be positive for up to 11 days [14, 69].

Quetiapine [70, 71] and verapamil [72] have both been demonstrated to cause false positives on methadone immunoassays.

The role of monitoring methadone serum levels during methadone treatment warrants some discussion. Currently, there is no recommendation to perform routine methadone levels in patients on methadone treatment. Currently, clinicians in NSW, Australia, only require a trough methadone level in order to apply to prescribe beyond 200 mg/day [73]. This is thought to identify patients that may be rapid metabolizers of methadone and thus require higher doses. At this stage, however, there is no clear plasma level at which methadone dosing is considered "effective." Trough levels tend to sit between 200 and 400 ng/ml [74, 75]. There have been a number of studies evaluating the relationship between methadone dose and plasma concentration, with some suggesting a strong relationship [76], some suggesting a poor relationship [77], while another has shown a strong relationship that only exists at doses less than 80 mg [78]. Further research is still required in this area. Specific stereoisomer testing for R- and S-methadone may improve the relevance of blood levels, but the assay is not widely available [79–81]. Serial measures of methadone levels may be helpful to detect rapid metabolizers but require patient attendance for many hours for multiple blood tests. This may be further complicated by often poor venous access, making this approach impractical for routine care.

44.10.7 Fentanyl

The main metabolite of fentanyl is norfentanyl [82, 83]. Because of its potency, estimated as

50–100 times that of morphine [84], only small concentrations are found in urine following prescribed or illicit use. Detection requires sophisticated techniques and sensitive analyzers that will not be available in many laboratories. Nonetheless, laboratories are improving their ability to detect fentanyl at smaller doses via GCMS and, with a smaller sample of matrix, even as low as 0.175 ml of serum [85]. Furthermore, new assays are now available for use in detecting fentanyl [86, 87], though these are not part of a standard urine drug screen.

Risperidone has been shown to cross-react with at least one fentanyl immunoassay [88]. Fentanyl metabolites are detectable via GCMS for at least 24 hours in urine following a single intravenous dose [84].

Street heroin has been found to be laced with fentanyl and its synthetic analogs, which can have potentially catastrophic consequences given its potency. The use of fentanyl testing in urine may therefore have a public health benefit as a warning to other users, though widespread use for this is not currently done [89].

44.10.8 Buprenorphine

Buprenorphine, widely used in opioid treatment programs, is not typically part of a standard urine drug screen panel, though it can be tested via immunoassay or GCMS [90, 91].

It is important to monitor the use of buprenorphine in patients on opioid treatment, especially those on takeaway dosing, as diversion of doses remains a risk [92]. Buprenorphine is dealkylated to form norbuprenorphine [90]. Both buprenorphine and norbuprenorphine can be glucuronidated, leaving four main metabolites in urine: buprenorphine, norbuprenorphine, buprenorphine-glucuronide, and norbuprenorphine-glucuronide [90, 93].

The laboratory may help with the detection of patients who spike their urines with their own supply of buprenorphine to give the impression that they are using the drug, when in fact they are diverting it [94]. The concentration of parent buprenorphine is typically lower than the other metabolites [95]. Therefore, norbuprenorphine/buprenorphine ratios are a good way to detect for spiked urines. In theory, all patients taking buprenorphine orally should have a norbuprenorphine/buprenorphine ratio greater than 1, and any ratio < 0.02 is considered to be spiked [90, 94]. One study has also suggested that norbuprenorphine levels may be able to estimate and guide the patient's dose of buprenorphine, though this is not validated or routine practice [96].

There are case reports that amisulpride [97], and high-dose morphine [98] can cause false-positive buprenorphine immunoassay results. The window of detection for buprenorphine is 4 days with a cutoff of 0.5 ng/ml [14].

44.10.9 Cocaine

The major metabolite of cocaine is benzoylecgonine, with around 45% of the dose excreted in the urine as such. Standard immunoassays show good reaction to benzoylecgonine, limited reaction to cocaine, and virtually no reaction to other metabolites. After use of 1.5 mg/kg intranasally, GCMS and immunoassay both appear to remain positive for around 2–3 days [99]. Interestingly, after administration of 20 mg of intravenous cocaine, immunoassays remain positive for only 2 days [100].

It is also worth noting that cocaine is still used as a vasoconstrictor and topical anesthetic for nasal surgery and that urines will test positive for similar timeframes as for illicit use [101]. Furthermore, passive inhalation of cocaine when smoked does not appear to cause false positives [34].

44.10.10 GHB

Gamma-hydroxybutyric acid (GHB) is particularly difficult to pick up on urine testing due to its short half-life and because it requires GCMS for detection, not immunoassay [14]. Furthermore, GHB is produced endogenously, and because of this, it has been suggested that 10 μg/ml is the cutoff for urine testing [25]. A 100 mg/kg dose of

GHB is undetectable in urine 12 hours later [102]. It is not routinely tested in the addiction medicine field.

44.10.11 Nitrous Oxide

The use of nitrous oxide among recreational drug users appears to be increasing, with around one quarter of ecstasy users admitting use in their lifetime [103, 104]. Subacute combined degeneration of the cord (SCID) has become a serious health issue in these patients [105]. While nitrous oxide is not tested in urine or other matrices, it is important for the addiction physician to be aware of the appropriate serum tests should a patient admit to using nitrous oxide recreationally. A normal B12 level is not reassuring because nitrous oxide inactivates B12, but it does not reduce serum levels, so serum B12 is often normal. Physicians should instead test for homocysteine levels. Vitamin B12 is important for the conversion of homocysteine to methionine, an important element for myelin production. An elevated homocysteine level suggests reduced levels of active B12, and potential risk of subacute combined degeneration of the cord [106, 107].

44.10.12 Ketamine and Phencyclidine

Ketamine has two major metabolites, norketamine and dehydronorketamine [108], which, along with ketamine itself, can all be tested via GCMS [109]. While not part of a typical urine drug screen, specific immunoassays are becoming increasingly available for ketamine as well [110, 111]. Ketamine is typically detectable for 3 days by GCMS when taken orally; however, dehydronorketamine can be detected for up to 10 days [112]. Quetiapine has been reported in two case reports to cause false positives on ketamine immunoassay [110].

Phencyclidine is now available on some urine drug screen panels, such as the Medtox Diagnostics EZ screen. Urine drug tests can detect PCP for up to 10 days post use. Ibuprofen, dextromethorphan, and metamizole have all been shown in both case reports and in spiked urine testing to cause false positives [113]. Venlafaxine has also caused false positives in both of these circumstances [114], while there has been a case report of desvenlafaxine doing likewise [115]. There have been cases reports of tramadol causing positive PCP result on immunoassay, though this appears to occur more readily at supratherapeutic doses [116, 117].

44.10.13 Lysergic Acid Diethylamide (LSD)

LSD is converted to a number of different metabolites, and only around 1% of the drug is excreted unchanged [118]. Despite this, most immunoassays are still directed at LSD itself [119], and these are typically positive for around 24 hours, though there has been a report of detection 80 hours post use [25].

Ritter et al. found 71 false-positive LSD results from immunoassay testing of almost 1900 positive samples [120]. Potential causative drugs included amitriptyline, bupropion, metoclopramide, labetalol, and calcium channel blockers; however, no confirmatory testing has been undertaken to prove which agents truly cross-react with the immunoassay. Ambroxol, however, has been seen in both case report and spiked urine testing to cause false-positive immunoassay results [121].

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Brief Intervention for Illicit Drug Use

45

Jennifer Harland, Susan Henry-Edwards, Linda Gowing, and Robert Ali

Contents

Abstract

Approximately 29.5 million people, or 0.6% of the global adult population, have a drug use disorder (United Nations Office on Drugs and Crime (UNODC), World Drug Report (ISBN: 978–92–1-148291-1, eISBN: 978–92–1-060623-3, United Nations publication, Sales No. E.17.XI.6), 2017). People who use illicit drugs often do not disclose their drug use due to the illegality and stigma associated with that use. The opportunistic nature of brief interventions for illicit drug use makes therapeutic engagement critical to effectiveness. In many settings time will be limited so that brief interventions also need to be efficient.

This chapter focuses on opportunistic brief interventions with people who use illicit drugs and are not engaged in treatment for their drug use. In this context the aim of the brief intervention is to reduce substance use and associated risk behavior as well as to prevent the development of dependence or to motivate the individual to obtain more struc-

J. Harland (✉) · S. Henry-Edwards (✉)
L. Gowing (✉) · R. Ali (✉)
University of Adelaide, Adelaide, SA, Australia
e-mail: jennifer.harland@adelaide.edu.au; susan.henry-edwards@adelaide.edu.au; linda.gowing@adelaide.edu.au; robert.ali@adelaide.edu.au

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tured treatment for their drug use. The objective is to reduce the overall burden of drug-related harms in the community or in particular target groups by identifying individuals who are experiencing, or are at risk of developing, drug use problems, to raise awareness of potential drug-related harms, and to intervene early before problems have developed or become severe. Brief interventions are part of a public health approach to drug use problems [3, 21].

This chapter provides practical information on the conduct of effective brief interventions covering the general approach to brief interventions, responding to the stage of change, and assessing risk.

Keywords

Brief intervention · Screening · Illicit drugs
ASSIST · Stages of change · FRAMES model
SBIRT

45.1 Introduction

Substance use is one of the major preventable causes of disease and disability [31]. Alcohol and tobacco are by far the most prevalent substances used globally [26], but the prevalence of illicit drug use is still substantial. In 2015 an estimated quarter of a billion people, or around 5% of the global adult population, used illicit drugs at least once [31]. Cannabis was the most commonly used drug, with a reported 183 million users globally. Amphetamine and prescription stimulants were used by 37 million people, and 35 million people used illicit opioids [31].

The magnitude of harm caused by illicit drug use is substantial and has increased over the last decade. In 2015 an estimated 28 million years of "healthy" life (disability-adjusted life years (DALYs)) were lost worldwide as a result of premature death and disability caused by drug use. Of those years lost, 17 million were attributable solely to drug use disorders, across all drug types. Around 70% of the global burden of disease caused by drug use disorders is attributable to opioid use [31], reflecting the high risk of overdose associated with opioid use and the transmission of blood-borne viruses (HIV and hepatitis C) through use by injection [11].

Treatment is effective in reducing illicit drug use, reducing risk behaviors and improving physical and mental well-being, but fewer than one in six persons with drug use disorders are provided with treatment each year. In part this reflects limited availability of and access to appropriate treatments [31], but it is also likely to reflect the hidden nature of illicit drug use.

The stigma associated with illicit drug use, and possible legal implications, means that people who use illicit drugs may be reluctant to disclose their use. They may not be aware of the risks of harm associated with their substance use and not see the connection to negative consequences. For all these reasons, people who use illicit drugs rarely seek treatment unless pushed by a crisis of some sort – legal, financial, family pressure, or acute health effects.

This is where brief interventions come in. Brief interventions have been used in a variety of ways, including as adjuncts to structured treatment for alcohol and other drug problems and to reduce risk behaviors in specific populations such as people with HIV. Brief interventions have also been used to structure brief conversations about healthcare in general [6]. In this chapter we are focusing on opportunistic brief interventions with people who use illicit drugs and are not engaged in treatment for their drug use. In this context the aim of the brief intervention is to reduce substance use and associated risk behavior as well as to prevent the development of dependence or to motivate the individual to obtain more structured treatment for their drug use. The objective is to reduce the overall burden of drug-related harms in the community or in particular target groups by identifying individuals who are experiencing, or are at risk of developing, drug use problems, to raise awareness of potential drug-related harms and to intervene early before problems have developed or become severe. Brief interventions are part of a public health approach to drug use problems [4, 21].

Brief interventions can take place in various settings, such as primary healthcare, and can be implemented by a variety of trained healthcare providers. They are low in cost and time efficient and can be effective across many levels of hazardous and harmful drug use. This makes brief interventions ideally suited for use as a method of health promotion and disease prevention with primary care patients [16, 34].

The opportunistic nature of brief interventions for illicit drug use makes therapeutic engagement critical to effectiveness. In many settings time will be limited so that brief interventions also need to be efficient.

Brief interventions are most useful for those who are at low to moderate risk of drug-related harm. They are not intended as a stand-alone treatment for people with significant drug use disorders although a brief intervention can increase the proportion of patients identified as high risk or dependent who subsequently attend their first appointment at a specialist drug and alcohol treatment facility [3, 18]. Hence it is important to tailor the intervention to the individual by reflecting the risk of drug-related harm. Another important aspect of tailoring the intervention to the individual is taking account of the person's current stage of behavioral change.

There is moderately good evidence for the effectiveness of brief interventions in primary care settings for alcohol and tobacco [22, 30] and growing evidence for other drugs.

Brief interventions consist of feedback about personal risk, explicit advice on change, and emphasis on individual responsibility for change and provide a variety of ways to effect change. Brief interventions in primary care can range from five minutes of brief advice to 15–30 minutes of brief counselling [24]. Shorter duration interventions are typically the requirement in acute care settings where time may be particularly limited.

This chapter provides practical information on the conduct of effective brief interventions covering the general approach to brief interventions (Sect. 45.2), responding to the stage of change (Sect. 45.3), and assessing risk (Sect. 45.4).

45.2 General Approach to Brief Interventions

The aim of a brief intervention is to help the person understand that their substance use is putting them at risk and to encourage them to reduce or give up their substance use. Brief interventions should be personalized and offered in a supportive, nonjudgmental manner. Brief intervention techniques include an empathetic style and support for the person's perception of self-efficacy or optimism that they can change [32].

A number of brief intervention models have been developed, based on principles of motivational interviewing. These include the Brief Negotiated Interview (BNI) [8]; "FLO" – Feedback, Listen, Options [12]; and the 5 As (ask, assess, advise, assist, and arrange follow-up) that are widely implemented for smoking cessation [29].

Experience and research into brief interventions for substance use have found that effective brief interventions comprise a number of consistent and recurring features. These features have been summarized using the acronym FRAMES: feedback, responsibility, advice, menu of options, empathy, and self-efficacy [25]. The FRAMES model is considered in detail here as it is used extensively in brief interventions for alcohol and other drug use and is the approach we recommend for people who use illicit drugs.

Feedback of Personal Status Relative to Norms

Feedback is the provision of personally relevant information which is pertinent to the individual and is delivered in a non-judgemental and objective way in the Spirit of Motivational Interviewing [25]. The provision of personally relevant feedback (as opposed to general feedback) is a key component of a brief intervention. This includes information about the individual's substance use, the level of risk associated with their use, and the benefits of reducing or stopping use.

Information about personal risks associated with current drug use patterns (e.g., low mood,

anxiety, relationship problems, health problems) combined with general information about substance-related risks and harms comprises powerful feedback.

Responsibility for Personal Change

A key principle of an effective brief intervention is to acknowledge and accept that a person is responsible for their own behavior and will make choices about their substance use. Adopting phrases such as "*Are you interested in seeing how you scored on this questionnaire*?" and "*What you do with this information I'm giving you is up to you*" enables the person to retain control over their behavior and its consequences and the direction of the intervention. This sense of control has been found to be an important element in motivation for change [24]. Using language such as "*I think you should…*" may create resistance in the interaction and not be beneficial to behavior change.

Advice to Change

A central component of effective brief interventions is the provision of clear objective advice regarding how to reduce the harms associated with continued use. This needs to be delivered in a non-judgemental manner and in the Spirit of Motivational Interviewing. People may be unaware that their current pattern of substance use could lead to problems or make existing issues worse. Ask permission to give advice and then provide clear, objective information. Explain that cutting down or stopping substance use is the best way to reduce their risk of harms both now and in the future. This will increase their awareness of their personal risk and provide reasons to consider changing their behavior.

Advice can be summed up by delivering a simple statement such as "*the best way you can reduce your risk of* (e.g. depression, anxiety, injuries) *is to cut down or stop using*." This is best followed by an open-ended question to help explore the person's readiness to change. Once again, the language used to deliver this message is an important feature and comments such as "*I think you should stop using substances*" does not provide clear, objective advice nor promote further discussion.

Menu of Options from Which to Choose in Pursuing Change

Effective brief interventions provide the individual with a range or menu of options to cut down or stop their substance use in the pursuit of change. This allows the individual to choose the strategies which are most suitable for their situation and which they feel will be most helpful. Providing choices reinforces the sense of personal control and responsibility for making change and can help to strengthen the person's motivation for change.

Examples of options for clients to consider include

- Keeping a diary of substance use (where, when, how much used, how much spent, with whom, why)
- Identifying high-risk thoughts and beliefs and challenging them
- Identifying high-risk associates and situations and exploring alternate strategies
- Identifying other activities instead of drug use (constructive use of leisure)—education, volunteering, hobbies, sports, gym, etc.
- Identifying non-drug rewards and pleasurable activities
- Identifying people who could provide support and help for the changes they want to make
- Attending a self-help or peer support groups
- Putting aside the money they would normally spend on substances for something else
- Setting goals and working toward achieving them

You can also assist by

- Providing information about other self-help resources and written information
- Providing information about groups or programs that specialize in drug and alcohol issues

Empathic Counselor Style

Empathy is taking an active interest and effort to understand another's internal perspective, to see the world through their eyes. It does not mean sympathy, a feeling of pity, camaraderie, or identification with the person. Statements such as

"*I've been there and know what you are experiencing, let me tell you my story*" are not useful. The opposite of empathy is the imposition of one's own perspective, perhaps with the assumption that the other's views are irrelevant or misguided. Empathy is the ability to understand another's frame of reference and the conviction that it is worthwhile to do so [23].

In a brief intervention, empathy comprises an accepting, nonjudgmental approach that seeks to understand the individual's point of view. It is especially important to avoid confrontation and blaming or criticism of the individual. Adopting a position of *curious intrigue* is helpful. Skilful reflective listening which clarifies and amplifies the person's experience and meaning is a fundamental part of expressing empathy. The empathy and understanding of the professional are important contributors to how well the individual responds to the intervention [25].

Support for Self-Efficacy

The final component of effective brief interventions is to encourage the person's confidence that they are able to make changes in their substance use. Exploring other areas where the individual has made positive change is helpful. People who believe that they are likely to make positive changes are more likely to do so than those who feel powerless or helpless to change their behaviour. It is particularly helpful to elicit self-efficacy statements from individuals as they are likely to believe what they hear themselves say, and belief in the possibility of change is an important motivator.

45.3 Linking to Stage of Behavioral Change

Brief interventions are structured and personalized discussions which aim to motivate clients to undertake positive behavior change. The transtheoretical model of behavior change developed by Prochaska and DiClemente presents behavioral change as occurring in distinct stages [27]. The aim of intervention is to support people to move through the stages of change. While a person's stage of change may not be formally measured or assessed, interventions that are tailored to the likely stage of change may be more effective.

The transtheoretical model of behavior change proposes several stages (pre-contemplation, contemplation, preparation, action, and maintenance). The model identifies a number of stages which are commonly experienced during the process of adopting a new behavior. Progression is not necessarily linear, and the time spent in each stage is highly variable.

People in the *pre-contemplation* stage generally do not link their substance use to any problems. Commonly, they are unconcerned by their drug use or related consequences and are not yet considering a change or are unwilling to change. Motivational interviewing strategies are appropriate for this stage of change. Such strategies involve exploration of both the pros and cons of substance use and development of discrepancies between a client's current behaviors and future ambitions/goals.

In the *contemplation* stage, the person acknowledges concerns and is considering the possibility of change but is still ambivalent or uncertain about that change. Motivational interviewing is again appropriate, with the aim of normalizing feelings of ambivalence and helping the client to move toward change.

In the *preparation* stage, the balance has shifted. Change is seen as worthwhile, and the person is gaining confidence in their capacity to change. The person is preparing to take action by gathering information that will assist them. The negative consequences of drug use are now seen as outweighing the benefits. The focus should be on helping the person consider barriers to change and ways to overcome those barriers, exploring options, eliciting from the person what has worked in the past for them or others, and assisting the client to enlist social support.

In the *action* stage, the person is actively taking steps to change but has not yet reached a stable state. They are implementing strategies to change their drug use pattern. It is important to support their engagement in change, reinforce the importance of remaining committed, and help to find new reinforcers of positive change, including assessment of the strength of family and other social supports.

In the *maintenance* stage, the person has succeeded in stopping their harmful drug use and is concentrating on continuing that progress. The focus in this stage is on building resilience, self-monitoring, identifying high-risk situations, and developing appropriate coping skills. It is important to affirm the person's resolve and self-efficacy and review long-term goals. It is helpful to encourage them to articulate the positive reasons for maintaining change to reinforce their decisions and reaffirm relapse prevention approaches.

A *relapse* (or lapse – a one off or short period) is a return to the old behavior that was the focus of change. Most people who try to make changes in their substance use behavior may relapse to substance use, at least for a time. This should be viewed as a learning process rather than failure. Few people change on the first attempt, and relapse is an opportunity to help people review their action plan. A review should examine time frames, what strategies did actually work, and whether the strategies used were realistic. For many people, changing their substance use gets easier each time they try until they are eventually successful.

Most people identified opportunistically for brief interventions aimed at illicit drug use are likely to be mainly in the pre-contemplation stage, with some in contemplation. The aim of brief interventions for people engaged in the least amount of change is to help them understand that their drug use is putting them at risk and to develop ambivalence about their drug use that would then lead to them preparing to take action to change their drug use.

The principles outlined here can also be adapted for people preparing for change but who lack the confidence and knowledge and for clients who are in the action stage.

45.4 Assessing Level of Risk

A wide variety of standardized questionnaires and biological tests have been developed to detect psychoactive substance use [3]. Biological tests are generally not suitable for routine screening prior to brief intervention as they are costly, invasive, can only detect recent use, and results are not available immediately. A major shortcoming of biological screening is that biological tests fail to assess a person's pattern of use and level of risk of harm or dependence and so do not provide a foundation for brief intervention. Hence, assessing a person's level of risk to inform a brief intervention will generally involve use of a screening instrument.

Many of the available screening instruments are specific to alcohol (e.g., AUDIT) or tobacco (e.g., Fagerstrom). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was developed under the auspices of the World Health Organization (WHO) by an international group of specialist addiction researchers and clinicians in response to the overwhelming public health burden associated with psychoactive substance use worldwide [19] and offers the advantage of screening for alcohol, tobacco, illicit drugs, and the unsanctioned use of pharmaceutical drugs.

Other characteristics that should be considered when selecting a screening instrument to assess risk prior to a brief intervention include —

- Acceptability: The instrument should be acceptable to both health workers and those being screened in terms of safety, simplicity, and ease and time of administration.
- Reliability/repeatability: The instrument must give consistent results when repeated more than once on the same individual under the same conditions. It should also give consistent results when administered by different people (inter-rater reliability).
- Validity: The instrument must accurately measure what it purports to measure (construct validity) and accurately separate those who have the condition from those who do not (discriminant validity). Discriminant validity has two components, sensitivity and specificity.
  - Sensitivity is the ability of the instrument to identify correctly those who have the condition, that is, "true positives."
  - Specificity is the ability of the instrument to identify correctly those who do not have the condition, that is, "true negatives."

  - In the context of brief interventions for illicit drug use, sensitivity should be emphasized over specificity so as to minimize the possibility of not identifying people at risk of harm from their drug use.
- Cost which will depend on whether the instrument is self-administered or administered by a health worker or clinician, how long it takes, and what special training (if any) is required.
- Non-judgemental and non-confrontational: This is important so that people feel able to report their drug use.
- Culturally neutral: A culturally neutral screening test will have wider acceptability with different populations both nationally and internationally.

45.4.1 The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

The ASSIST V3.1 (Appendix A) is an eight-item questionnaire designed to be either self-administered or by a health worker. For most people, the ASSIST can be completed in about five minutes and can be incorporated into routine consultation. The ASSIST is available as a web-based version which can be self-administered or administered by a health worker and as a smartphone/tablet application for self-administration (https://assistportal.com.au/).

The ASSIST has been through rigorous scientific testing to ensure that it is a reliable and valid instrument in international settings and able to link into a brief intervention [20]. The ASSIST has shown good cross-cultural neutrality, has been validated for use in adult populations (between 18 and 60 years of age), and is appropriate for use with adolescents.

The ASSIST obtains information about lifetime and recent use (last three months) of the following substances:

- Tobacco
- Alcohol
- Cannabis
- Cocaine
- Amphetamine-type stimulants (ATS)
- Inhalants
- Sedatives and sleeping pills (benzodiazepines)
- Hallucinogens
- Inhalants
- Opioids
- "Other drugs"

"Other" drugs are those that do not readily belong in any of the other drug categories. This could include Kava, Datura, Khat, Kratom, gamma hydroxybutyrate (GHB), and any other drugs of concern in the local population. There may be other substances native to some regions which don't easily fit into any of the other substance classes and need to be put into this "other drugs" category.

The ASSIST can identify a range of issues related to substance use including the risks associated with acute intoxication, regular use, dependent or "high risk," use and injecting behavior. Taken together, these questions provide an indication of the level of risk associated with the person's substance use and whether use is hazardous and likely to be causing harm (now or in the future) if use continues.

The score obtained for each substance falls into a "low," "moderate," or "high' risk category. Scores in the mid-range on the ASSIST are likely to indicate hazardous or harmful substance use ("moderate risk"), and higher scores are likely to indicate substance dependence ("high risk"). The level of risk determines the most appropriate intervention for that level of use ("no treatment," "brief intervention," or "referral to specialist assessment and treatment," respectively).

45.4.2 Linking Assessed Risk to a Brief Intervention

The ASSIST-linked Brief Intervention was specifically designed for people who are at *moderate risk* from their substance use, according to their ASSIST scores, to provide them with a structured appropriate brief intervention depending on their stage of change, that is, people who are *not* dependent, but are using substances in a risky, hazardous, or harmful way that may be creating health, social, legal, occupational, or financial

problems for the person or has the potential to create those problems should the substance use continue.

The ASSIST-linked Brief Intervention is based on the FRAMES model and motivational interviewing techniques. It follows ten main steps:

1. *Asking* if they are interested in seeing their questionnaire scores
2. Providing personalized *Feedback* to clients about their scores using the ASSIST Feedback Report Card
3. Giving *Advice* about how to reduce risk associated with substance use
4. Allowing people to take ultimate *Responsibility* for their choices
5. Asking how *Concerned* they are by their scores
6. Weighing up the *Good things* about using the substance against the
7. *Less good things* about using the substance
8. *Summarizing and Reflecting* on statements about their substance use with emphasis on the less good things
9. Asking how *Concerned* they are by the less good things
10. Giving clients *Take-home materials* to bolster the brief intervention

The suggested ten-step ASSIST-linked Brief Intervention is particularly appropriate for clients who are in the contemplation or pre-contemplation stage of change.

While the majority of people screened in primary care settings are likely to be at low to moderate risk of substance related harm, a proportion will be at high risk and may have a substance use disorder (including dependence). Brief interventions are not intended as a stand-alone intervention for people who are dependent or at "high risk" from their substance use. However, a brief intervention should be used to encourage such people to accept referral to specialized drug and alcohol assessment and treatment, either within a primary care setting or at a specialized alcohol and drug treatment agency.

45.4.3 The ASSIST-Lite

Translating the ASSIST into routine use in health services has proved problematic. Substance use disorders are not systematically screened, diagnosed, or treated in general medical settings, and time constraints on staff appear to be the main barrier [1]. In 2008, an American Preventive Service Task Force called for a research and development initiative to *provide questionnaires short enough to be potentially useful in the practice setting with acceptable accuracy and reliability*. The ASSIST-Lite was developed to address this need and is ideally suited for opportunistic and routine screening for substance use in primary, general medical, and welfare service settings [1].

The ASSIST-Lite is a short form of the ASSIST. The ASSIST-Lite screens for risk of harm from substance use, specifically, tobacco, alcohol, cannabis, stimulants including amphetamine-type stimulants, and cocaine, sedatives, and opioids including prescription opioids. There is also the opportunity to ask about any other psychoactive substance not listed. The ASSIST-Lite identifies which substances are of concern and gives an indication of the severity of substance-related risks and harms. Consequently, it can form a valuable part of a comprehensive health assessment.

The ASSIST-Lite risk score refers to risk of harm from current patterns of substance use. Harm is broadly defined and includes health, legal, social, financial, work, and family issues. The risk of harm score for each substance helps to initiate and frame a brief discussion with individuals about their substance use. Like the full ASSIST, the score obtained from the ASSIST-Lite for each substance falls into a "low," "moderate," or "high' risk category which determines the most appropriate linked brief intervention for that level of use.

A copy of the ASSIST-Lite is included in Appendix B. The ASSIST-Lite is available as a web-based platform and as a smartphone/tablet application for self-completion (available at https://assistportal.com.au/).

The ASSIST and ASSIST-Lite can be readministered after three months to monitor progress and changes over time. Interventions can be stepped up if the score has increased, and the Brief Intervention can be used to intervene early if it appears that other issues are developing.

45.5 Settings for Brief Intervention

Primary care settings such as general practice, community health centers, and other local health services are the first point of contact with the health system for most people. Primary care provides a wide range of services including health promotion, prevention and screening, early intervention, treatment, and management of a variety of chronic health conditions. This includes preventive activities such as immunization, as well as screening and early intervention for high blood pressure, obesity, high cholesterol, and other lifestyle risk factors. Screening and brief intervention for illicit drug use fit well with this role.

In the developed world, 85% of the population visit a primary healthcare clinician such as a general practitioner at least once a year [10], and there is evidence that people who have substance use-related problems have more frequent consultations [5, 17]. Widespread screening in primary care settings increases the likelihood of identifying and intervening with people who use illicit drugs. As a result of their position in the healthcare system, primary care clinicians are likely to see a wide cross-section of the community and hence are more likely to see people at an earlier stage in their drug use when risk and harm are lower. They have a unique opportunity to provide comprehensive, continuing, and person-centered healthcare as well as to link those in need to specialist services when required.

Primary care workers often have an ongoing relationship with clients of their service which enables them to develop rapport and demonstrate genuine concern for their welfare. People expect their primary care clinician to be involved in all aspects of their health and are likely to feel more comfortable about discussing sensitive issues such as drug use with someone they know and trust. The ongoing nature of the relationship means that such discussions can be spread out over time and form part of a number of consultations. Specialist drug and alcohol services may be associated with stigma which can deter some people from seeking assistance for substance use problems. Primary healthcare settings are not associated with this stigma making people more likely to attend a primary care service.

People who use alcohol and other drugs are also over represented in hospital emergency care presentations [14]. Australian research found that while alcohol is the most common substance used by intoxicated people who attend the emergency department, the contribution of other drugs is substantial [15].

Attendance at an emergency department is often a time of crisis when patients may be more willing to accept help and advice [8, 13, 33]. A brief intervention delivered in the context of presentation to a hospital emergency department can be used to help the patient gain insight into the consequences of their substance use and may be a motivating factor to encourage behavioral change [8] or engagement in structured treatment. Interventions in the emergency setting would have a public health aim [7], with those presenting in emergency department comprising a higher-risk population [28].

Providing brief interventions for substance use to people presenting to hospital emergency departments has the potential to facilitate management and discharge of some patients and may reduce the likelihood of repeat presentations [2, 9].

Screening and brief intervention can also be undertaken in specialist medical services such as mental health services and sexual health services where substance use is more prevalent than in the general population. A number of services worldwide have embedded the ASSIST and linked brief intervention into their routine practice demonstrating the feasibility of implementing brief interventions for illicit drug use in a wide range of contexts.

Appendix A: WHO - ASSIST V3.1

WHO - ASSIST V3.1

CLINICIAN NAME		**CLINIC**	
CLIENT ID OR NAME		**DATE**	

INTRODUCTION (Please read to client. Can be adapted for local circumstances)

The following questions ask about your experience of using alcohol, tobacco products and other drugs across your lifetime and in the past three months. These substances can be smoked, swallowed, snorted, inhaled or injected (show responsecard).

Some of the substances listed may be prescribed by a doctor (like amphetamines, sedatives, pain medications). For this interview, we will not record medications that are used as prescribed by your doctor. However, if you have taken such medications for reasons other than prescription, or taken them more frequently, at higher doses than prescribed or in ways in which it wasn't intended, please let me know.

While we are also interested in knowing about your use of various illicit drugs, please be assured that information on such use will be treated as strictly confidential.

NOTE: BEFORE ASKING QUESTIONS, GIVE ASSIST RESPONSE CARD TO CLIENT

Question 1 (please mark the response for each category of substance)

In your life, which of the following substances have you ever used? *(NON-MEDICAL USE ONLY)*	**No**	**Yes**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	☐	☐
b. Alcoholic beverages (beer, wine, spirits, etc.)	☐	☐
c. Cannabis (marijuana, pot, grass, hash, etc.)	☐	☐
d. Cocaine (coke, crack, etc.)	☐	☐
e. Amphetamine type stimulants (speed, meth, ecstasy, etc.)	☐	☐
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	☐	☐
g. Sedatives or Sleeping Pills (Diazepam, Alprazolam, Flunitrazepam, Midazolam etc.)	☐	☐
h. Hallucinogens (LSD, acid, mushrooms, trips, Ketamine, etc.)	☐	☐
i. Opioids (heroin, morphine, methadone, Buprenorphine, codeine, etc.)	☐	☐
j. Other - specify:	☐	☐

Probe if all answers are negative:
"Not even when you were in school?"

If "No" to all items, stop interview.

If "Yes" to any of these items, ask Question 2 for each substance ever used.

Question 2

In the past three months, how often have you used the substances you mentioned *(FIRST DRUG, SECOND DRUG, ETC)*?	**Never**	**Once or Twice**	**Monthly**	**Weekly**	**Daily or Almost Daily**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	2	3	4	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	2	3	4	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
d. Cocaine (coke, crack, etc.)	0	2	3	4	6
e. Amphetamine type stimulants (speed, meth, ecstasy, etc.)	0	2	3	4	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	2	3	4	6
g. Sedatives or Sleeping Pills (Diazepam, Alprazolam, Flunitrazepam, Midazolam etc.)	0	2	3	4	6
h. Hallucinogens (LSD, acid, mushrooms, trips, Ketamine, etc.)	0	2	3	4	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
j. Other - specify:	0	2	3	4	6

If "Never" to all items in Question 2, skip to Question 6.

If any substances in Question 2 were used in the previous three months, continue with Questions 3, 4 & 5 for each substance used.

Question 3

During the past three months, how often have you had a strong desire or urge to use *(FIRST DRUG, SECOND DRUG, ETC)*?	**Never**	**Once or Twice**	**Monthly**	**Weekly**	**Daily or Almost Daily**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3	4	5	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3	4	5	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3	4	5	6
d. Cocaine (coke, crack, etc.)	0	3	4	5	6
e. Amphetamine type stimulants (speed, meth, ecstasy, etc.)	0	3	4	5	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3	4	5	6
g. Sedatives or Sleeping Pills (Diazepam, Alprazolam, Flunitrazepam, Midazolam etc.)	0	3	4	5	6
h. Hallucinogens (LSD, acid, mushrooms, trips, Ketamine, etc.)	0	3	4	5	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3	4	5	6
j. Other - specify:	0	3	4	5	6

Question 4

During the past three months, how often has your use of *(FIRST DRUG, SECOND DRUG, ETC)* led to health, social, legal or financial problems?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	4	5	6	7
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	4	5	6	7
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	4	5	6	7
d. Cocaine (coke, crack, etc.)	0	4	5	6	7
e. Amphetamine type stimulants (speed, meth, ecstasy, etc.)	0	4	5	6	7
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	4	5	6	7
g. Sedatives or Sleeping Pills (Diazepam, Alprazolam, Flunitrazepam, Midazolam etc.)	0	4	5	6	7
h. Hallucinogens (LSD, acid, mushrooms, trips, Ketamine, etc.)	0	4	5	6	7
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	4	5	6	7
j. Other - specify:	0	4	5	6	7

Question 5

During the past three months, how often have you failed to do what was normally expected of you because of your use of *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products					
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	5	6	7	8
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	5	6	7	8
d. Cocaine (coke, crack, etc.)	0	5	6	7	8
e. Amphetamine type stimulants (speed, meth, ecstasy, etc.)	0	5	6	7	8
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	5	6	7	8
g. Sedatives or Sleeping Pills (Diazepam, Alprazolam, Flunitrazepam, Midazolam etc.)	0	5	6	7	8
h. Hallucinogens (LSD, acid, mushrooms, trips, Ketamine, etc.)	0	5	6	7	8
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	5	6	7	8
j. Other - specify:	0	5	6	7	8

Ask Questions 6 & 7 for all substances ever used (i.e. those endorsed in Question 1)

Question 6

Has a friend or relative or anyone else ever expressed concern about your use of *(FIRST DRUG, SECOND DRUG, ETC.)?*	**No, Never**	**Yes, in the past 3 months**	**Yes, but not in the past 3 months**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, meth, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Diazepam, Alprazolam, Flunitrazepam, Midazolam etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, trips, Ketamine, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 7

Have you ever tried to cut down onusing *(FIRST DRUG, SECOND DRUG, ETC.)* but failed?	**No, Never**	**Yes, in the past 3 months**	**Yes, but not in the past 3 months**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, meth, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Diazepam, Alprazolam, Flunitrazepam, Midazolam etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, trips, Ketamine, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 8 (please markthe response)

	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
Have you ever used any drug by injection? ***(NON-MEDICAL USE ONLY)***	☐	☐	☐

IMPORTANT NOTE:

Clients who have injected drugs in the last 3 months should be asked about their pattern of injecting during this period, to determine their risk levels and the best course of intervention.

PATTERN OF INJECTING	INTERVENTION GUIDELINES
4 days per month, on average, over the last 3 months or less	**Brief Intervention including the "Risks of Injecting" card**
More than 4 days per month, on average, over the last 3 months	**Further assessment and more intensive treatment***

HOW TO CALCULATE A SPECIFIC SUBSTANCE INVOLVEMENT SCORE.

For each substance (labelled a. to j.) add up the scores received for questions 2 through 7 inclusive. Do not include the results from either Q1 or Q8 in this score. For example, a score for cannabis would be calculated r example, a score for cannabis would be calculated as: **Q2c + Q3c + Q4c + Q5c + Q6c + Q7c**

Note that Q5 for tobacco is not coded, and is calculated as: **Q2a + Q3a + Q4a + Q6a + Q7a**

THE TYPE OF INTERVENTION IS DETERMINED BYTHE PATIENT'S SPECIFIC SUBSTANCEINVOLVEMENT SCORE

	Record specific substance score	no intervention	receive brief intervention	more intensive treatment *
a. tobacco		0 - 3	4 - 26	27+
b. alcohol		0 - 10	11 - 26	27+
c. cannabis		0 - 3	4 - 26	27+
d. cocaine		0 - 3	4 - 26	27+
e. amphetamine		0 - 3	4 - 26	27+
f. inhalants		0 - 3	4 - 26	27+
g. sedatives		0 - 3	4 - 26	27+
h. hallucinogens		0 - 3	4 - 26	27+
i. opioids		0 - 3	4 - 26	27+
j. other drugs		0 - 3	4 - 26	27+

Now use ASSIST FEEDBACK REPORT CARD to give client brief intervention.

Appendix B: ASSIST-Lite

Alcohol, Smoking and Substance Involvement Screening Test
ASSIST-Lite

Instructions

The questions ask about psychoactive substance use in the PAST 3 MONTHS ONLY.

Ask about each substance in order and only proceed to the supplementary questions if the person has used that substance.

On completion of all the questions, count the number of "yes" responses to obtain a score for each substance, and mark the risk category.

Provide a brief intervention relevant to the risk category.

In the past 3 months	YES	NO
1. Did you smoke a cigarette containing tobacco?	☐	☐
1a. Did you usually smoke more than 10 cigarettes each day?	☐	☐
1b. Did you usually smoke within 30 minutes after waking?	☐	☐
Score for tobacco (count "yes" answers)	☐	
Risk category: ☐ Low (0) ☐ Moderate (1 or 2) ☐ High (3)		
2. Did you have a drink containing alcohol?	☐	☐
2a. On any occasion, did you drink more than 4 standard drinks of alcohol?	☐	☐
2b. Have you tried and failed to control, cut down or stop drinking?	☐	☐
2c. Has anyone expressed concern about your drinking?	☐	☐
Score for alcohol (count "yes" answers)	☐	
Risk category: ☐ Low (0 or 1) ☐ Moderate (2) ☐ High (3 or 4)		
3. Did you use cannabis?	☐	☐
3a. Have you had a strong desire or urge to use cannabis at least once a week or more often?	☐	☐
3b. Has anyone expressed concern about your use of cannabis?	☐	☐
Score for cannabis (count "yes" answers)	☐	
Risk category: ☐ Low (0) ☐ Moderate (1 or 2) ☐ High (3)		
4. Did you use an amphetamine-type stimulant, or cocaine, or a stimulant medication not as prescribed?	☐	☐
4a. Did you use a stimulant at least once each week or more often?	☐	☐
4b. Has anyone expressed concern about your use of a stimulant?	☐	☐
Score for stimulants (count "yes" answers)	☐	
Risk category: ☐ Low (0) ☐ Moderate (1 or 2) ☐ High (3)		
5. Did you use a sedative or sleeping medication not as prescribed?	☐	☐
5a. Have you had a strong desire or urge to use a sedative or sleeping medication at least once a week or more often?	☐	☐
5b. Has anyone expressed concern about your use of a sedative or sleeping medication?	☐	☐
Score for sedatives (count "yes" answers)	☐	
Risk category: ☐ Low (0) ☐ Moderate (1 or 2) ☐ High (3)		
6. Did you use a street opioid (e.g. heroin) or an opioid-containing medication not as prescribed?	☐	☐
6a. Have you tried and failed to control, cut down or stop using an opioid?	☐	☐
6b. Has anyone expressed concern about your use of an opioid?	☐	☐
Score for opioids (count "yes" answers)	☐	
Risk category: ☐ Low (0) ☐ Moderate (1 or 2) ☐ High (3)		
7. Did you use any other psychoactive substances?	☐	☐
If yes, what did you take?		
(Not scored, but prompts further assessment)		

Rapid guide to a Brief Intervention

Low risk: General health advice and encourage not to increase use.

Moderate risk: Provide a brief intervention using the FRAMES Model and offer take home information

High risk: Provide a brief intervention using the FRAMES Model and encourage further assessment by a specialist drug and alochol service. Facilitate referral and provide take home information.

Note: FRAMES - Feedback, Responsibility, Advice, Menu of options, Empathy, Self-efficacy.

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46 Screening and Assessment for People with Substance Use Disorders: A Focus on Developed Countries

Brian Rush

Contents

Abstract

This chapter outlines the rationale for a more proactive concerted effort for screening and assessment of at-risk consumption, substance use disorders, and related comorbidity, with a special focus on a broad system approach that engages multiple services and sectors alongside specialist programs and providers. This aspect of clinical practice as well as treatment system development should be a priority given the strong evidence concerning under-detection in routine practice and the excellent performance of a host of screening and assessment tools and processes. When used for clinical decision making, best practice calls for a staged approach to maximize efficiency of the overall screening and assessment process and ensure a link to measurement-based care and subsequent outcome monitoring. Grounded in a conceptual framework that articulates this staged approach, several specific tools are highlighted. The essential principle for service and system planning is that these tools must be tailored to the setting and target population

B. Rush (✉)
Centre for Addiction and Mental Health, Toronto, ON, Canada
e-mail: brian.rush@camh.ca

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for which they are being implemented. Whether working in generic settings such as primary care or specialized treatment settings, a collaborative approach, drawing upon multidisciplinary, multi-provider, and multi-sectoral expertise, is needed across the stages of screening and assessment. This approach also needs to be accompanied by a collaborative response protocol for level-of-care placement inclusive of adaptive treatment and support for smooth transitions. There are many challenges to implementing and evaluating the effectiveness of screening and assessment tools and processes, and more research is needed on the facilitators and barriers to implementation at both the level of the individual service provider and within collaborative, shared care arrangements.

Keywords

Screening · Assessment · Outcome monitoring
Collaboration · Systems approach

46.1 Introduction

The purpose of this chapter is to provide an overview of screening and assessment tools and processes in the context of middle- to high-income (i.e., "developed") countries. In this context, there are important similarities but also differences in the many other books and practice guidelines synthesizing this work from various disciplinary perspectives (e.g., psychiatric [26], psychotherapy [35], behavioral [86], psychosocial [85], or social work perspectives [42]). Like previous work, there is an acknowledgement of important principles and practices that may be seen as universal in nature, for example, the need for an evidence-based approach grounded on a comprehensive bio-psycho-social-spiritual model; sensitivity to individual differences in culture, diversity, and developmental age; the critical importance of empathy, listening skills, and therapeutic alliance; and the appropriate involvement of family and significant others. These aspects are critical elements of the interface between clinician and client. Such similarities notwithstanding, this chapter emphasizes more of a systems approach, recognizing that in so-called developed countries, the greater resource base offers an opportunity for a collaborative approach to engaging people in need, identifying and assessing their strengths and problem areas, offering a wide range of service options along a continuum of care, and adapting services based on measurement of outcomes. This collaborative approach may involve more than one professional, organization, and service delivery sector – a scenario that professionals working in low-income countries may only dream about in terms of collegial support for their work. Further, many screening and assessment tools that complement clinical skills and experience are not available and/or validated in many low-income countries. This is another advantage conferred on moderate- to high-income countries that have capacity for research and development.

In short, this chapter acknowledges screening and assessment as a core component of a broader "whole systems," public health approach to treatment and support for substance use, addictions, and co-occurring conditions [5, 76]. Given this foundation, this chapter is aimed at people working from a range of professional disciplines, for example, psychology, social work, nursing, family practice, psychiatry, and other medical and nonmedical specialists. Thus, some readers working from a particular disciplinary perspective may benefit from additional, reference texts such as those noted above.

Although there are many important intercountry differences in the capacity for screening and assessment, it is also important to recognize that many "developed" countries are far from homogenous in terms of community need and capacity to respond. Taking Canada as but one example, there is a tremendous range within the country in terms of rurality/urbanicity, multiculturalism, Indigenous versus non-Indigenous populations, and substance use patterns and related harms. These and many other factors all influence beliefs about substance use and addiction, the perceived value of treatment, help-seeking behavior, and no doubt cultural interpretation of concepts such as "assessment" or

"treatment." There is also wide variation in availability and accessibility of options for treatment and support, an obvious factor critical to screening and assessment considerations.

46.2 Rationale for Screening and Assessment

It is widely recognized that only a small minority of people with mental health and substance use-related concerns seek help from either community professionals or less formal services and that, among that do, the largest proportion will access a primary healthcare provider or other health and social service professional [87, 88]. Although many people with mental health and substance use- related problems, or who are at risk of such problems, are in contact with various service providers, these risks or problems are often not identified [62]. These contacts are missed opportunities for offering advice, more extended consultation, or referral for additional support. This highlights the importance of broadening the base of treatment through a system-wide, public health response [5] with generic community services, including primary care, hospitals, social services, educational, and justice-related services, being proactive in asking questions about mental health, substance use, and addiction-related issues. The aim is to identify concerns, increase opportunities for early identification, provide access to more in-depth assessment and other services and supports, and link the person to more specialized services when needed. For people with low- to moderate risk, or less severe mental health and substance use problems, engaging in proactive, opportunistic screening and on-site, brief intervention is intended to reduce risks and harms. For those with higher risk, or more severe and complex problems, opportunistic screening is intended to open a pathway to more comprehensive assessment, an appropriate treatment and support response, and improved health outcomes. Savings are also anticipated in future medical-, social-, and criminal justice-related costs.

Service providers differ in their attitudes and beliefs about the role of systematic screening and assessment to support their work with people seeking help: beliefs that reflect personal experience, training, and organizational context. Some professionals rely on their training and experience to guide problem identification and client-focused decisions. Some may have philosophical and ethical concerns related to asking about mental health and substance use issues, considering it to be intrusive or possibly harmful due to potential stigmatization and labeling (e.g., in educational settings). Some may doubt the increased efficacy and efficiency of these tools over their routine decision-making processes, while others may be reluctant to engage in consistent, structured screening due to concerns that they do not have the expertise or resources to respond appropriately. Research, however, suggests that critically important mental health and substance use concerns are missed when clinicians do not use structured tools and processes to prompt thorough questioning [93].

Given the high level of heterogeneity in demographic, cultural, psychosocial, and clinical characteristics of people needing treatment and support for substance use problems, it is axiomatic that no approach will meet everyone's needs. This calls for a thorough investigation of needs and strengths and a co-constructed matching of this profile to available service options across a continuum of care. The focus on screening and assessment is intended to increase the efficiency of client intake and engagement, improve individual treatment outcomes, and minimize service delivery costs across the system as a whole [40]. Best practices for treatment and support of people with co-occurring disorders who are already engaged with specialized services also call for more proactive screening of these co-occurring problem areas [71]. This includes screening for mental health problems among people seeking substance use treatment, as well as screening for high-risk/hazardous substance use and addiction-related problems among people seeking mental health treatment and support [70].

Research also shows that screening is most effective when combined with other staged investigations and matched therapeutic and motivation-based interventions [32]. Collaborative approaches can serve to mitigate the reluctance of profession-

als to use formal screening techniques by bringing together complementary services and resources, ultimately building capacity for improved service to individuals who come to them for assistance.

46.3 Collaborative Models for Screening and Assessment

Many service providers external to the specialized mental health and substance use treatment sector do not have the expertise and resources to identify mental health, substance use, and co-occurring concerns. Further, most specialist service providers do not have the resources to respond to the breadth of complex issues and problems that are identified through many screening tools. Collaborative care models provide the opportunity for various providers to bring together their collective strengths and capabilities to construct a system whereby individuals are screened and can receive required services in a seamless manner [2]. As such, screening processes must be connected to well-articulated response protocols in order to be useful and effective. These protocols should describe required actions among all partners based on positive results on screening tools, including recommendations for more in-depth screening and assessment, and follow-up consultation and referrals.

There are various models of collaboration that can incorporate screening, assessment, and referral protocols, and these include

- Single-site assessment process incorporating multidisciplinary teams – Single assessment processes reduce the number of assessments between mental health, addictions, and various health and social service professionals in order to enable a seamless care process [61].
- Integrated treatment and support for people with co-occurring disorders, whereby competencies and processes related to screening and assessment are key criteria for defining integrated programs as "concurrent disorder capable" [54].
- Centralized access point to care – This approach aims to reduce the number of points of entry of care for users, in some cases to a single-access point in order to reduce the number of professionals and organizations prospective to whom clients and their families have to tell their story [74].
- Network model with distributed common tools – Rather than a single point of access, this approach uses common screening and assessment tools across a network of providers and with electronic sharing of the information and joint treatment and support planning.
- Screening, brief intervention, and referral to treatment (SBIRT) – This approach requires health and social service professionals to use brief screening instruments to identify people at risk of, or experiencing, mental health and/or substance use problems and who then receive brief intervention on treatment on-site or who are proactively linked to specialist providers depending on severity [7].
- Co-located substance use specialists in generic settings – This involves either assigning/hiring a substance use worker to perform in-house screening and brief assessment or co-locating a worker from a specialized substance use service into the nonspecialized setting, for example, an emergency department [13]

46.4 Best Practices for Screening and Assessment

Through a treatment system lens, there are many disciplines and service delivery settings potentially involved in the screening and assessment process. An individual situation may require input from a medical, psychiatric, nursing, psychological, psychosocial rehabilitation, social work, and/or spiritual perspective. A collaborative approach to screening and assessment requires mutual interprofessional respect for the unique contributions that each has to offer to a client- and family-centered approach. The uniqueness of the various perspectives notwithstanding common principles include

- A "whole-person perspective" on strengths and needs
- Close engagement of family and other loved ones, while respecting client's preferences for privacy of information

– A sensitivity to diversity and related health equity issues
– A strong emphasis on creating a welcoming, motivation-based, therapeutic interface
– Adherence to an evidence-based approach

An evidence-based approach encompasses several factors including clinician expertise, exploration of person characteristics and contextual variables using psychometrically sound tools, critical thinking skills, personal and collateral input, and knowledge of evidence-informed interventions [42]. Screening and assessment must be seen as a process that continues over time as more information is shared and therapeutic relationships strengthen. A collaborative, longitudinal approach is particularly critical for the assessment of complex, co-occurring disorders given the need to disentangle etiological sequencing (e.g., depressive symptoms induced by heavy alcohol use). In a collaborative approach to screening and assessment, the sharing of information across service providers is also critical. If possible, this should be done through e-health technology but minimally through telephone, email, or written communication.

Best practice entails a staged approach that links screening, assessment, and outcome monitoring with a family of tools and related decision-making processes that are developmentally appropriate and delivered through a diversity-based approach to ensure equitable access and subsequent assessment and treatment. This approach is articulated in the conceptual framework for screening and assessment described below (see Fig. 46.1). The framework can assist in choosing the "right" tools and using them with the "right" people at the "right" time. It is recommended that in order to effectively apply the framework, it be considered in the context of a multi-sectoral continuum of care and the specific collaborative models and service delivery settings under consideration. Thus, application of the framework is very context-specific. For example,

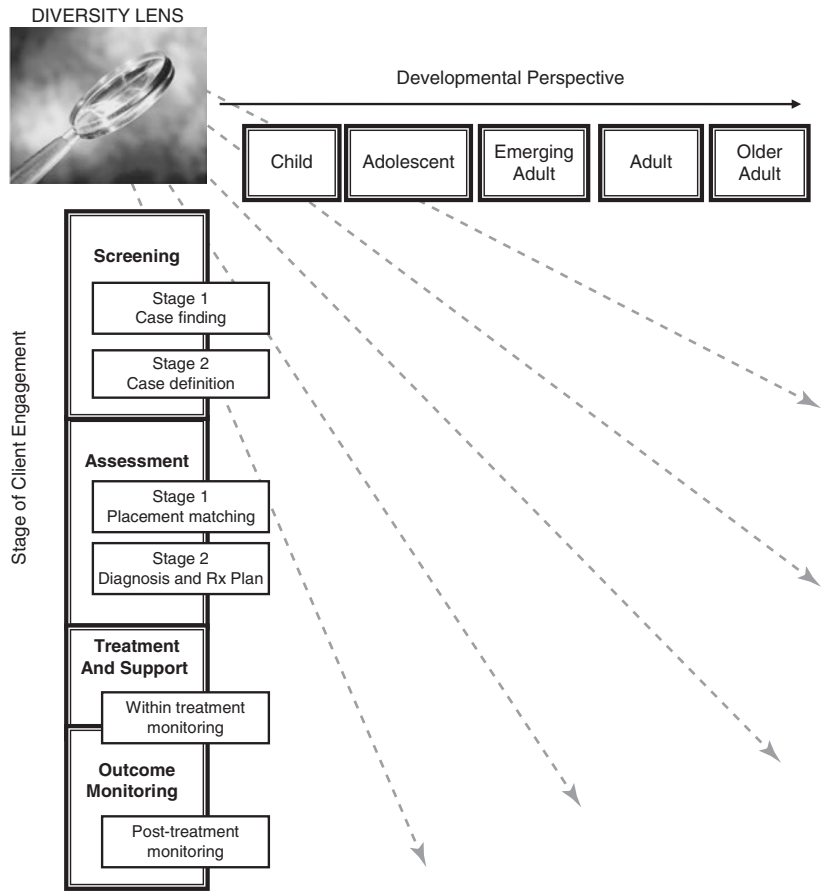

Fig. 46.1 Conceptual framework for screening and assessment. (Adapted from Rush and Castel [70])

the required level of treatment and support may not be readily available due to waiting time or the lack of service availability within the jurisdiction or via realistic distance/travel time. Collaborative arrangements with existing services may be required in order to offer the best service available at that point in time and to maintain client engagement. In the case of people with co-occurring disorders, provision of mental health services will often reduce substance use and ameliorate substance use-related problems [27]. Evidence reviewed by these same authors also suggests the reverse to be true for the provision of substance use treatment and consequent reduction of many mental health-related symptoms and improved functioning. Parikh [67] discusses several evidence-based mental health interventions that can be delivered in substance use services.

In short, it is important to work with local resources as best as possible while advocating for additional resources with a need-based planning model [75]. Alternative therapist-assisted and/or self-management tools delivered through the Internet or mobile-based technology are also increasingly available.

46.4.1 Diversity Lens

Every individual has a unique and complex set of strengths, circumstances, and challenges shaped in large part by the social determinants of health and including, for example, gender, sexual orientation, culture, ethnicity, social location, geography, political views, and religious/spiritual affiliation. As such, each component of this framework must be considered through a "diversity lens" when implementing tools, interpreting the results, and providing feedback to individuals in the context of day-to-day service delivery.

46.4.2 Developmental Perspective

The horizontal axis of the framework articulates the developmental trajectory across the life span as a frame of reference to also guide the choice of screening and assessment tools and processes. At each stage of this trajectory, there are specific developmental tasks and challenges that an individual must navigate, further complicated by the diversity lens noted above. Importantly, most tools are validated for use with groups of individuals defined by age rather than stage. For example, some emerging adults in the 18–24 range may be well-served by screening and assessment with adult measures and being treated in the adult sector, while others with adolescent measures and corresponding services in the youth sector. Therefore, tools and services that can be applied differentially to match developmental stage, rather than being bound by strict age boundaries, are preferred. The GAIN-Short Screener [21] is appropriate for use from age 10 to older adulthood and is, therefore, particularly helpful for collaborative, system-level application [52].

Developmental stage and consideration of service delivery settings that may be unique to specific stages are also important considerations for determining when during the engagement, treatment, and support process to ask different types of screening questions. For example, for young people being seen on an outreach basis in their school or street environment, it would not be appropriate to begin asking screening questions about sensitive topics such as high-risk sexual behavior, trauma experiences, or illegal behavior before a trusting relationship has been initiated. This will also be the case for many other settings and populations, especially those impacted by trauma. Interpretation and action in response to screening results also need to be developmentally informed. Considerable attention has been paid to this issue with respect to children, adolescents, and adults, but much attention has gone to further articulating the role of developmental stages in service transitions for transitional-aged youth and older adults.

46.4.3 Screening

In the context of substance use and addictions, and the broader field of mental health, screening is a relatively brief process designed to identify individuals who are at risk of having particular problems or diagnosable disorders that warrant

immediate attention, intervention, or more comprehensive review. The organizational context and population served will dictate whether screening will start at Stage 1 or 2, as further described below.

46.4.3.1 Stage 1 Screening: Risk Assessment/Case Finding

This stage of screening involves the use of psychometrically sound, typically self-report, questionnaires that cast a fairly wide net to determine the possibility of a particular problem area or mental/addictive disorder and which requires further investigation. In the substance use area, Stage 1 tools may also focus on the level of risk associated with alcohol and drug use per se, the AUDIT perhaps being the best known option for alcohol [6] and the ASSIST for other drugs, excluding tobacco [91]. Having a menu of Stage 1 tools to choose from, ranging from brief one- to three-item instruments to somewhat longer tools that focus on a small number of domains, can facilitate the implementation of systematic screening protocols in emergency rooms, primary care offices, and other service delivery settings where severe time constraints may otherwise preclude a more detailed, systematic screening approach.

Stage 1 tools are characterized by their brevity (typically between 1 and 20 items; completion time less than 5 min) and low-threshold training requirements and scoring algorithms. There have been recent developments toward very brief screeners (one to three items) for alcohol or other drugs in order to facilitate screening in busy settings such as primary care or emergency departments (e.g., [68, 82]) or with high-need populations that cannot tolerate completion of long questionnaires (e.g., people with psychosis: [50]). As noted, the AUDIT [6] is a Stage 1 tool focused on the level of risk of alcohol consumption. The NIDA-Quick Screen focuses on other drug use [66], as do short versions of the ASSIST also developed to facilitate use in high-volume clinical settings [4, 84]. Others are focused on consequences, including substance use/abuse or dependence (e.g., DUDIT, [39]; CAGE, [24]; BASIC, [12]; TWEAK, [77]; and CRAFFT, Knight et al. [46]).

The screening for mental health problems/disorders is also highly relevant for the assessment and treatment of people with identified substance use concerns. With respect to screening for mental health challenges, there is an important distinction between disorder-based tools and those based on a dimensional approach, such as measuring mental distress. Others that are longer such as the Beck Depression Inventory [8], the Beck Anxiety Inventory [9], or screeners for PTSD (SPAN, [15, 60]) and trauma [45] are best considered follow-up Stage 2 tools because of their length and diagnostic specificity. Disorder-based tools that are extremely short, such as those using one to three items for identifying depressive and/or anxiety disorder (e.g., the ADD, [57]), are considered Stage 1 screeners. However, Stage 1 mental health screeners also include brief dimensional measures such as the K6/K10 [44], the five-item mental health component of the SF-36 [11, 89]; the Psychological Screening Inventory (PSI: [48]); and either the Brief Symptom Inventory or the BSRS [23, 49], both being shorter versions of the Symptom Checklist 90-R [10, 22]. For children and adolescents, the Strengths and Difficulties Questionnaire serves as a useful Stage 1 mental health screener [33].

A small number of Stage 1 screening tools focus on *both* mental health and substance use, and these are highly valued because of their broader coverage and, therefore, their applicability in multiple settings involved in a collaborative care arrangement. The GAIN-SS [21] is one such tool rapidly growing in popularity across North America and elsewhere and available in multiple languages.

Biological tests for alcohol and drug use may also be helpful and have the advantage of ease of application in medical settings and their utility as a supplement to self-reported information. Limitations include cost, lack of specificity, and, in some instances, sensitivity to recent substance use. Biological testing includes alcohol breathalyzer testing, measures of tissue damage from chronic substance use such as reflected in the liver enzyme gamma-glutamyl transferase (GGT) or red blood cell mean corpuscular volume (MCV), and hair, saliva, and urine analysis (see [35, 86], for brief reviews).

Time and resources permitting, brief screening across other selected domains is also recommended. Screening for other health problems such as traumatic brain injury, cognitive impairment, fetal alcohol spectrum disorder (FASD), HIV/AIDS, and tobacco use is also of critical importance to treatment and support planning and may be called for in some healthcare settings using additional, brief screeners.

46.4.3.2 Stage 2 Screening: Case Definition

This second step in a staged approach to screening involves the use of psychometrically sound tools that are more specific and longer than those used in Stage 1 and which aim to tentatively identify one or more specific disorders or problem areas. This may include alcohol or other drug use disorders and other mental disorders such as psychotic disorders, major depressive disorder, a variety of anxiety disorders including PTSD, eating disorders, and ADHD. Although more specific and detailed than Stage 1 screeners, the information gathered through the tools in this category of the staged approach is still NOT sufficient on which to base a formal diagnosis, although some of the names of the tools can be misleading in this regard. The administration of a Stage 2 screening tool may involve the same or a different service provider than the one undertaking the Stage 1 screening. In any instances involving a transition to a new partner in a collaborative care process, a motivational approach and transition support to ensure ongoing engagement are critical, especially for people with complex co-occurring conditions.

Screening tools such as the Psychiatric Diagnostic Screening Questionnaire (PDSQ: [94]) and the Modified Mini Screen [3] are particularly helpful as diagnosis-based, Stage 2 screeners. Rush et al. [72] validated the PDSQ, as well as the psychiatric subscale of the widely used Addiction Severity Index for identifying mental disorders among people seeking substance use treatment. Magruder et al. [53] found both the PDSQ and the Conners' Adult ADHD Rating Scale which also performed well in adult substance use treatment settings. For adolescents, the POSIT [20] is more focused on specific problem areas rather than diagnosis (e.g., substance use, health, school, family) and is a well-validated option for Stage 2 screening in several settings. Others for children and youth are the Child Behavior Checklist (CBCL: [1]) and the DISC-R [51] and cover most mental disorders, including substance use disorders. For more discussion on specific screening tools and processes for children and youth, see the narrative review conducted by Rush et al. [69] and synthesized by the Centre for Addiction and Mental Health [17]. As noted earlier, tools such as the Beck Depression Inventory [8] and the Beck Anxiety Inventory [9] are considered to be Stage 2 tools due to their specificity in terms of diagnosis and length. This grouping also includes several mental health screening tools that are dimensional rather than diagnostic in nature such as the longer version of the GHQ-30 and the full SCL-90-R [22].

46.4.4 Assessment

In the staged framework, assessment is also conceptualized as involving two phases. Stage 1 assessment is focused primarily on further information gathering and placement/referral to the most appropriate service setting (i.e., level of care). Upon engagement in the appropriate setting, Stage 2 assessment goes further in examining strengths and needs across several bio-psycho-social-spiritual domains including health and mental health status, family/social situation, environmental risk factors, etc.

One helpful way to conceptualize the distinction between Stage 1 and Stage 2 assessment is that between "placement" and "modality" matching [31, 59]. Placement matching, the aim of Stage 1, refers to initial client assignment to a treatment setting with a certain resource intensity and, therefore, significant cost implications. Modality matching (the aim of Stage 2) refers to client assignment on the basis of the optimal clinical approach and intervention(s), including philosophical and goal orientation such as reduced substance use versus abstinence, based on the full profile of client strengths and needs. The overall assessment process needs to occur within a stepped-care, adaptive treatment strategy that

makes ongoing adjustments as new information arises, including the response to treatment, and supported transitions across the various levels of service [63, 64].

46.4.4.1 Stage 1 Assessment: Information Gathering and Service Placement

The essential feature of a Stage 1 assessment, especially in the context of collaborative care across multiple service settings, is the intention to gather enough information on both strengths and needs, including immediate needs for physical and psychosocial stabilization, to formulate an initial placement/referral in an appropriate level of care. This first step involves continued information gathering that is optimally done through the use of valid tools and structured interviews. For substance use services, this would include a determination of the need for withdrawal management which may be initiated in one of the three levels of care: home/mobile, community/medical, or, in the case of complex co-occurring mental and physical problems, a hospital-based service with adequate medical and psychiatric supports. The CWAW-Ar is an assessment tool that supports determination of the need for withdrawal management services [83]. A complementary assessment tool is available for measuring intensity of opiate withdrawal (COWS: [90]). Withdrawal management often needs to be accompanied by a period of stabilization prior to formal engagement in treatment and special care needs to be given to withdrawal management for opioid use disorder given the potential risk of overdose as a result of reduced tolerance and the risk of relapse.

Aside from withdrawal management, a Stage 1 substance use assessment should also determine the need for community or residential treatment at varying levels of duration and intensity. These levels of care are articulated in considerable detail in the ASAM criteria for placement/referral to substance use services [28, 29] and can be tailored for the purposes of need-based planning in specific jurisdictions [75].

It is critical to reemphasize that the initial placement/referral based on the Stage 1 assessment be undertaken in the context of a stepped care, potentially multiservice model – that is, stepping up to a higher level of care if required and stepping down on the basis of progress toward the individual's goals. At moderate-to-high levels of severity and case complexity, this typically requires transition support, including case management and shared e-health information. It also requires monitoring of outcomes, within and posttreatment (see below). The ASAM model specifies the dimensions across which a clinician must explore strengths and needs in order to make the appropriate placement match [29]. These dimensions include

- Acute intoxication and/or withdrawal potential
- Biomedical conditions and complications
- Emotional, behavioral, or cognitive conditions and complications
- Readiness to change
- Relapse, continued use of continued problem potential
- Recovery environment

It is highly recommended that these areas be examined with a semistructured or structured interview approach facilitated by validated instruments that support the initial placement/referral.

Assessment tools and processes for Stage 1 assessment include the GAIN-Q3 Standard MI or the GAIN-I-Lite – these tools being part of the GAIN "family" of substance abuse screening and assessment tools (www.chestnut.org). As with the GAIN-SS, these brief assessment tools are appropriate for use with individuals from age 10 and up. Another instrument for Stage 1 assessment is the Recovery Attitude and Treatment Evaluation (RAATE: [30, 58, 65]).

46.4.4.2 Stage 2 Assessment: Case Conceptualization and Comprehensive Treatment Plan

The next stage of the assessment process involves the creation of a case conceptualization, formulation, and/or diagnosis leading to an individualized and adaptable treatment plan. The language around this overall process changes depending on

the discipline and service delivery setting. The central idea, however, is to pull together all the information that has been gathered from validated screening tools, undertake additional information gathering as needed through assessment questionnaires, structured and semistructured interviews, collateral contacts, and case notes from previous service contacts (if available). The resulting case conceptualization or diagnosis informs the treatment plan, including responding to psychosocial and clinical needs and strengths, and facilitating linkage to services. The term "modality matching" summarizes the intention of a Stage 2 assessment, although this may also involve revision of the placement decision made at an earlier stage.

Stage 2 assessment is seen as being grounded in the present context of the person's life situation and problem-focused [42]. This approach, however, should not exclude consideration of critical underlying factors such as trauma, including intergenerational trauma, and neuropsychological mechanisms. A thorough health assessment including a full psychiatric assessment may also be required and is especially indicated for individuals presenting with more complex co-occurring conditions.

It is beyond the scope of this report to delve into all the critical issues involved in the person–clinician interface for purposes of comprehensive assessment and treatment and support planning. There are many excellent reference texts that approach this from various disciplinary perspectives and cited at the outset of this chapter. All such experts acknowledge the role of clinician experience and skills in conducting semistructured or structured interviews that operationalize core principles and practices such as sensitivity to individual differences in culture, diversity, and developmental age, the need for empathy and establishing therapeutic alliance, and the appropriate involvement of family and significant others. In the substance use field, there is a need for such interviews to cover several areas including, but not limited to, substance use history, including age of first use and onset of negative consequences, severity of substance use disorders, level of insight into past and current challenges, social supports and environment risk factors (e.g., for relapse), medical and psychiatric comorbidity, current phase of use (e.g., intoxicated or in withdrawal), and pressures to seek help and the person's readiness/motivation for change. For many of these areas, the approach is to explore these areas at a deeper level than investigated in Stage 1.

In the substance use field, there have been significant efforts to create integrated assessment packages to support individualized treatment plans and subsequent follow-up determination of outcome. Two well-known comprehensive substance use assessment packages are the Addiction Severity Index [55] and the GAIN-I (www.chestnut.org). The GAIN-I is now used extensively in North America and has the added advantage of being conceptually and instrumentally linked to the GAIN-SS (Stage 1 screener) and the GAIN-Q3 or GAIN-I-Lite (Stage 1 assessment). Another example, with a stronger focus on mental health, is the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) which, although designed primarily as a research tool, provides systematic coverage of alcohol/drugs and mental health experiences and symptoms and functional impairment [37]. There is also the option to administer the full structured interview for DSM-IV disorders (DSM-IV) [25] although this would need to be supplemented with other substance use – specific tools assessing, for example, readiness to change.

46.4.5 Treatment and Support and Outcome Monitoring

Outcome monitoring is a critical component of the staged approach to screening and assessment because of the need to establish baseline status early in the treatment and support process and to inform service delivery on an ongoing basis via measurement-based care and/or engage the client in post-discharge follow-up processes. An important distinction is made between within-treatment and posttreatment outcome monitoring, both of which consider the contact for client and program assessment purposes, as an extension of the treatment and support process itself. This is conceptually quite different than a traditional "research" follow-up and much more likely to engage admin-

istrative and clinical staff, as well as clients themselves, in the outcome monitoring process.

46.4.5.1 Stage 1: Within-Treatment Monitoring

Within-treatment outcome monitoring tracks progress on an ongoing basis with very brief but highly relevant clinical tools applied at the front end of periodic therapist–client interactions. Variously referred to as measurement-based care [80], adaptive treatment sequencing [63, 64], routine outcome monitoring [16], or progress monitoring [34], this model evolved largely from the work of Lambert in the mental health area (e.g., [47]) and, in the substance use field [56]. Occurring at the clinical interface of therapist and client, it is critical that the assessment and outcome measures be brief, be implemented within the flow of the clinical encounter, and return feedback immediately in a useful format to further the therapeutic relationship and the client's progress toward goals. Appropriate within-treatment outcome monitoring can be accomplished with repeat application of some screening tools that are sensitive to change over time such as the GAIN-SS [21] and the Brief Addiction Monitor [14]. Others such as Lambert's [47] Outcome Questionnaire (OQ) have been designed specifically to assess psychological processes that cut across many types of mental health problems, including substance use and addictions.

46.4.5.2 Stage 2: Posttreatment Monitoring

Posttreatment outcome monitoring, sometimes referred to as "recovery monitoring" [18], involves the repetition of selected screening/assessment measures at some interval after program admission, such as 3, 6, 12, or 24 months, and determination of changes in these measures [73]. In addition, the follow-up contact is an opportunity to reengage the individual in treatment if indicated, using a guided, motivational return-to-treatment protocol [79]. Posttreatment monitoring is useful as an accountability and program evaluation tool and can also be helpful in identifying clients who may be struggling and need further assistance to recoup gains made in treatment.

Ideally, posttreatment follow-up also involves repeat application of one or more assessment tools or subscales by phone or face-to-face interview. The GAIN-I and GAIN-Q3-standards (www.chestnut.org) on the Addiction Severity Index [55] are useful measures for outcome monitoring. Other measures have been constructed directly from client's reported experience of "recovery" [19]. Locating clients and obtaining good follow-up rates (ideally over 80%) are the Achilles' heel of posttreatment follow-up for substance use programs. There are protocols for achieving substantially higher follow-up rates [78], and these can benefit from collaborative networks working together to locate and engage people in the follow-up process.

46.5 Implementation and Evaluation of Evidence-Based Screening and Assessment

The context in which screening takes place must be carefully considered in both implementation and evaluation of screening and assessment tools and processes. As already mentioned, the role and purpose of screening should be well understood and articulated in the context of the mandate and objectives of the service provider. Organizational policy must also support the implementation of screening and related protocols. Required staff competencies and program design should fit within clear service delivery protocols addressing where, when, and how screening will be administered and how the information gathered will be used. Personnel who are administering the tools must be trained to introduce, administer, score, discuss, and take appropriate action based on the screening results. All of this needs to be clearly conveyed to individuals engaging with the service so that they understand how screening can be helpful and provide fruitful ground for evaluative inquiry.

As noted above, implementing formal screening tools and processes is a logical fit in the specialized substance abuse treatment sector. In these settings, clients have already been

identified as needing further screening (e.g., for co-occurring conditions), assessment, or treatment. In other settings where routine screening and assessment of various health concerns are already taking place (i.e., emergency settings, primary care), the rationale for extending screening to identify at-risk substance use and substance-related problems is also clear. Screening in settings such as schools, employment counseling, and justice settings is also important given the evidence that rates of substance use and mental health problems are high and often not identified. While these settings provide important opportunities for early identification and early intervention, there are a number of potential risks that must be considered, including stigma resulting from identification and labeling, social exclusion, limitation of opportunities, and false-positives consuming scarce treatment resources. Risks associated with identification may be greater for some specific groups of people, for example, severe sanctions may be imposed on those identified as being involved in substance using activities by some schools, employment programs, shelter and housing providers, supported housing, long-term care facilities, families, and specific ethno-cultural groups and communities.

With respect to implementation of assessment tools and processes, the issue of staff competencies and qualification is more salient than with respect to screening tools, many of which can be undertaken with much less rigorous training. Importantly, the increasing level of integration of mental health and substance use services [70] is bringing the mental health perspective on "recovery" [81] closer to the substance use field with significant implications for screening and assessment. Among other things, the mental health recovery orientation to service delivery is contributing to the development of what is sometimes referred to as "single-session therapy by walk-in or appointment" that promises brief assessment of the most immediate needs to be addressed largely *from the perspective of the person presenting for assistance* [36]. The focus is very much on rapid linkage which, in many settings, contrasts with a more medical/psychiatric paradigm that requires thorough and, typically, diagnostic assessment.

Models of collaboration within which screening and assessment are core activities provide the field with rich evaluation opportunities, including outcome and process evaluation, and an opportunity to monitor trends and performance. Outcomes can be examined at the individual (i.e., client and clinician), organizational, and community level. For example, at the organizational level, outcome indicators could include changes in staff attitudes, skills, and behavioral engagement in screening and assessment practices and change in referral practices, as well as client perceptions of care. At the community level, indicators could include increased numbers of new clients referred to treatment and reduced number of emergency visits. It is also of interest to evaluate the extent to which the development of collaborative models of screening and assessment contributes to broaden collaborative processes across agencies/service providers – for example, building partnership capital to engage in other joint planning and service delivery. Using a consistent screening tool across a collaborative group of service providers provides an opportunity for decision-makers, funders, and researchers to look at presenting needs across settings and monitor trends over time within the collaborative as well as in comparison to the general population [38].

46.6 Conclusion

There is a very strong rationale for a more proactive concerted effort to screen for mental health problems and at-risk consumption of alcohol and other drugs and related addiction problems given the evidence concerning the level of underdetection in routine practice and the excellent performance of a host of screening tools and processes. Screening in multiple sectors, along with follow-up assessment and intervention, is one strategy to broaden the scope and reach of treatment and support beyond the traditional sector of specialized substance use services. There are many reasons to engage in more proactive screening, and both individual and collaborating part-

ners need to be clear about how the information will be used, including making improvements at the system level. When used for clinical decision making, best practice calls for a staged approach to maximize efficiency of the overall screening and assessment process. The specific tools and processes must be tailored to the setting and target population for which they are being implemented. For example, some tools will work best for screening in primary care and other generic health and social service settings, and others are more appropriate for screening in specialized mental health and substance use settings. That said, whether working in generic settings such as primary care or specialized settings, a collaborative approach, drawing upon multidisciplinary, and potentially multi-provider and multi-sectoral expertise, is needed across the stages of screening and assessment, along with a collaborative response protocol for level-of-care placement/referral for treatment and support.

The evidence is quite strong with respect to the ability of screening tools and processes to identify individuals needing brief intervention or other treatment and support. This evidence underlies the best practice guidelines that call for targeted screening in generic settings such as primary care and universal screening for all clients engaged with specialized mental health and substance use services. However, the effectiveness literature tells us that screening is only one part of the process of engagement and the results are more equivocal in terms of the impact of the screening per se on subsequent case management and health outcomes, the literature on SBIRT in the substance use field being an important exception. Collectively, the literature that cuts across the mental health and substance use area reminds us that screening alone may make little difference without a detailed response plan and follow-up intervention. Further, there is ample evidence that screening for different levels of risk for alcohol and drug use, accompanied by brief intervention or referral to treatment, is effective in engaging people in both these response options and subsequent outcomes [43]. That being said more work is needed on teasing out the most effective ingredients of the overall SBIRT protocol and addressing the challenges implementing SBIRT protocols in healthcare and other settings [41, 92].

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Stepped Care Models in Addiction Treatment

47

Ambros Uchtenhagen

Contents

Abstract

Stepped care models aim at matching treatment intensity to defined patient characteristics in a systematic way, thereby avoiding misplacements and making best use of available treatment resources at the same time. In principle, treatment planning for new patients starts with the least intensive care, progressing to more intensive regimes for nonresponders. Such models have been introduced in psychiatry and in other medical fields.

Models of stepwise patient placement in addiction treatment are known from Northern America (Sobell model, model of the American Society of Addiction Medicine, ASAM) for adults and adolescents and special models for dual-diagnosis patients. Another model comes from Europe (the Dutch model for triage and evaluation in addiction treatment MATE; special model for judicial patients). The various elements and procedures of the ASAM and MATE models are described and compared.

An overview on evaluation studies and reviews is presented, concerning feasibility, validity, reliability, effectiveness, and cost-effectiveness of stepped care models. Outcomes are partly positive, but limitations are mentioned, and more research is asked for.

Keywords

Level of care · Needs assessment · Patient placement · Treatment planning

A. Uchtenhagen (✉)
Swiss Research Foundation for Public Health and Addiction, Zurich University, Zurich, Switzerland
e-mail: ambros.uchtenhagen@isgf.uzh.ch

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47.1 Introduction

47.1.1 A Concept for Patient Placement

It is normal practice to assign a new patient to an appropriate and readily available treatment and to switch a patient not responding to that treatment to another one, be it another intervention type, another medication, or another setting. The therapist makes his or her choice on the basis of guideline recommendations, scientific studies, or personal experience, eventually also on the basis of patient preference.

The concept of stepped care combines a systematized version of such practice with an attempt at matching treatment intensity to patient characteristics. Screening the new patient for specific characteristics provides the basis for treatment indication and placement, starting with the least intensive intervention and stepping up intensity for nonresponders.

Main principle: Patients should be offered the least intensive and intrusive care at first contact, except in case of emergencies and defined complications which ask for an intensive treatment. Otherwise, only nonresponders should receive care along a scale of increased intensity. This principle is aiming to protect patients from intrusive care they do not need and to make best use of available treatment resources by avoiding misplacements. "Stepped care models represent attempts to maximise the effectiveness and efficiency of decisions about allocation of resources in therapy" [11].

47.1.2 Models of Stepped Care

Approaches to stepped care in addiction treatment have been described repeatedly [16]. By now, stepped care models have been introduced in some fields of psychiatry. Guidelines of the National Institute for Clinical Excellence (NICE) provide stepped care models in the UK for the treatment of depression and anxiety [20]. In the USA, such resource allocation issues are mentioned for anxiety disorder, panic disorder, eating disorder, and alcohol dependence [11].

47.1.2.1 From First Line to Intensive Care

In the model proposed by the Sobells [4, 24], the recommended treatment should start with the least restrictive intervention in terms of cost and personal inconvenience for patients. The first step might even involve facilitating "natural recovery" outside of professional services. Stepping up requires a decision about patient progress and depends on the type of disorder and the effectiveness of available treatments. The decisions may be made on the basis of guidelines but should not disregard the risk of inappropriate stepping up and of missed stepping up and should include considerations about costs of treatments at different levels.

47.1.2.2 The ASAM Patient Placement Model

The American Society of Addiction Medicine (ASAM) started to develop the patient placement criteria PPC in 1991, and in 1994 the National Institute of Drug Abuse (NIDA) funded a validity study. Revised versions were published in 1996 (ASAM PPC-2) and in 2001 (ASAM PPC-2R). A further revision will be based on DSM-5 to come.

The follow-up version of the placement criteria is published under the name of ASAM criteria (available in a third edition, referenced under the American Society of Addiction Medicine [2]).

The basis of the model is a concept of individualized treatment: assessment at intake is made in a range of biopsychosocial dimensions (multiaxial DSM diagnoses); assessment dimensions include also readiness to change, continued problem potential, and recovery environment. This is followed by an identification of priority problems, leading to defining the appropriate model and level of service. Progress assessment is used as a basis for eventual reassignment [14, 16, 17].

Placement criteria have been set up for adults and for adolescents. Special attention is also paid to co-occurring mental and substance-related dis-

orders, in patient assessment, as well as in the specifications of services [15]. For dual-diagnosis patient, separate risk dimensions are set up: dangerousness/lethality, interference with addiction recovery efforts, social functioning, ability for self-care, and course of illness. The criteria also advocate for an adequate availability of treatment; by incorporating more use of outpatient care – especially for those in early stages of motivation for change – the criteria help to reduce waiting lists for residential treatment [17].

A supplement was published to delineate specific criteria for the use of pharmacotherapies for alcohol use disorders, for detoxification, and relapse [10].

47.1.2.3 MATE: A Model for Patient Assessment and Referral

The Dutch model for measurement in the addictions for triage and evaluation MATE [21, 22] is a national project, aiming at constructing and testing of a new instrument for the assessment at intake of all problems and needs in relevant domains in substance abuse treatment; the instrument should also be useful as a framework for the application of existing instruments in selected domains for matching, patient allocation, and treatment evaluation in the addictions. The instrument should help to make rational and transparent decisions about providing which and how much treatment to which patients. It was tested for feasibility, reliability, and validity in a population of heavy users, and in a subproject an instrument was developed and tested for judicial clients.

The assessment of substance use disorders at intake is made on the basis of the international classification systems ICD/DSM. Assessment of personal and social functioning is made in order to determine which type of services will be needed; this part of the new instrument is based on the WHO international classification system of functioning, disability, and health ICF. Existing instruments are used for the assessment of comorbidities, new modules for treatment history, motivation, and criminality. Overall, the MATE instrument is composed of ten modules. A manual and a protocol with detailed instructions were published in Dutch.

The MATE was adopted and further developed in Germany. A German version of the instrument was tested and implemented [6–8, 23].

47.1.3 The Main Elements of Stepped Care Models: A Comparative Overview

Stepped care models use three essential elements: patient indicators used for determining the appropriate level of care, treatment typology in regard to intensity of care, assessment, and referral procedures. The following figures summarize the relevant information on these elements in the ASAM and MATE models (Tables 47.1 and 47.2; Figs. 47.1 and 47.2).

MATE criteria were developed for Germany by the German Psychiatric Association and published by the German Ministry of Health.

Detailed criteria listed in the German evaluation protocol for treatment evaluation

Headings:	*A 1–12*	*Seriousness of condition*
	B 1–5	*Intensity of treatment*
	C 1–2	*Invasive interventions*
	D 1–6	*Comorbidities*

Source: [8]

Table 47.1 Patient characteristics used for determining appropriate level of care

ASAM assessment dimensions	MATE patient indicators
Acute intoxication and/or withdrawal potential	Addiction severity
Biomedical conditions and complications	Psychiatric impairment
Emotional, behavioral, cognitive conditions/complications	Social stability
Readiness to change	Treatment history 0–1
Relapse/continued use, continued problem potential	Treatment history 2
Recovery environment	Treatment history 3–5
	Treatment history >5

Source for ASAM: Mee-Lee and Shulman [17], Table 27.1. Source for MATE: Schippers and Broekman [21].

Table 47.2 Treatment typology

ASAM levels of care	MATE levels of care
0.5. Early intervention	1. Short outpatient
I. Outpatient treatment	2. Outpatient
II.1. Intensive outpatient	3. Day care/residential
II.5. Partial hospitalization	4. Care (in- and outpatient)
III.1. Low-intensity residential treatment	
III.3. Medium-intensity residential treatment	
III.5. Medium−/high-intensity residential treatment	
III.7. Medically monitored intensive inpatient	
IV. Medically managed intensive inpatient OMT. Opioid maintenance therapy	
Levels of care for adult detoxification	
I-D. ambulatory detoxification without extended on-site monitoring II-D. ambulatory detoxification with extended onsite monitoring	
II 2-D. clinically managed residential detoxification III 7-D. medically monitored inpatient detoxification IV-D. medically managed inpatient detoxification	

Source for ASAM: Mee-Lee and Shulman [17], Table 27.2. Source for MATE: Schippers and Broekman [21].

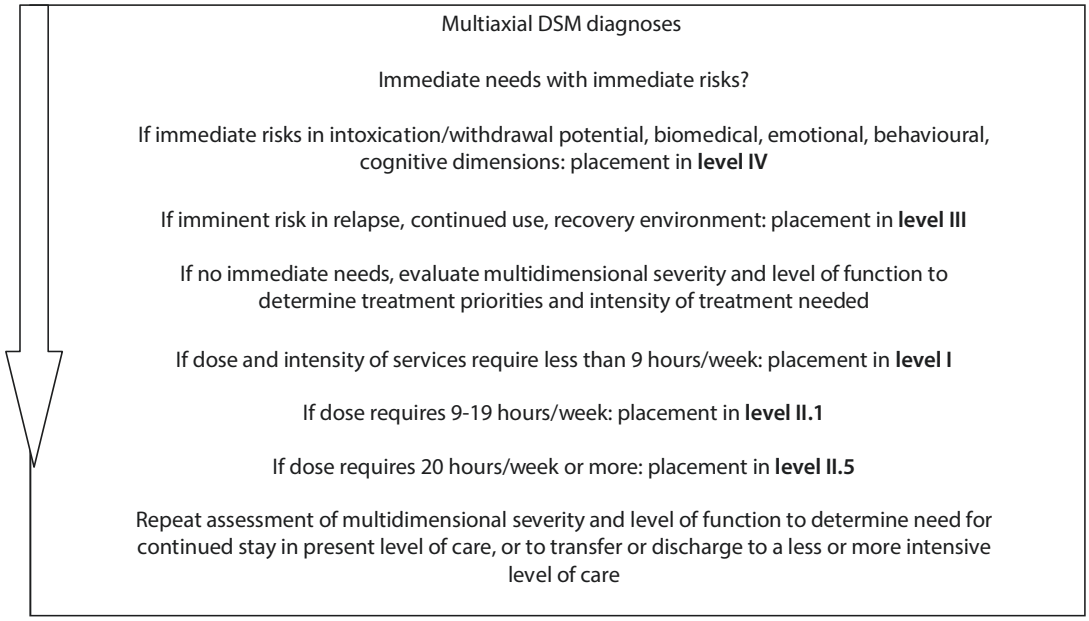

Fig. 47.1 Assessment and referral procedures in ASAM PPC-2r. (Source: [16], Fig. 6–1)

47.1.4 The NICE Model of Stepped Care

The National Institute for Health and Clinical Excellence (NICE) published recommendations for the psychological treatment of depressions and anxiety disorders in a framework of a stepped care system. The guiding principles are to deliver best possible outcomes while burdening patients as little as possible and to provide scheduled reviews how to step up or down to more or less intensive treatment if appropriate. The system includes three levels of intensity of care (starting with primary care, moving up to self-help interventions, and then to cognitive behavioral therapy) [19].

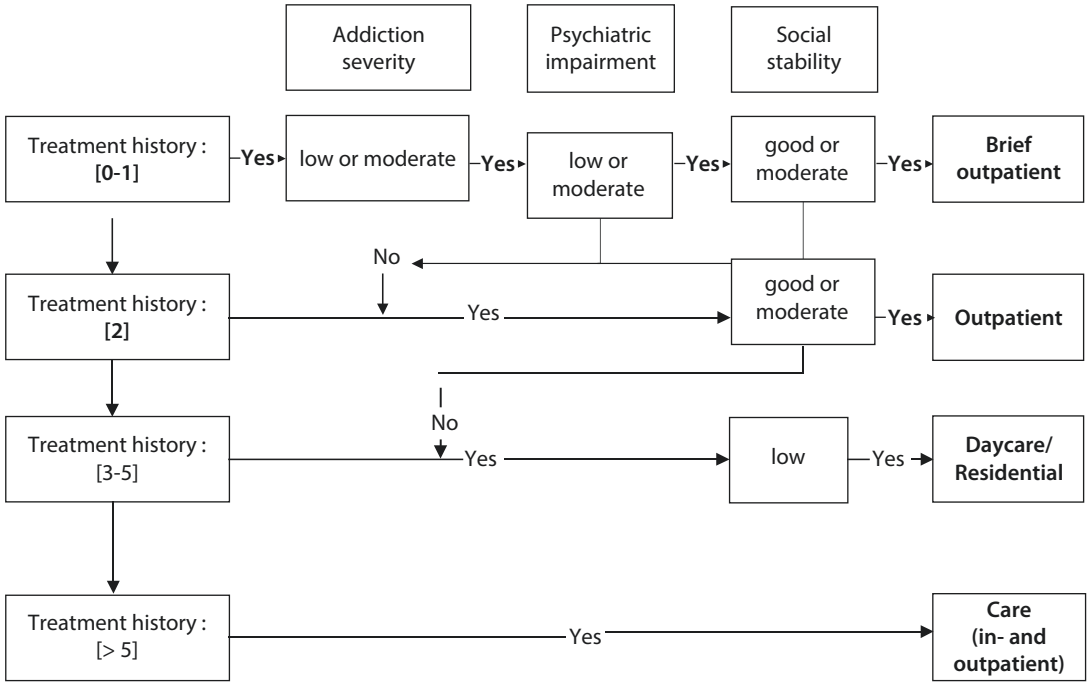

Fig. 47.2 MATE guidance for matching and referral. (Source: [18], Fig. 2)

47.1.5 Evaluation Results and Perspectives

A systematic review was made on the efficacy of stepped care models involving different levels of psychosocial treatment for alcohol use disorders and nicotine dependence, with or without medication [12]. Little evidence was found to suggest that stepping up nonresponders to more intensive therapy improved outcomes. In one study, the application of a stepped care approach was found to reduce treatment costs compared with usual care. There was some evidence that the greater differentiation between the intensity of the interventions offered at each step, the better the outcome. Further research is needed to evaluate the efficacy of stepped care approaches to providing psychosocial treatment.

A summary of research on the ASAM patient placement criteria is presented in the *Textbook of Substance Abuse Treatment*. The authors conclude as follows: "More than a decade of research of the ASAM PPC supports the predictive validity and the cost-effectiveness of the use of PPC. Based on this research, a variety of computer assisted assessment and placement tools are in development" [16, p. 88]. Another overview is presented in the *Principles of Addiction Medicine*. Nine evaluation studies were performed involving 3641 subjects; controlled studies found that "treatment based on the ASAM PPC are associated with less morbidity, better client functioning, and more efficient service utilization than mismatched treatment" [17, p. 398].

The ASAM placement criteria have been further developed in a guidebook on the treatment of substance abuse issues under the title of ASAM Essentials [1].

Feasibility and field testing of the MATE in a treatment-seeking population were performed in two large treatment settings. Construct validation with related instruments and evaluation of the dimensional structure of modules were performed. Among the results are a satisfactory inter-rater reliability and concurrent validity, indicating the usefulness of the instrument for allocating patients to substance abuse treatment, even in a heterogeneous population [22].

However, there were some problems with clinicians not complying with the guidelines, resulting in mismatched patients usually allocated to outpatient treatment instead of early interventions [18].

A recent manual provides guidance for implementation and comparative research [5]. This manual is now available in English, German, Dutch, Italian, Danish, French, Slovenian, and Portuguese (https://www.mateinfo.eu/german/index).

Another systematic review of stepped care in psychological interventions was made [3]. It identified the underlying assumptions on which the benefits of stepped care depend: equivalence in terms of clinical outcomes, efficiency in terms of resource use and costs, and acceptability of "minimal interventions" to patients and therapists. The review concludes that more research is needed in terms of rigorous evaluations of the underlying assumptions.

A comparison of minimal interventions with a stepped care model for patients with alcohol use disorders in the UK evidenced greater cost savings, greater motivation for change, and greater reduction of alcohol consumption for stepped care 6 months after randomization [9].

47.2 Further Developments

Stepped care models have a considerable potential to improve patient-service matching with improved outcomes and improved use of treatment resources. Stepped care is also considered to be an important element of individualized treatment [13]. A wider implementation of existing or new models however is slow and may meet problems if not politically supported.

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48 Therapeutic Communities for Addictions: Essential Elements, Cultural, and Current Issues

George De Leon, Fernando B. Perfas, Aloysius Joseph, and Gregory Bunt

Contents

G. De Leon (✉)
BST at the School of Nursing, NYU, New York, NY, USA

Department of Psychiatry, NYU School of Medicine, New York, NY, USA

F. B. Perfas
Daytop International Training Academy, New York, NY, USA
e-mail: FPerfas@daytop.org

A. Joseph
Daytop International, Inc., New York, NY, USA
e-mail: AJoseph@daytop.org

G. Bunt
Daytop Village, Inc., New York, NY, USA

Department of Psychiatry, NYU Langone Medical Center, New York, NY, USA
e-mail: gbunt@daytop.org

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Abstract

The therapeutic community (TC) is a major treatment modality serving a wide spectrum of substance abuse clients worldwide. The weight of the research evidence developed over some 40 years demonstrates that the TC is an effective and cost-effective treatment particularly for substance abusers with serious social and psychological problems in addition to their drug abuse. This chapter provides an overview of the essential elements of the TC approach: its perspective, method, program model, and adaptation for special populations, settings, and different cultures.

TCs have been successfully modified for special populations of substance users including those with co-occurring disorders, adolescents, women with children, criminal justice clients in prisons, and community-based settings. TC programs have been implemented in Europe, Asia, Africa, Latin America, and the Middle East. And, despite ethnic, social-political, and religious differences, TCs have retained their essential elements and effectiveness across a variety of cultures.

Its evolution over some 50 years has surfaced key issues that challenge the TC to maintain the integrity of its unique social psychological approach – community as method. Several of these are briefly highlighted including funding, workforce, research, treatment fidelity, and the diversity of TC programs. In the current context, the TC is compelled to reassert its place and mission in human services – that of promoting recovery and right living.

Keywords

Therapeutic community · Cultural diversity · Treatment efficacy · International · Treatment perspectives · History

48.1 Introduction

Drug-free residential programs for substance abuse appeared a decade later than did therapeutic communities (TCs) in psychiatric hospitals pioneered by Maxwell Jones and others in the United Kingdom. The term therapeutic community evolved in these hospital settings, although the two models arose independently.

The TC for substance abuse emerged in the late 1950s as a self-help alternative to existing conventional treatments. The originators were recovering alcoholic and drug-addicted individuals [20, 21]. Although its modern antecedents can be traced to Alcoholics Anonymous and Synanon, contemporary TCs for addictions are sophisticated human services institutions. Today, the label therapeutic community is generic, describing a variety of short- and long-term residential and nonresidential programs that serve a wide spectrum of substance abuse clients. Although the TC approach has been adapted for different populations and settings, it is the perspective and method of the traditional long-term residential prototype for adult substance abusers that have documented effectiveness in rehabilitating substance-abusing individuals.

48.2 Essential Elements

48.2.1 The TC Perspective

The TC perspective or theory shapes its program model and its unique approach, community as method. The perspective consists of four interrelated views of the substance use disorder, the individual, recovery process, and healthy living.

48.2.1.1 View of Disorder

Drug abuse is viewed as a disorder of the whole person, affecting some or all areas of functioning. Cognitive and behavioral problems are often present, as are mood disturbances. Thinking may be unrealistic or disorganized; values may be confused, nonexistent, or antisocial. Frequently, the patient exhibits deficits in verbal, reading, writing, or marketable skills. Moral or even spiritual issues, whether expressed in existential or psychological terms, are apparent. Thus, the TC perspective considers the problem to be the individual, not the drug, and addiction is a symptom, not the essence of the disorder.

48.2.1.2 View of the Person

In TCs, individuals are distinguished along dimensions of psychological dysfunction and social deficits rather than according to drug use patterns. Regardless of differences in social background, drug preference, or psychological problems, most individuals admitted to TCs share clinical characteristics (Table 48.1). Whether they are antecedent or consequent to serious involvement with drugs, these characteristics are commonly observed to correlate with chemical dependency. More important, in TCs, a positive change in these characteristics is considered to be essential for stable recovery.

48.2.1.3 View of Recovery

In the TC perspective, recovery extends beyond drug freedom, involving a change in lifestyle and in personal identity. The primary psychological goal is to change the negative patterns of behavior, thinking, and feeling that predispose the individual to drug use; the main social goal is to develop the skills, attitudes, and values of a responsible drug-free lifestyle.

In many TC residents, vocational and educational problems are marked; middle- class, mainstream values are either missing or not sought. Usually these residents emerge from a socially disadvantaged sector. Their recovery in the TC is better termed *habilitation*, the development of a socially productive, conventional lifestyle for the first time. Among individuals from more advantaged backgrounds, the term *rehabilitation* is more suitable, which emphasizes a return to a lifestyle previously lived, known, and perhaps rejected.

Table 48.1 Typical behavioral, cognitive, and emotional characteristics of substance abusers in therapeutic communities

Low tolerance for all forms of discomfort and delay of gratification
Problems with authority
Inability to manage feelings (particularly hostility/anger, guilt, and anxiety)
Poor impulse control (particularly sexual or aggressive impulses)
Poor judgment and reality testing concerning consequences of actions
Unrealistic self-appraisal regarding discrepancies between personal resources and aspirations
Prominence of lying, manipulation, and deception as coping behaviors
Personal and social irresponsibility (e.g., inconsistency or failures in meeting obligations)
Marked deficits in learning and in marketable and communication skills

48.2.1.4 View of Right Living

TCs adhere to certain precepts and values that constitute a view of healthy personal and social living that guide and reinforce recovery. For example, community sanctions address antisocial behaviors and attitudes; the negative values of the street, jails, or negative peers; and irresponsible or exploitative sexual conduct. Positive values are emphasized as being essential to social learning and personal growth. These values include truth and honesty (in word and deed), a work ethic, self-reliance, earned rewards and achievement, personal accountability, responsible concern (being one's brother's or sister's keeper), social manners, and community involvement. The precepts of right living are constantly reinforced in various formal and informal ways (e.g., signs, seminars, in groups and community meetings).

48.2.2 The TC Approach: Community as Method

The TC approach can be summarized in the phrase "community as method" [2, 3]. A parallel concept – "community as doctor" – in the psychiatric or democratic TC was first coined by Rapoport [16]. Theoretical writings offer a definition of "community as method" as follows: the *purposive* use of the community to teach individuals to *use* the community to change themselves. The fundamental assumption underlying the TC approach is that individuals obtain maximum therapeutic and educational impact when they engage in and learn to use all of the activities, elements of the community as the tools for self-change. Thus, community as method means that the community itself provides a *context* of relationships and activities for social learning. Its

membership establishes the *expectations* or standards of participation in community activities; it continually *assesses* how individuals are meeting these expectations and *responds* to them with strategies that promote continued participation.

48.2.3 TC Program Model

The key components of the program model are its social organization (structure), peer and staff roles, groups and individual counseling, community enhancement meetings, community management elements, and program stages. Each component reflects an understanding of the TC perspective, and each is used to transmit community teachings, promote affiliation, and self-change.

48.2.3.1 Social Organization

The TC social organization is stratified with relatively few staff of the TC at the top complemented by resident peers at junior, intermediate, and senior levels. This peer level-to-community structure strengthens the patient's identification with a perceived ordered network of individuals. More important, it arranges relation- ships of mutual responsibility at various levels in the program.

The daily operation of the community itself is the task of the residents, who work together under staff supervision. The broad range of resident job assignments illustrates the extent of the self-help process. Residents perform all house services (e.g., cooking, cleaning, kitchen service, minor repair), serve as apprentices, run all departments, and conduct house meetings, certain seminars, and peer encounter groups.

The TC is managed by the staff, who monitor and evaluate patient status, supervise resident groups, assign and supervise resident jobs, and oversee house operations. The staff members conduct therapeutic groups (other than peer encounter groups), provide individual counseling, and organize social and recreational projects. They make decisions about resident status, e.g., discipline, promotion, transfers, discharges, furloughs, and treatment planning.

48.2.3.2 Peers as Role Models

Peers, serving as role models, and staff members, serving as role models and rational authorities, are the primary mediators of the recovery process. TC members who demonstrate the expected behaviors and reflect the values and teachings of the community are viewed as role models. TCs require multiple resident and staff role models in order to maintain the integrity of the community and ensure the spread of social learning effects.

48.2.3.3 Staff Members as Rational Authorities

Staff members foster the self-help learning process through performance of their managerial and clinical functions described above but also as role models and rational authorities. TC residents often have had difficulties with authorities who have not been trusted or who have been perceived as guides and teachers. There- fore, residents need a positive experience with an authority figure who is viewed as credible, supportive, corrective, and protective so that they may gain authority over themselves (personal autonomy). As rational authorities, staff members provide the reasons for their decisions and explain the meaning of consequences particularly in terms of recovery and personal growth.

48.2.3.4 Therapeutic Educational Activities (Groups and Individual Counseling)

Various forms of group process and individual counseling provide residents with opportunities to express feelings and resolve personal and social issues. They increase communication and interpersonal skills, bring about examination and confrontation of behavior and attitudes, and offer instruction in alternative modes of behavior. The main forms of group activity in the TC are peer-led encounter groups, staff-led therapy, and tutorial groups. Other groups that convene regularly or held as needed supplement the main groups. These vary in focus, format, and composition and include gender, ethnic, age-specific, or health theme groups. Additionally, cognitive-behavioral tutorials using manualized curricula are employed for targeted areas such

as relapse prevention, criminal thinking, trauma and PTSD, etc.

One-to-one counseling balances the needs of the individual with those of the community. Peer exchange is ongoing and is the most consistent form of informal counseling in TCs. Staff counseling sessions may be regularly scheduled or conducted as needed. The focus of staff counseling is to address issues that may impede progress and to facilitate the patient's adjustment to and constructive use of the peer community. Counseling is also employed for the purpose of developing an individualized treatment plan.

48.2.3.5 Community Enhancement Activities (Meetings)

Community enhancement activities are the facility-wide meetings that convene daily. These include the morning meeting, the seminar, the house (evening) meeting, and a general meeting. Some of these are held almost daily, while others are called when needed. These gatherings are necessary for building the spirit of community to which members are expected to participate actively. Though different in format, all meetings have the common objective of facilitating the individual's assimilation into the community. The purpose of the morning meeting is to instill a positive attitude in the community at the beginning of the day, motivate residents, create camaraderie, and strengthen unity. Seminars are community-wide teaching sessions led by peers or staff presenting topics that directly or indirectly relate to the TC perspective on recovery and right living. House meetings are coordinated by senior residents to transact community business. General meetings take place only when needed and are usually called so that negative behavior, attitudes, or incidents in the facility can be addressed. While these activities are often facilitated by senior residents, staff are available to oversee them. Community enhancement also occurs in a variety of nonscheduled, informal activities as well. These include activities related to rituals and traditions, celebrations (e.g., birthdays, graduations, phase changes, job changes), ceremonies (e.g., those relating to general and cultural holidays), and memorial observances for deceased residents, family members of residents, and staff members.

48.2.3.6 Community and Clinical Management Elements

Community and clinical management elements maintain the physical and psychological safety of the environment and ensure that resident life is orderly and productive. Thus, they strengthen community as a context for social learning. The main elements that are staff managed, although with some input from the senior resident social hierarchy, are privileges, disciplinary sanctions, surveillance, and urine testing. How- ever, peer confrontation in the form of verbal correctives, affirmations, and feedback (e.g., reactions, advice, information) are ongoing community management activities.

48.2.3.7 Program Stages and Phases

Recovery in the TC is a developmental process that can be understood as a passage through program stages of learning. The learning that occurs at each stage facilitates change at the next, and each change reflects movement toward the goal of recovery. Three major program stages characterize change in long-term residential TCs – *orientation-induction*, *primary treatment*, and *reentry* – and may include additional substages or phases. The original time frame for these stages was grounded in a planned duration of treatment ranging up to 24 months. Current stage and phase durations are shorter commensurate with decreased overall planned durations. Regardless of temporal changes completion of each stage is a celebrated event marking acknowledged programmatic and clinical progress.

Completion marks the end of active program involvement. Graduation itself, however, is an annual event conducted in the facility for individuals who have completed all program stages and have successfully spent some time outside the treatment facility. Thus, the TC experience facilitates a process of change that must continue throughout life; and what is gained in treatment are tools to guide the individual on a path of continued change. Completion, or graduation, therefore, is not an end but a beginning.

48.2.3.8 Aftercare

TCs have always acknowledged the patient's efforts to maintain sobriety and a positive lifestyle beyond graduation. Until recently, long-term TCs addressed key clinical and life adjustment issues of aftercare during the reentry stages of the 2-year program. As noted, funding pressures have resulted in shorter planned durations of residential treatment and the stages and phases therein. This has underscored the necessity for aftercare resources to address both primary treatment and reentry issues. Thus, many contemporary TCs offer post-residential aftercare treatment and social services within their systems, such as intensive day treatment and step-down outpatient ambulatory treatment or through linkages with outside agencies.

48.2.4 The Effectiveness of Therapeutic Communities

Over the past four decades, a considerable scientific knowledge base has developed with follow-up studies on thousands of individuals treated in TCs. The most extensive body of research bearing on the effectiveness of addiction TC programs has amassed from field outcome studies. These all employed similar longitudinal designs that follow admissions to TCs during treatment and 1–5 years (and in one study up to 12 years) after leaving the index treatment.

These studies show that TC admissions have poor profiles in terms of severity of substance use, social deviance, and psychological symptoms. The striking replications across studies leave little doubt as to the reliability of the main conclusion. Namely, there is a consistent relationship between retention in treatment and positive posttreatment outcomes in TCs. Replication studies overseas seem to follow the same trend. This conclusion is supported in the smaller number of controlled and comparative studies involving TC programs (for a recent review of the TC outcome literature in North America, see [4]). Overall, the weight of the research evidence from multiple sources (multi-program field effectiveness studies, single-program controlled studies, meta-analytic statistical surveys, and cost-benefit studies) is compelling in supporting the hypothesis that the TC is an effective and cost-effective treatment for certain subgroups of substance abusers, particularly those with serious social and psychological problems in addition to their drug abuse.

48.2.5 Adaptations and Modifications of the TC for Special Populations and Settings

The traditional TC model described in this chapter is actually the prototype of a variety of TC-oriented programs. Today, the TC modality consists of a wider range of programs serving a diversity of patients who use a variety of drugs and present with complex social and psychological problems in addition to their substance abuse. Client differences as well as clinical requirements and funding realities have encouraged the development of modified residential TC programs with shorter planned durations of stay (3, 6, and 12 months) as well as TC-oriented day treatment and outpatient ambulatory models. Having become overwhelmed with alcohol and drug abuse problems, correctional facilities, medical and mental hospitals, and community residences and shelters have implemented TC programs within their settings. Additionally, the TC approach has shown to be effective within these specialty settings [4].

Most community-based traditional TCs have expanded their social services or have incorporated new interventions to address the needs of their diverse residents. These changes and additions include family services, primary healthcare specifically geared toward HIV-positive patients and individuals with AIDS, aftercare services particularly for special populations such as substance-abusing inmates leaving prison treatment, relapse prevention training, components of 12-step groups, mental health services, and other evidence-based practices (e.g., cognitive-behavioral therapy, motivational interviewing). Mostly, these modifications and additions

enhance but do not substitute for the basic TC approach, community as method. Research literature documents the effectiveness and cost-effectiveness of modified TCs for special populations including homeless mentally ill chemical abusers, those in criminal justice settings, and adolescents (e.g., [2, 6, 9, 17, 19]).

48.2.6 TCs Worldwide

Over some five decades, TC programs have been implemented worldwide. In Europe, the establishment of drug-free therapeutic communities was the main treatment response to the emerging heroin problems in the 1960s and 1970s. The original American TC model was adapted to the European culture, and it integrated the long-standing local traditions and influences. Between 1968 and 1983, the TC approach spread rapidly across virtually all countries in Europe including the United Kingdom and subsequently to Asia, Africa, and Latin America. Globally, it is conservatively estimated that there are over 3000 TCs operating in hospital, prison, juvenile centers, outpatient, and community-based settings.

48.2.7 TC Outcome Research Worldwide

The North American research literature is the most extensive and has been briefly cited above. There is a modest but developing research literature on TCs worldwide particularly of European programs. The main conclusion from recent reviews of the European outcome studies may be briefly summarized.

"Length of stay in treatment and participation in subsequent aftercare were consistent predictors of recovery status. The authors conclude that TCs can promote change regarding various outcome categories. Since recovering addicts often cycle between abstinence and relapse, a continuing care approach is advisable, including assessment of multiple and subjective outcome indicators" [18]. Similar conclusions are obtained in outcome studies of TC programs in Peru and Thailand [10, 11] and Australia [15].

Although treatment process studies are few, emerging research has supported hypotheses concerning the generality of the perspective, model, and method of TC. Utilizing a common assessment instrument (the Survey of Essential Elements Questionnaire SEEQ; [12]), these studies emphasize that differences exist between standard and modified TCs in essential elements within cultures but that the similarities in elements outweigh the differences across cultures [7, 8, 10, 11].

48.2.8 Cultural Adaptations of the TC

Given the complexity of the TC as a social psychological approach, it is understandable that its implementation has been influenced by cultural context. Even within North America, for example, TC programs have adapted to ethnic diversity factors [5]. The adaptation of the TC to cultural diversity or context factors is still greater at the global level.

Beyond the above studies supporting the generality of the essential elements, there has been relatively little empirical research that focuses on cultural influences in the adaptation of the TC. However, a considerable descriptive literature of TCs in different cultures has unfolded over some four decades. Some reports can be found in scientific journals, but most are contained in the published conference proceedings of international and regional TC associations, e.g., the World Federation of Therapeutic Communities (WFTC), the European Federation of Therapeutic Communities (EFTC), the Australasian Therapeutic Communities Association (ATCA), the Latin-American Federation of Therapeutic Communities, and the Asian Federation of Therapeutic Communities.

These writings, along with the few empirical studies and the years of observations by trainers, consultants, and others, have identified various cultural context influences that are embedded in TC programs (see some examples in Table 48.2). It is beyond the purview of this chapter to discuss

Table 48.2 Some examples of cultural elements shaping the unique TC characteristics in different cultures

Gender. In cultures where there are strict norms regarding the mixing of the sexes, there are separate TCs for men and women. The segregation is not driven by clinical rationale intended to better meet the unique needs of a particular gender but more for moral and reasons of propriety.
Religion. In most Eastern TCs, religion and religious practices are integrated into the TC structure. Those who belong to minority religions are encouraged to practice their faith. Major religious holidays are observed, and program activities are tailored around celebrations of such holidays. Even dietary practices are observed.
Social organization. The traditional hierarchical structure of the TC is highly compatible with the formal and often rigid social structure in most conservative cultures. The TC hierarchical structure lends clarity which is consistent with the formal social structures of most of these societies. The delineation and lack of ambiguity of job positions and social status in the community promote social harmony. It also defines the social roles of and expectations from the community members.
Role of the recovering addict as therapist. In most Oriental or Eastern cultures, academic credentials are preferred over experiential training. The contributions of the "recovering" person as therapist are not greatly appreciated, unless the person has a college degree in addition to personal experience. It requires a paradigm shift to consider, for example, a recovering addict or a recovered mentally ill person who become therapists themselves.
Time orientation or temporal perception. Eastern culture has a fluid perception of time in contrast to Western society's highly structured time perception, "on-time" versus "in-time" orientation. Time orientation or how and when activities are implemented has implications in terms of operational efficiency and outcomes. The result-oriented and purpose-driven structure and schedule of the TC compel timeliness in order to comply with the demands and expectations of supporting and maintaining the community. Timeliness is observed across the board out of necessity, transcending cultural temporal perception.
The professional as TC staff. Many TCs outside the United States were founded by professionals who employed the services of TC-recovered ex-addicts as clinical staff along with professional staff. Working as a team, the combination creates a very progressive TC by exploiting the unique contributions of each.
Family. The importance of the family and their role in treatment in various cultures are evident in the popularity of family associations [14]. Some TCs, such as in the case of Indonesia, were conceived by parents who originally sent their children to a Malaysian TC for treatment. In due time, they initiated a TC movement in their own country. Malaysian and Chinese TCs consider family and religion (spirituality) to be central to treatment [1].

these in detail, but several working conclusions are offered concerning the TC's adaptation to cultural influences.

First, the TC perspective (i.e., views of the whole person disorder, recovery, and right living) and its approach (community as method) can be preserved and integrated within diverse cultures. Second, empirical research is needed to abstract a more complete list of cultural influences and to assess their impact on outcomes. Finally, across all cultures, maintaining *fidelity* of practice is necessary to assure the optimal effectiveness of the TC approach, a general issue which is briefly discussed in the last section of this chapter.

48.2.9 Issues and Challenges to the TC

The evolution of the contemporary therapeutic community (TC) for addictions over the past 45 years may be characterized as a movement from the marginal to the mainstream of substance abuse treatment and human services. Currently, TCs serve a wide diversity of clients and problems; they have reshaped staffing composition, reduced the planned duration of residential treatment, reset its treatment goals, and, to a considerable extent, modified the approach itself. These evolutionary changes have surfaced key issues that challenge the TC to maintain the integrity of its unique approach. Several of these are briefly highlighted: funding, workforce, research, treatment fidelity, and the diversity of TCs. Though interrelated, these issues are discussed separately.

Additionally, in the United States, many TC programs have "converted" or begun mergers with physical health clinics with the notion that TC integration with primary healthcare services will produce better outcomes [13]. However, it should be noted this integration may exacerbate the challenges of maintaining treatment fidelity.

48.2.10 Funding and Planned Duration of Treatment

Issue: The success of the TC approach has been demonstrated primarily for residential programs with planned durations of treatment of at least 9–12 months. In recent years, however, fiscal support has been steadily decreasing for long-term treatment in general and for residential treatment in particular. Thus, for the large majority of TCs that depend upon public funding, planned duration of treatment has been reduced often *below the threshold* of time needed to yield positive outcomes. This adjustment to funding pressures potentially undermines the viability of the TC as a cost-effective modality in the health-care system.

48.2.11 Workforce

Issue: The expansion of the TC to serve special populations in special settings has resulted in a number of problems in the recruitment, retention, and development of experienced staff. General problems include low salaries, limited career goals, and difficult working conditions. However, a specific workforce issue arises from the *diversity of staff* in TCs. The increased number of traditional professional staff from mental health and social services has posed a special challenge to the TC. Based on their education and training, traditional professional staff utilize concepts, vernacular, and methods that often counter or subvert the fundamental mutual self-help features of the TC. Moreover, most professionals and ex-addict paraprofessionals who work in TCs do not undergo rigorous and supervised training on the TC model and its practice.

48.2.12 Research

Issue: Despite decades of therapeutic community (TC) outcome research, some critics have questioned whether the TC is an evidence-based treatment for addictions. Given the relative lack of randomized, double-blind control trials, it is concluded that the effectiveness of the TC has not been "proven." Such conclusions contain serious implications for the acceptance and future development of the TC.

A new research agenda should build on the existing knowledge base that documents the contribution of the TC as a major health and human services modality. This agenda should include studies that demonstrate (a) *health and social benefits* (e.g., reduction in drug/alcohol use and social deviancy and increase in employment, education, and overall psychological well-being), (b) *cost-benefits* of both long-term TCs and shorter-term residential programs for specific subgroups of substance abusers, and (c) *collateral benefits* which refers to the *prevention* of trans-generational drug use, HIV, STDs, as well as family breakdown among treatment successes.

48.2.13 Treatment Fidelity

Issue: Understandably, TCs have pursued financial solvency by expanding to serve a wide variety of populations, e.g., mental health, homeless, corrections, juvenile justice, and childcare. Contracts have obligated TCs to meet regulations of community, state, and federal agencies and often to incorporate practices based upon different professional views of treatment.

This expansion outward of the TC, however, has been at the expense of *inward* refinement of the approach itself. It is one thing to modify and adapt the TC for special populations, settings, and shorter durations of treatment. It is quite another to ignore the development of the TC's unique approach, *community as method.* Thus, if the TC is to retain its unique identity within mainstream human services, it must address the complex issue of treatment *fidelity.*

TC effectiveness and fidelity of treatment are closely related. High-fidelity treatment produces better outcomes [7]. The key strategies needed to assure high-fidelity TCs are staff training based upon critical elements, teaching curricula grounded in a uniform definition of community as method, and appropriate training models that integrate didactic and experiential learning.

Table 48.3 Classification of TC programs

Standard TC programs. These are guided by the TC perspective, retain essential components of the program model, and utilize community as method as the primary approach. They are mainly housed in residential settings, with longer planned durations of treatments, serving the more severe substance abusers (primarily client driven).
Modified TC programs. These are guided by the TC perspective, incorporate essential components of the model, but adapt community as method for special populations (e.g., co-occurring disorders, criminal justice substance abusers, juveniles) and settings (hospitals, shelters, prisons). Key adaptations are more staff directed, greater emphasis on individual differences, moderated intensity of group process, and a more flexible program structure. Additionally, these programs incorporate strategies and services which have proven useful in addressing particular problems and special populations, including pharmacotherapy (e.g., methadone, buprenorphine, psychotropic medications) as well as varieties of counseling and family therapy (client and staff driven).
TC-oriented programs. These *are not* guided by the TC perspective and do not adhere to community as method. Typically, these serve less severe clients in short-term residential or day treatment settings and are eclectic in their approach. They select elements of the TC (e.g., community meetings, peer support group, etc.) but mainly utilize services and practices that are not specific to the TC (primarily staff driven).

48.2.14 Diversity of TC Programs

Issue: The TC approach and model have been successfully adapted and modified for various populations and settings. However, within the wide diversity of programs that represent themselves as TCs, many do not actually implement the TC approach that has proven successful. This often results in variable treatment outcomes and fosters misperceptions of the therapeutic community as an effective evidence-based approach. The credibility of the TC modality in health and human services will require classification of the diversity of programs as well as the development of standards of quality assurance.

48.2.15 Classification of TC Programs

The range of TC programs for substance abuse and related problems can be organized into three broad categories. These are based upon the extent to which a program is guided by the TC perspective (whole person, recovery, and right living), adheres to the approach (community as method), and retains essential components of the program model (see Table 48.3).

Thus, not all programs that label themselves as therapeutic communities are actually TCs. Clarification of differences in programs, the clients they serve, the goals of treatment, and the fidelity of the particular treatment strategies utilized, is necessary to preserve the integrity of the TC approach.

Finally, TCs worldwide are also undergoing many of the evolutionary changes described above, including modifications for special populations and particularly adapting to fiscal pressures to reduce time in residential treatment. A notable development is the rapprochement between the addiction TC and the psychiatric TC pioneered by Maxwell Jones that has been prominent in Europe. Both of these TC approaches share many of the common elements of community as method to treat populations with both substance use and personality disorder. Nevertheless, maintaining uniformity and fidelity of the TC approach in light of these changes remains a challenge.

48.3 Conclusion

Arguably, the therapeutic community for addictions (TC) is the first formal treatment approach that is explicitly *recovery oriented.* Surely, AA and similar mutual self-help approaches facilitate recovery, but these represent themselves as support, not treatment. Pharmacological approaches, notably, methadone maintenance, have as their treatment goal the reduction or elimination of illicit opiate use; and behavioral approaches, such as cognitive-behavioral therapy (CBT), contingency contracting, and motivational enhancement (MET), focus upon reduction, and not necessarily abstinence and recovery, in targeted drug use. In the TC perspective, however, the primary goal of treatment is *recovery* which is broadly defined as changes in lifestyles and identities.

Thus, in the current context of substance abuse policy and issues (e.g., various treatment options, harm reduction strategies, the economic pressures on health care), the overarching challenge of the TC is to reassert its unique place and mission – that of promoting recovery and right living.

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Spiritual Aspects of the 12-Step Method in Addiction Treatment

49

Marc Galanter

Contents

Abstract

This chapter is directed at defining the nature of spirituality and its relationship to empirical research and clinical practice. An understanding of the spiritual experience can be achieved on the basis of diverse theoretical and empirically grounded sources. Furthermore, the impact of spirituality on addiction in different cultural and clinical settings is explicated by illustrations of its application with regard to Alcoholics Anonymous, Narcotics Anonymous, and Danshukai (Japan).

Keywords

Spirituality · Addiction · Alcoholics anonymous · Treatment · Recovery

49.1 Introduction

49.1.1 AA as a Spiritual Recovery Movement

How does spirituality relate to recovery from addiction? There is a parallel between the way attitudes are transformed in intensely zealous groups and the way the denial of illness and the self-defeating behaviors of people with alcohol and substance use disorders may be reversed through induction into 12-step groups like AA.

Members of the lay public may conclude that certain healthcare issues are inadequately

M. Galanter (✉)
Division of Alcoholism and Drug Abuse, Department of Psychiatry, NYU School of Medicine, New York, NY, USA
e-mail: marcgalanter@nyu.edu

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addressed by the medical community, particularly when doctors are not sufficiently attentive to the emotional burden that an illness produces. When mutually supportive groups of laymen coalesce to implement a response to this perceived deficit, they may form a spiritual recovery movement [15], one premised on achieving remission based on beliefs independent of evidence- based medicine. Such movements may ascribe their effectiveness to higher metaphysical or nonmaterial forces and claim to offer relief from illness.

AA can be considered as a highly successful example of a spiritual recovery movement, as such movements have three primary characteristics. They (a) claim to provide relief from disease, (b) operate outside the modalities of established empirical medicine, and (c) ascribe their effectiveness to higher metaphysical powers. The appeal of such movements in the contemporary period is due in part to the fact that physicians tend not to attend the spiritual or emotional concerns of their patients [16].

Clearly, the attitudes and behavioral norms that AA espouses are much more in conformity with the values of the larger culture than those of zealous religious sects. The expectation of avoiding drunkenness in AA, normative in our culture, illustrates this. People who are highly distressed over the consequences of their addiction are therefore candidates to respond to the strong ideologic orientation of AA toward recovery and are operantly reinforced by the relief produced by affiliation with the group's ideology and behavioral norms, all related to abstinence and a spiritually grounded lifestyle. Significantly, AA generates distress in its members by pressing them to give up their addictive behaviors, but the distress associated with this conflict is relieved if they sustain affiliation and cleave to the group [20, 21].

49.2 Spiritual Aspects

49.2.1 Spirituality as a Psychological Construct

Two empirically grounded perspectives have played a material role in framing how we conceptualize recovery. One is derived from a model of psychopathology modeled on the work of Emil Kraepelin [27]. He framed an approach that now characterizes the contemporary medical model for mental disorders, categorizing disease entities diagnosed on the basis of explicit and discrete symptoms. This approach is evident in the development of criteria for substance use disorders employed in recent editions of the symptom-based *Diagnostic and Statistical Manual of Mental Disorders* [2]. From this perspective, a state of remission, colloquially called recovery in rehabilitation circles, can take place with the resolution of the specific symptoms listed as diagnostic criteria. A second perspective on recovery derives from behavioral psychology, whose model of stimulus-response sequences has led to the ordering of experience around discrete phenomena that can be observed by a researcher or clinician. From this perspective, recovery can also be defined in terms of observable, measurable responses to substance use, lending credence to recovery as a process defined in behavioral terms.

Both perspectives are well suited to the study of psychopathology and have lent the addiction field approaches to studying addiction as a disorder, one that is compatible with research approaches employing experimental controls that are used in the physical and biological sciences. Both have therefore had heuristic value in promoting a research field that has yielded many advances in addiction treatment. There is a third perspective, however, that is defined on the basis of addicts' reports of their own subjective experience. These experiences are not directly observable by the clinician but are available only as reported through the prism of the person's own introspection and reflection. This model is more difficult to subject to measurement, but instruments are being developed that can be applied for its study, as will be discussed below. This approach is inherent in the spiritually oriented psychology of Carl Jung [25], who had a direct influence on Bill W's framing of the Alcoholics Anonymous ethos [5]. James [24], often described as the father of American psychology, also discussed mental phenomena in terms of subjectively experienced mystical or spiritual experience. (In fact, he wrote that "the drunken consciousness is one bit of the mystic conscious-

ness" [p. 378].) The need for spiritual redemption was vital in the writings of Viktor Frankl, who wrote *Man's Search for Meaning* [14], and has recently been espoused with regard to psychotherapy by William Miller [31].

This third perspective is related to the model of spiritually grounded recovery we will discuss here, insofar as it emphasizes the achievement of meaningful or positive experiences, rather than a focus on observable, dysfunctional behaviors. Research on this third approach would typically rely on self-report scales, such as those which can be facilitated by development of instruments like the Life Engagement Test [34], the General Well-Being Schedule, or our own Spiritual Self-Rating Scale [17]. We will consider its role in AA, models for how it takes place, and ways it can be measured. In this respect, recovery can be understood as a process whereby an abstinent addicted person is moving toward a positive adaptation in life. This movement can take place with varying degrees of success, depending on the person's own innate capacities and the circumstances in which they find themselves.

49.2.2 Spirituality and Religious Experience

The relative role of spiritual experience in the 12-step recovery process has been investigated from a variety of perspectives, generally in relation to patients' experience in AA. Kelly et al. [26] reviewed studies that applied mediational tests to ascertain how AA achieves beneficial outcomes and found little support for a role of AA's specific spiritual mechanisms. In fact, with regard to religiosity, Tonigan et al. [36] found that, although atheists were less likely to attend AA meetings, those who did join derived equal benefit as did spiritually focused individuals. On the other hand, in one study on persons recovering from cocaine dependence [13], respondents attributed their positive outcomes to religion and spirituality. Additionally, Zemore [39] followed-up a large sample of substance abusers 1 year after inpatient treatment and found that increases in spirituality contributed to the increment in total abstinence associated with 12-step involvement.

Our own experience, as well, is compatible with these findings, as we have found in multiple settings [19] that spirituality is integral to recovery in 12-step groups. This was particularly evident among long-term members.

49.2.3 Spiritually Grounded Recovery in AA

The AA "program of recovery" is mentioned in numerous places in the *Big Book*, Alcoholics Anonymous [1], and is associated there with terms such as "spiritual experience" and "spiritual awakening" and with working AA's 12 steps. Four of the steps include the word God, which is qualified "as we understood Him." Some clarity is lent to this latter phrase in the *Big Book* where it is pointed out that "with few exceptions, our members find that they have tapped an unsuspected inner resource which they presently identify with their own conception of a Power greater than themselves" (p. 569–570). Flexibility on the issue of theistic belief is also made clear in one chapter that addresses any alcoholic person "who feels he is an atheist or agnostic," encouraging their membership as well. The text points out for these members that even "We Agnostics…had to face the fact that we must find a spiritual basis for life" (p. 44) in order to achieve recovery, implying therein the fellowship's distinction between spirituality and theistic religion.

This issue of theistic connotation, however, is as yet resolved relative to the judicial system, where the application of AA is sometimes constrained because of potential church/state conflicts. It is open to question, however, whether the theistic connotations of AA can be modified without vitiating the program's effectiveness. In this relation, it should be noted that in a 5-year follow-up of recovering cocaine-dependent patients, the strength derived from religion and spirituality significantly distinguished between those who had a highly favorable outcome from those who did not [13]. Additionally, attendance at religious services distinguished significantly between criminal justice clients referred for substance abuse treatment who had a positive outcome and those who did not [3].

Spirituality among long-term members is likely instrumental in sustaining the integrity of the fellowship itself. The prominence of spiritually committed long-term members at meetings, and their availability to serve in the sponsorship role, creates readily available models for earnestly held sobriety. They serve as role models for believing commitment to the 12-step spiritual ethos to help newcomers achieve stabilization in membership. Nonetheless, some people attending NA meetings may find it hard to identify with the spiritual orientation of long-term members.

In the clinical context, recovery is based on a person's behavioral and physiologic status, which can be assessed by recourse to criteria employed in the DSM. Some of these criteria are also embodied in the Addiction Severity Index [30], which is employed widely in research to evaluate recovery. These items can be assessed relatively easily, as they are premised on observable behavior or delineated by symptomatology described by patient, family member, or clinician. A spiritually grounded definition of recovery, however, can be useful as well.

Such a concept relates to the importance of non-demographic subject factors, originally proposed as "quality-of-life" issues [4] – among which spirituality can be considered. In this context, a series of suitable criteria for "diagnosing" addiction (a more apt term than "substance dependence") could be developed. They could then be used to assess the spiritual aspect of recovery associated with the 12-step experience. Resolution of these issues could be considered as important to the spiritual aspect of recovery from addiction. A series of criteria could include items such as

- Loss of sense of purpose due to excessive substance use
- A feeling of inadequate social support because of one's addiction
- Continued use of a substance while experiencing moral qualms over its consumption
- Loss of the will to resist temptation when the substance is available

Another aspect of the DSM format can be considered as well. The manual stipulates "course specifiers" of remission such as "on agonist therapy" and "in a controlled environment." These are included because they are explanatory to the clinician. To them could be added "fully engaged in a program of 12-step recovery," which would be equally explanatory to many clinicians.

But are spiritually grounded criteria measurable? In recent years, methodologies have been developed and validated that could be used to assess outcome based on such subjectively experienced criteria. They employ a systematic approach to measurement and can be used to describe spiritually related states:

A. Affective state:
   (i) A sense of well-being, measured by the General Well-Being Schedule [11] (which we employed) or the Subjective Happiness Scale [28]
   (ii) Contentment with one's life circumstances, measured by the Satisfaction with Life Scale [10]
   (iii) Positive affect, assessed with the Positive and Negative Affect Schedule [37], dealing with both variables as separate dimensions, rather than bipolar ends of the same scale
   (iv) Feelings of support, employing a Scale for Perceived Social Support [6]
B. Existential variables: Meaningfulness in one's life: assessed by the Purpose in Life Test [8].
C. Flow: The experience associated with engaging one's highest strengths and talents to meet achievable challenges, as measured by Experience Sampling [9] or the Flow Scale [29].
D. Spirituality: The Spirituality Self-Rating Scale, which we developed and applied to both substance-abusing and non-substance-abusing populations [17], as well as other such scales. By means of our own scale, we were able to distinguish different populations of substance abusers' level of spiritual orientation from the of non-substance populations.

E. Personality assessment: The Classification of Strengths [33], a series of characteristics based on categories of moral excellence drawn from observations across different cultures.
F. AA involvement: Measures of the degree of affiliation and commitment to the AA fellowship [23].

A methodology for defining recovery based on measurements like these may not have the same appeal to biomedically oriented clinicians as does the conventional symptom-based approach, as these measurements are based on self-report of the person's subjective state. Furthermore, the enthusiasm of newfound recovery may yield a Hawthorne effect. The biomedical format currently applied in diagnosis derives from the school of Kraeplin and subsequent investigators like those who developed the Feighner criteria [12] in the 1970s and then in the ensuing DSM system. Spiritual variables, however, have a lineage as well, from William James, Carl Jung, and Bill W.

Spiritual awakening, a key aspect of 12-step recovery, is designated in the twelfth step of Alcoholics Anonymous (AA). Of long-term AA members who reported having had such an awakening, two-thirds reported no craving for alcohol or drugs at the time of the survey. Their responses reflected a major experiential transformation [18], which can be likened to religious conversion, because both involve a major transformation in personal disposition toward a spiritually oriented perspective on life. Pargament [32], who defined *religion* broadly as "the search for significance in ways related to the sacred" (p. 32), wrote of religious conversion as taking place only when a change comes about in both the destinations and pathways of a person's life in connection to the sacred.

49.2.4 Danshukai

The worldwide growth of secular but spiritual mutual aid organizations promoting addiction recovery has led to the option of people achieving addiction recovery outside of professional treatment. One example of the diverse approaches worldwide is Danshukai.

Japan has a history of recovery by mutual support in the Danshukai movement. Danshukai draws on Zen Buddhism and contains elements that parallel AA, such as undercutting denial, a process of amends, and service [38]. Danshukai meetings, however, typically include family members and offer prayers for those who have passed. The meetings are also much more structured than AA meetings, with decreased emphasis on anonymity. Attendees sign in on their entering the meeting, use their full names, and may wear Danshukai pins, indicating their membership.

49.2.5 AA in the Professional Context

The spiritually oriented 12-step approach has been integrated into professional treatment in some settings where it serves as the overriding philosophy of an entire program or, in others, where it is one aspect of a multimodal eclectic approach. The Minnesota Model for treatment, typically located in an isolated institutional setting, is characterized by an intensive inpatient stay during which a primary goal of treatment is to acculturate patients to acceptance of the philosophy of AA and to continue with AA attendance after discharge [7]. Although a variety of exercises are included during the stay, this approach has been criticized as dogmatic because of its sole reliance on the 12-step approach. The outcome of this model, however, has been shown to yield positive results in a survey of patients discharged from one such setting (Hazelden, in Center City, MN) [35], but randomization of patients treated in Minnesota Model facilities with those treated by means of an alternative approach is needed.

A more eclectic option is illustrated in the integration of 12-step groups into a general psychiatric facility for the treatment of patients dually diagnosed for major mental illness and substance abuse. The importance of spirituality in such a highly compromised population was

evidenced in our studies [17] in which such patients ranked spiritual issues like belief in God and inner peace higher than tangible benefits like social service support and outpatient treatment. One inherent advantage of this format is that it benefits from the introduction of an inspirational approach to patients who, as Goffman has pointed out [22], have become "degraded" by stigmatization due to their psychiatric disorders.

In summary, spirituality is a matter of personal meaning that is widely accepted. It is also central to the recovery process from addiction for many AA members. The fellowship of AA, in fact, can be considered a movement developed in relation to people's spiritual needs. Although spirituality is subjectively experienced, it can be assessed systematically in given individuals by employing currently available empirical techniques. By such means, an important aspect of addiction recovery can be defined and studied.

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50 Addiction Recovery in Services and Policy: An International Overview

David Best and Rebecca Hamer

Contents

Abstract

This chapter provides an overview of the changes occurring in the recovery field in the United States and internationally, with special emphasis on the growing focus on recovery as the guiding vision for drug policy and as a framework for treatment. 'Recovery' goes beyond substance use to encompass improved functioning in all life areas and the realisation of individual aspirations. As substance use disorders are often chronic and relapsing, recovery is conceptualised as a process that unfolds

D. Best (✉)
University of Derby, Derby, UK
e-mail: D.Best@derby.ac.uk

R. Hamer
Sheffield Hallam University, Sheffield, UK

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over time and requires a continuing care approach. We describe emerging service models, including recovery-oriented systems of care (ROSC) and the centrality of peer-driven recovery supports as part of a social and community emphasis on recovery sustainability. We conclude with some recommendations on strategies that professionals, peers and communities can be used to promote recovery amongst substance-using individuals.

50.1 Introduction

As healthcare evolves, healthcare professionals are grappling with new systems and care models whilst continuing to diagnose and treat human conditions such as substance misuse. However, the way society views addiction has changed over time – from moral failing or crime to chronic brain disease [77], with resulting changes in how addiction is addressed by healthcare services. In this chapter, we describe recent developments in a recovery orientation to substance problems. The chapter examines global research innovations, policy and practice responses and the integration of recovery-oriented approaches into healthcare and social care services.

50.2 Recovery as a Guiding Vision of Substance Use Services and Policy

There are two empirically based elements to the shift in policy and practice: the reconceptualisation of problem drug use as a chronic disorder requiring both treatment and ongoing recovery support and the broadening of what 'recovery' means. First, research in the past 20 years has concluded that addiction is best understood as a chronic disorder equivalent to diabetes, asthma or hypertension [77]. However, unlike these other conditions, treatment for problem drug use (PDU) has historically been delivered using an acute care model: intense episodes of care during which a person, often in crisis, is assessed, treated and discharged in a relatively short time [27, 56]. Growing evidence for long addiction and treatment 'careers' consisting of multiple cycles of treatment episodes [28, 45] followed by return to active addiction [94] has led to the conclusion that the acute care model is inadequate [44, 56, 78, 79, 87]. Kelly [56] contends that medical intervention alone is insufficient in achieving and maintaining recovery and that it is imperative for ongoing, long-term recovery support to be delivered following stabilisation and treatment phases. A continuum of care model consistent with chronic disease is also aligned with the experience of persons in recovery who overwhelmingly describe recovery as 'a process' versus 'an end point' [60].

The second element of the paradigmatic shift was summarised by McLellan and colleagues as'*the immediate goal of reducing alcohol and drug use is necessary but rarely sufficient for the achievement of the longer-term goals of improved personal health and social function and reduced threats to public health and safety – i.e., recovery*' ([79], p. 448). The emerging recovery-oriented model provides a continuum of support designed to promote and sustain improvements in substance use and psychosocial functioning. This reconciles a public health response with a strength- and community-based focus that places the individual at the heart of their own recovery journey and emphasises personal empowerment and individual ownership of recovery. Promoting recovery requires giving individuals the tools and strategies to develop 'capital', a strength-based approach that has gained prominence in both psychology [96] and criminology [92] and is embodied in the addiction field by the construct of 'recovery capital' [35].

Hennessy [40] asserts that the concept of recovery capital provides an exploratory framework with which to identify assets and obstacles to recovery to be built upon or ameliorated in order to support recovery journeys. Amongst the six recovery capital (RC) models included in Hennessy's [40] systematic review, recovery is characterised as ongoing and dynamic, is variable between and within individuals, consists of a broad range of resources from macro, meso- and individual levels, which can interact to further

build or deplete RC, and suggests that places, communities and resources can all intersect to generate and embed recovery capital. Finally, recovery is contagious through individuals, groups and society [40].

50.3 What Does 'Recovery' Mean?

The term 'recovery' has been widely used for decades but, until recently, had remained poorly defined. Researchers typically used the term in studies by measuring short-term abstinence (typically a year or less), some from a single substance (e.g., alcohol) and others from all substances (for a discussion, see [60]). In 2005, the Center for Substance Abuse Treatment (CSAT), convened a panel of experts representing a number of key stakeholder groups [20]. The following year, the Betty Ford Center convened a smaller panel of experts and stakeholders that published the first consensus definition of 'recovery' as 'voluntarily maintained lifestyle composed characterised by sobriety, personal health, and citizenship' ([10], p. 221).

The UK Drug Policy Commission [99] echoed these definitions whilst asserting that recovery can be achieved through a diverse range of strategies, including substitution therapy if desired, to provide a holistic continuum of care and support.

White [105] expands upon this, asserting that recovery consists of three elements: sobriety, improvements in global health (referring to the physical, emotional, ontological, life meaning and purpose) and citizenship. The Substance Abuse and Mental Health Services Administration [93] further elaborated a dual conception of recovery for both mental health and problem drug use, delineating ten guiding principles for recovery:

1. Hope: The power of hope is fundamental for individuals, families and communities to feel recovery is possible.
2. Relational: Recovery entails the formation of strong relationships with those who share hope and a vision for recovery, through which new positive identities and roles may be established, providing a sense of belonging, community and agency.
3. Person driven: Recovery is a personal journey, and it is fundamental that each recovery journey is navigated according to individual self-determination.
4. Culture: Recovery pathways are unique according to cultural values and beliefs.
5. Many pathways: The routes to recovery are diverse and comprise a broad spectrum of formal or informal support.
6. Holistic: Recovery is a multi-faceted process entailing improvements across all domains of quality of life and wellbeing.
7. Peer support: Peers are fundamental in providing mutual aid, modelling prosocial behaviour and possibilities to PDU and to communities. Furthermore, peer involvement provides those in recovery with new alternative identities to share their experience to help others and opportunities to reintegrate with and give back to their communities.
8. Strengths/responsibility: Individuals, families and communities all have assets that can be built upon to strengthen recovery.
9. Respect: Discrimination, stigma and ostracisation present significant obstacles to recovery, and so it is crucial that recovery systems recognise the bravery of those pursuing recovery and that their rights are respected.
10. Addresses trauma: Mental health problems and PDU are often preceded and exacerbated by experiences of trauma, whilst trauma similarly presents obstacles to recovery. Therefore, services and systems must be trauma aware and work to ameliorate the destructive effects of posttraumatic stress disorder (PTSD).

Correspondingly, Bassuk et al. [7] attest that *'as a broader definition of recovery gains traction, it is critical that future research expands to mirror the various domains of recovery by including outcomes related to housing, employment, educational status, quality of life, functioning, trauma exposure, mental health status and social support networks'*.

50.4 Recovery Prevalence

According to Huskamp and Iglegart [49], 82% of people with substance use disorders do not receive adequate treatment, whilst abstinence rates are complicated by very high mortality rates. Thus, whilst Grella and Lovinger [37] reported an abstinence rate of 80% in the surviving sample, the rate reduced to 30% if the individuals who had died were included in the study. In their review of remission rates, Hser et al. [45] contradicted the idea of 'maturing out' by suggesting that abstinence rates drop to around 30% after 10 years and then remain relatively stable, irrespective of age or chronicity of use. They concluded that opioid addiction is a chronic disorder characterised by frequent relapse, but that 'longer treatment retention is associated with a greater likelihood of cessation, whereas incarceration is negatively linked to subsequent abstinence' (p. 85).

In a review of 415 population and clinical studies between 1868 and 2011, around half of study participants reported remission from substance use disorders at the final study follow-up point. In Fleury et al.'s [31] systematic review and meta-analysis of 21 papers examining remission from substance use disorder, a standard remission rate of 54% and a conservative remission rate of 35% were reported after a mean of 17 years.

In a population-based representative US sample ($n = 39{,}809$), Kelly et al. [55] found that of respondents answering 'yes' to -'Did you use to have a problem with alcohol or drugs but no longer do?' 9.1% of the sample were in recovery, of whom 46% self-identifying as 'in recovery', whilst 53.9% reported 'assisted' pathway use. Assisted pathways were most common for opioid users and least common for cannabis users.

50.5 What Does Adopting a Recovery Orientation Mean for Addiction Treatment Services?

The paradigm shift discussed above mean that recovery supports need to be expanded in time, in philosophy and in scope. In terms of time, PDUs have thus far been addressed using intensive, short-term episodes of professionally delivered services. Whilst treatment is generally reported to be effective [101, 102, 103], return to active use following treatment, even amongst those who had achieved abstinence, is high [28, 45, 64, 78, 79]. Kelly [57] notes that in early recovery, people experience higher levels of stress-causing hormones such as cortisol and corticotropin, and thus their ability to learn new skills is hindered whilst their vulnerability to stress-triggered relapse is greater. Consequently, the ongoing recovery support favoured by Kelly [56] factors biological, neurobiological and psychosocial domains within ongoing support, monitoring and intervention to navigate potential or actual relapses along the recovery journey. Kelly [56] identifies four fundamental types of such ongoing recovery support:

- Emotional support
- Tangible support (e.g., links to housing)
- Informational support (advice/learning)
- Social support (sense of belonging)

Recovery support services are increasingly diverse and accessible, and Kelly [56] identifies six types of recovery support services (RSS) in the USA:

- Peer-based recovery support services
- Recovery community centres
- Recover support in education
- Mutual-aid organisations
- Recovery housing
- Clinical models

Most studies exploring the effectiveness of peer recovery support confirm the benefit to participants [7, 29, 98]. Although endorsement of the value of PBRSS is 'tentative', peer support can play a significant role in reducing relapse, building greater trust and relationships between service users and providers, forging prosocial networks and providing greater satisfaction and retention in treatment, so that there is support for integrated peer and professional support [29]. However, the specifics regarding the

impact of different levels of peer ability and experience, intervention intensity, duration, frequency and context in addition to the efficacy of peer support for specific populations remains to be explored [7].

Despite the supportive evidence, Greer et al. [36] have identified several barriers and disadvantages peer workers suffer. Stigma from non-peer workers can isolate peers in the workplace and diminishes their achievements. Peer work is also often subject to exploitation, low wages and the expectation of volunteering. As peers often go above and beyond as their motivation is to help their communities, this can be practically, emotionally and financially under-appreciated by employers who do not provide the necessary support, esteem and compensation given the dedication, expertise and passion of most peer workers. Peers may be at heightened risk from vicarious trauma and compassion fatigue which may endanger their own recovery. Further, the interference of peer work with welfare payments can result in individuals being disadvantaged. In Canada, peer work is separated entirely from welfare support and payments, ensuring that their contribution to their communities is suitably facilitated and valued. The BC Centre for Disease Control website features Peer Engagement Best Practice guidance as a result of their 3-year Peer Engagement and Evaluation Project (PEEP).

SAMHSA has begun to develop relevant guidelines ([7], p. 8). Awareness of discrimination, barriers and needs is fundamental if services and systems are to recognise the expertise, value and power that peers bring to recovery services and communities. In addition to asserting PBRSS as an 'evidence-based practice', additional research is required to implement peer support and to foster experiential experts whose knowledge, perspective and empathy inspire recovery [7, 29].

A recovery orientation requires the provision of comprehensive services to address needs in all life areas impaired during active addiction and where improvements are considered an inherent part of recovery, for example, physical and mental health, employment, economic, family and social life. Services addressing these issues have thus far often been referred to as 'ancillary' in status or 'aftercare' in the timing of delivery in spite of their importance to clients and their role in the transition to stable recovery [65]. Laudet and White [62] examined challenges and life priorities in a sample of 356 community-based persons in abstinent recovery and found that working on one's recovery (e.g., staying sober and 'making recovery a priority') was consistently cited as the top priority (cited by 34–49% across stages). Employment was the second most frequently mentioned priority, cited by the same percentage of persons abstinent over 3 years as working on one's recovery (34.1% each).

As both approaches originate from different models, Galanter [33] contends that treatment and recovery support must be defined as separate but related stages. The implication is that the partnership and streamlining of relationships and referrals between professional treatment and ongoing recovery support services hold great potential for improving service users' recovery chances.

50.6 Recovery-Oriented Systems of Care (ROSC)

In the United States, the shift to a recovery orientation in treatment has been primarily spearheaded by the Substance Abuse and Mental Health Services Administration (SAMHSA), whilst in the United Kingdom, impetus to formalise recovery orientation has come from the English and Scottish Government, as discussed below. The need for this new model was perhaps stated most explicitly by a SAMHSA lead: 'Recovery is more than abstinence from alcohol and drugs; it's about building a full, meaningful, and productive life in the community. Our treatment systems must reflect and help people achieve this broader understanding of recovery' ([23], p. 2). ROSC's goals are to intervene early with individuals, to support sustained recovery and to improve the health and wellness of individuals and families. The ROSC model proposes a multisystem, person-centred continuum of care in which a comprehensive menu of coordinated

services and supports is tailored to individuals' recovery stage, needs and chosen pathways [22, 23]. Services and supports are provided in a comprehensive array of domains, including education and job training, housing, childcare, transportation to treatment and work, case management, spiritual support as well as prevention services, for example, relapse prevention, recovery support, education for family members, peer-to-peer services and coaching, self-help and support groups [53, 97].

Services are intended to address the multitude of life areas adversely affected by active substance use and to respond to clients' changing needs across their lifespan. ROSC is responsive to calls for a shift from the acute care model to one more akin to the model used in other chronic conditions [48, 50, 77, 106]. From a systems perspective, this means that the care coordination function of services is conferred a more prominent role in treatment design and delivery. Key principles guiding the recovery orientation include primacy of participation; promoting access and engagement; ensuring continuity of care; employing strength-based assessment; offering individualised recovery planning; functioning as a recovery guide; community mapping, development and inclusion and identifying and addressing barriers to recovery [58, 59].

Implementing ROSC internationally will require transformative changes in agencies and systems, which has implications for the training and evaluation of peer and professional staff and service managers and those responsible for commissioning services.

50.7 What Do Recovery-Oriented Addiction Services Systems Look Like?

In supporting the transition to continuing care approaches, the most common form of aftercare consists of a stepped down course of services typically following intensive inpatient or residential treatment [73, 74, 76]; in spite of its established existence and intuitive appeal, few clients access these resources, and the evidence for effectiveness remains limited [34, 73]. In the past decade, clinicians have also started to capitalise on health technology such as telephone-based continuing care [75], and several large treatment agencies are developing proprietary web-based online recovery maintenance and support programmes for clients to use after they leave service. Ashford et al. [5] explored digital recovery support services (DRSS), observing that these can take the form of websites, online forums, social networking, smartphone apps and text messaging services. The authors reported that DRSS has not been demonstrated to facilitate and support recovery journeys, due largely to the anecdotal and qualitative nature of accounts. However, its popularity and proliferation support these testimonials. In the USA, 11% of adults in recovery have used one or more DRSS and their digital format can provide more available and accessible recovery support, particularly for especially stigmatised populations [5].

50.8 Individual Recovery Support Services Elements

A range of recovery support services (RSS) have been described in recent articles and monographs that also review the emerging science [53, 61, 97, 104, 105]. Unlike professionally delivered aftercare, peer-based RSS are not only delivered after treatment but can also be provided alongside professional services. This is important as there are often barriers to treatment that include wait lists, finances, stigma and ambivalence about seeking professional help [3, 26, 65, 109]. RSS are often delivered by peers, individuals who have experiential knowledge [17] and work as volunteers or as paid service workers [53] to assist others in initiating and maintaining recovery and enhancing their quality of life [105]. Many individuals in recovery report that being in the company of peers is helpful [35, 63, 71, 86]. In Glasgow, Scotland, one study found that the two strongest predictors of positive quality of life in recovery were spending time with other people in recovery and engagement in meaningful activities, including working, training, volunteering and involve-

ment in community groups [12]. A series of systematic and scoping reviews have surmised the overall promise of peer and self-help group supports in alcohol and drug recovery, albeit this endorsement is tentative due to the lack of methodological rigor and depth of exploration within research [7, 8].

One key aspect of peer involvement is around assertive linkage to prosocial groups. Manning et al. [70] showed significantly greater engagement in mutual aid groups during and after residential treatment when supported by peer assertive linkage (compared to doctor referral or written information). Following up on this, O'Connell et al. [88] used a similar design with patients with co-occurring disorders but added ongoing peer support and found that this condition was associated with lower psychotic symptoms at 9 months and better ongoing treatment engagement.

Andreas et al. [1] reviewed the Peers Reach Out Supporting Peers to Embrace Recovery (PROSPER), a programme involving peer-run groups, coaching, workshops and seminars and extensive training and supervision for peers. Engagement in the programme resulted in increases in self-efficacy, perceived social support, and quality of life. In a Native American context, Kelly et al. [55] found that participation in a peer recovery support service that was community based resulted in reduced recent alcohol and drug use and better rates of employment and stable housing.

Parkman et al. [90] found three factors to determine the efficacy of self-help groups (in this case, for alcohol treatment): attendance, involvement (as a measure of active engagement) and location (proximity to the meeting place and the home of a key worker). Some of the benefits of peer groups are their impact on social networks and sense of identity, as it is the active participation and inclusion in a prosocial group that correlates with positive recovery outcomes.

Perhaps the most well-known and widely available peer self-help model is 12-step mutual aid [54]. In a review article of 12-step facilitation, Kelly [55] reported that eight of the fifteen studies found that the 12-step facilitation produced superior outcomes on at least one of the outcome indicators. In the same review, Kelly [55] concluded *that 'the evidence in this regard is strong. TSF interventions and AA participation is associated with improved substance use outcomes, particularly prolonged abstinence and remission, and is likely to be highly cost-effective'* (p. 18). In a 16-year follow-up study of alcohol treatment, [83] reported that, following the initial 6 months of treatment, 12-step involvement was associated with better outcomes than further professional treatment. Humphreys and Moos [47] have argued that whilst an initial episode of specialist treatment may be beneficial, long-term 12-step engagement may be a better predictor of outcomes over time.

There are other models of peer-based recovery support, including the sober residence, a home that offers mutual help-oriented, financially self-sustaining, self-governed, democratic communal-living environments where individuals in recovery can reside for as long as they choose after inpatient treatment or incarceration, during outpatient treatment or as an alternative to treatment [91]. Recovery residences or sober living houses provide stable housing and a structured, prosocial living environment, and such housing comprises a critical component on the continuum of recovery-oriented systems of care [81].

Recovery housing is derived from mutual aid traditions, the most prevalent of which in the States is Oxford Houses Inc., who have established 2287 houses across 44 states [85]. The benefits of the model in terms of substance use and related domains (e.g., employment, criminal involvement) have been documented in peer-reviewed studies across subpopulations [2, 51, 52, 68, 69, 82], as has been its cost-effectiveness [67, 89]. Chavarria et al. [21] conducted a 2-year followup comparing Oxford Houses Inc. and a standard continuing care model and reported that at 2 years, the clients of Oxford Houses Inc. were more than twice as likely to be abstinent, had higher monthly incomes and were less likely to be incarcerated.

There are now national standards governing recovery houses, although there is a lack of empirical findings correlating recovery resi-

dences with improved outcomes. Mericle et al. [80] found that the type of recovery house resulted in varying results – houses that were part of a group or a wing of a larger organisation led to increased chances of abstinence, whilst those affiliated with a treatment programme improved employment outcome.

50.9 Therapeutic Communities

Therapeutic Communities (TCs), such as San Patrignano in Italy and River Garden Auchincruive in Scotland, also provide residential, peer designed and led environments in which recovery is facilitated and maintained by the mutually supportive recovery community. Therapeutic Communities (TCs) were developed in the 1960s in the USA in response to the lack of capacity in healthcare and social care services to respond to the treatment needs of problem drug users. These were often privately funded and centred around self-help. Although they filled a certain gap in provision, there were issues of professionalism, the ability to upscale consistently and with leadership powers creating unmoderated, abusive and punitive cultures within communities [100]. Synanon, founded by Charles Dederich, was implicated in intolerance of relapse and aggressive shaming measures such as head shaving, verbal abuse and making residents who failed to adhere to house rules wear signs featuring stigmatising and debasing labels in public [108]. Whilst some such practices persisted until the late 1970s, radicalised communities were increasingly replaced as recognition of variation in recovery, addiction experiences and populations; professional standardisation and progressive policies and procedures permeated the TC field [19].

In a significant departure from the dictatorial early days of Synanon, TCs in various countries across Europe have since developed to meet the needs of specific populations with complex needs such as women and children and individuals with dual (concurrent mental health) diagnoses [100]. TCs are also being established in prisons, and transitioning programmes also assist in reintroducing those who have achieved recovery into the community [100]. Therapeutic Communities have thus evolved to encompass the current broader vision of recovery, recognising the breadth of need and experience amongst PDU populations and the importance of community reintegration and cohesion. Whilst TCs in Europe were initially inspired by the revised American equivalents, European theories and techniques plus staff comprising of trained professionals and a focus on the family unit marked these communities apart [100].

Vanderplasschen et al. (2014) conducted a literature review of 28 articles set in the USA and 21 undertaken in Europe exploring the efficacy of TCs. The authors note that '*There is some evidence for the effectiveness of TC treatment in terms of reduced substance use and criminal activity, at least in the USA. A small number of studies also showed positive effects on employment, social functioning and general mental health'*. This implies that TCs have been at least tentatively evidenced to provide the multi-faceted improvements in quality of life and social integration now associated with recovery. However, Vanderplasschen et al. [100] also attest that TCs are less effective than other treatments; although, as with other interventions, positive outcomes are strongly correlated with retention and completion. The European evidence base is also methodologically limited; although this similarly suggests TCs offer reductions in problem drug use and criminal justice experiences alongside holistic improvements in quality of life and well-being. With regards to prison-based TCs, evidence provides a strong endorsement with regards to recidivism when compared to other interventions [100].

Recommendations to ensure the future of TCs include demonstrating efficacy and value for money as emphasis on cost-efficacy continues to permeate addiction and recovery landscapes, a focus which holds implications for the training and payment of employees in TCs [100]. Within a social model of recovery, the TC movement has evidenced the importance of peer-based interventions and suggested a recovery pathway independent of 12-step mutual aid, with a fundamentally different conceptualisation of addiction

and recovery. The TC approach is entirely consistent with four core tenets of recovery-oriented services: a care coordination across a range of service sectors requiring case management skills and 'outward-looking' specialist treatment services, an increased role for peers, a recognition of the validity of 'expertise by experience' and a continuity of care model that acknowledges the need for integrating acute services with those targeting longer-term changes in wellbeing and social integration.

50.10 What Can Professionals, Peers and Communities Do to Promote Recovery Amongst Problem Drug Users?

For professionals to adapt and embrace the shift to recovery-focused practice, Best et al. [16] emphasise the need for clinicians to transition from 'doing to' to 'working with' service users in order to help them move on. Correspondingly, Humphreys [46] refers to the 'gatekeeper myth' that 'holds that the path to recovery can only be walked with the aid of highly educated specialists in addiction treatment'. The gatekeeper myth and dominance of the professional is, however, being eroded by recovery strategy and practice that places the individual, those with lived and living experience, and communities at the heart of recovery. The individual nature of recovery also means policy; practice and research must pay particular attention to marginalised populations whose cultural and individual needs must be considered.

Whilst women's drug-using careers are shorter and women begin their recovery at an earlier stage than men (Best et al. 2015), they also face a host of issues which complicate and exacerbate their experiences of addiction and recovery.

Women with histories of substance use problems commonly have lifelong experiences of stigmatisation, deprivation, violence and abuse [25, 107]. The symptoms of trauma include dissociation, numbing and avoidance and often aggression/defensiveness which are often both attempted to be managed by survivors through drug and alcohol abuse and which have often been misinterpreted in services as unwillingness, disobligingness and disinterest in recovery [39].

Herman's [41] pioneering three-stage recovery model advocates for stabilisation in order to provide PTSD survivors with the sense of safety and control essential from which to begin their recovery. The need for all services and systems working with women to be trauma informed continues to gain increasing traction in research findings, strategy and practice recommendations [6, 24, 25, 39, 41].

50.11 The Recovery Landscape in Europe

The final section of the chapter will focus on the gradual emergence of a recovery movement in Europe and the policy and research innovations that have underpinned this transition, starting with the UK, where recovery policies have dominated addiction services since 2008. The origins of a recovery orientation in addiction policy are different in Scotland from England, with Scotland's Road to Recovery [95] building on the success of the Scottish Recovery Network for mental health. In England, the UK Drug Strategy [42] had its origins in the mounting critique of a treatment system predicated on low-intensity treatments [11] and a dissatisfaction with the prevailing treatment system and philosophy [4]. The 2017 English Drug Strategy comprised a continuation of 2010's strategy which marked a discursive and practical shift away from a focus on crime prevention (which relied on maintenance and harm reduction) to a focal inclusion of 'promoting recovery' as one of the main objectives. The English strategy also built upon its predecessor by proposing to:

1. *'Provide stronger governance for delivering the strategy, including a Home Secretary-chaired board and the introduction of a National Recovery Champion.'*
2. *'Expand the data we collect on levels of drug misuse and recovery from dependence and*

develop a set of jointly owned outcome measures to drive action across a broader range of local services.'

3. *Expand on the two overarching aims of the 2010 strategy: to reduce illicit drug use and increase the rate of individuals recovering from their dependence'*

Recent drug strategy in England makes consultation with peers a requirement in treatment providers' decision-making processes and explicitly references the important role peers can have in designing, implementing and reviewing drug and alcohol treatment systems [43]. The UK strategy describes peer support as 'an essential component of successful recovery', emphasising its importance throughout the recovery journey in enhancing treatment engagement and outcomes in addition to reducing stigma. An aspect of PHE's avowed recognition of PBRSS is their intention to explore digital support services in the form of online forums and mandate that community services must develop in line with peer involvement.

Similar to the English endorsement of recovery policy, Scotland's 2008 Road to Recovery and its refresh 'Rights, Respect and Recovery' [95] represented a shift in treatment monitoring in which services were to focus on producing measurable recovery outcomes. In Scotland, the Road to Recovery strategy established the Scottish Recovery Consortium to coordinate services, individuals and communities under a common aim whilst ensuring experiential expertise remains focal in-service design, implementation and in policy and public advocacy and representation. The SRC has an explicit strength-based focus on the benefits recovery brings to society as opposed to the previously dominant narrative of the destructive effects of addiction. Scotland's 2018 Rights, Respect and Recovery was developed in consultation with peers, and acknowledges the nation's flourishing peer recovery groups and communities. Furthermore, the strategy devotes a chapter to 'developing recovery-oriented systems of care', which presents peer involvement as a human rights-based approach to be implemented through advocacy services promoting participation, equality, empowerment and accountability via peer champions and navigators.

There has been a more recent transition towards recovery-informed policy in Belgium and the Netherlands. In the Netherlands, recovery policies have historically been formulated locally and from the grass roots movements in the absence of national or state policy. Recovery was not explicitly mentioned in national policy until 2010 when a charter was formulated in agreement with 15 professional specialist treatment organisations, wherein it was agreed that quality of life and societal reintegration ought to be the focal principle of recovery interventions [72].

Belgium's recovery strategy comprises a 2016 concept paper which delineates recovery to entail *'strengths-based support, client participation and input, quality of life, social recovery, and attention to different life domains'* [9].

Bellaert et al. [9] contend that this communitarisation is impeding the implementation of parallel mental health and addiction recovery strategies in Belgium due to the division of funding sources, commissioning and implementation bodies, an obstacle the authors suggest may be resolved through bridging between authorities and systems.

The impact of national and policy variations on recovery pathways is currently subject to research investigation in the Recovery Pathways (RECPATH) study in England, Scotland, the Netherlands and Belgium and is an exploration of recovery pathways by gender [14]. The study has a focus on gender differences in recovery pathways and has used the Life in Recovery method ([30]; Best et al. 2015) to screen for recovery stages and to identify candidate mechanisms for recovery. This builds on work by Kelly [55] on mechanisms for behaviour change in Alcoholics Anonymous (AA). Kelly argues that social-network change (along with cognitive transformations) is critical in male recovery, but that increases in abstinence self-

efficacy was the primary mechanism of behaviour change brought about by attendance at the 12-step mutual aid groups for women.

This is crucial in developing a plausible science of recovery in which mechanisms of change can be linked to predictors to increase our understanding of life-course changes. The developing evidence base around recovery capital (summarised by [40]) UK–US research collaborations have been central in developing two key measurement instruments – the Assessment of Recovery Capital [38] and, more recently, the REC-CAP [18]. In both of the underpinning studies, there is evidence supporting a strength-based approach to building resources that are predicated on engaging in prosocial networks and the resulting engagement in meaningful activities.

The UK recovery research model has, consequently, focused on social catalysts for recovery, including the Social Identity Model of Recovery [13] and the Social Identity Model of Cessation Management [32]. In each of these approaches, recovery is seen as resulting from changes in social networks (from using to recovery focused), resulting in shifts in belonging and connected changes in attitudes, values and beliefs.

Much of this work links to a mental health approach to recovery-oriented interventions that is based on a review of the evidence by Leamy et al. [66] that concluded that effective recovery interventions required five change mechanisms – they had to generate positive Connections; they had to inspire Hope; they had to offer positive changes in Identity; they had to support linking people into Meaningful activities; and they had to create Empowerment, summarised in the acronym CHIME. This model has been adapted for the addiction recovery space by Best et al. [15], who has argued that assertive linkage into prosocial groups has the potential to generate the sense of hope that recovery is possible. In this model, hope is seen as the key driver of a dynamic engine in which a virtuous circle of meaningful activity generates a positive sense of identify and growing self-esteem that further perpetuates the cycle of change and recovery growth.

50.12 Conclusion

Whilst there is a growing evidence base around personal recovery pathways and journeys and an increasingly credible evidence base, driven largely by US research, two other key themes are emerging. The first is that recovery models and methods are increasingly influencing policy and practice not only outside of the United States but in the non-English speaking parts of Europe. Secondly, there is a growing awareness that recovery is not a solipsistic activity and that effective recovery models (including policies) require a social and community framing and an improved evidence base around what constitutes an effective and integrated recovery-oriented model of care.

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51 Strategies of Drug Prevention in the Workplace: An International Perspective of Drug Testing and Employee Assistance Programs

David E. Smith, Lisa Marzilli, and Leigh Dickerson Davidson

Contents

Abstract

Drug testing in the workplace is not universal and is regulated by various governmental agencies at the federal, state, and municipal levels, as well as by select industries. Safety-sensitive occupations are typically targeted and various industries and agencies have specific drug testing protocols. In the United States, drug testing is highly structured and much of it falls under the purview of a Presidential Executive Order issued in 1986, with subsequent legislation calling for a drug-free workplace. An assigned Medical Review Officer (MRO) resolves any questionable results, be it a false-negative or false-positive drug test report.

In the European Union and other countries, drug testing is much less uniform, as attitudes to workplace alcohol and drug use are quite variable with no "standard approach." While the use of illicit drugs spurred widespread drug testing in the United States, prescribed medications that may impact workplace safety

D. E. Smith (✉) · L. D. Davidson
David E. Smith, MD & Associates,
San Francisco, CA, USA
e-mail: DrSmith@DrDave.org

L. Marzilli
Dominion Diagnostics Lab, Narragansett, RI, USA

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have become a controversial issue and have not been fully addressed. Many companies establish Employee Assistance Programs (EAPs) that are designed to help employees deal with life issues, including work–life stressors, family issues, financial concerns, relationship challenges, productivity issues, and concerns of substance use and abuse. Various services are provided to the employee, largely free of charge, relating to substance misuse and its effect on job performance. While the effectiveness of US programs is easier to assess due to consistency in approach, the variability of European programs makes them more difficult to evaluate.

Keywords

Addiction · Drug testing · Employee Assistance Programs · Medical Review Officer · Substance abuse · Workplace safety

51.1 Introduction

The majority of people using alcohol and other drugs, both legal, such as prescription medications, and illicit, are employed.

Substance misuse in the workplace is a major public health and economic issue, as the majority of substance misusers are employed. Substance use disorder (SUD), including alcohol use, is associated with increased accidents, absenteeism, and health costs. Therefore, modern concepts of drug use prevention, including drug testing, apply to the workplace and, when effected, produce benefits for both the employee and the employer.

As defined by DuPont [10], drug use prevention can be divided into three levels:

1. The primary strategy is aimed at preventing any illegal drug use. Drug use laws vary from country to country, so a broader concept relates to preventing use that produces impairment and threatens safety. Experts such as DuPont stress that any drug use by youth when the brain is still developing can be problematic, and a drug-free workplace can be a motivating factor for youth to avoid drug use.
2. Secondary prevention focuses on reducing the consequences of illicit drug use, such as workplace accidents and health costs for chronic diseases, for example, hepatitis and heart disease.
3. Tertiary prevention focuses on the individual who has a defined addictive disorder that requires treatment. With the passage of the Affordable Care Act in the United States, substance abuse is viewed as a medical issue that requires treatment before the individual can return to duty. If cleared, these individuals are protected by the Americans with Disabilities Act of 1990 (ADA) as long as they maintain their recovery in an appropriate monitoring system.

The secondary and tertiary levels of prevention are applicable to the workplace to reduce injury, accidents, and medical complications; all of which are costly to the employer and damaging to the worker. Different reduction strategies are used for each level, with drug testing and Employee Assistance Programs considered essential.

Most substance misuse in the workplace falls into one of the following areas: desired improvement in performance/productivity, relief of boredom, alleviation of physical and/or psychological pain/discomfort, addiction, or self-medication to relieve the side effects (e.g., hangovers, anxiety, etc.) of alcohol and other drugs. Substances ranging from opioids to stimulants may be used, depending on the user's objectives and preferences [25].

Drug-facilitated work impairment may not be noticeable or significant in ordinary situations. Emergencies, however, or unexpected demands on the worker, may precipitate unfortunate consequences. In addition, preoccupation with issues resulting from the worker's substance misuse, such as family arguments or contemplation of procuring more drugs, may reduce the worker's attentiveness to the requirements of

the job. The employer may also be impacted by the worker's theft or misuse of company resources to obtain additional drugs, absenteeism, turnover, violation of governmental guidelines for a drug-free workplace, or adverse publicity [25].

Cannabis use, particularly its principal psychoactive ingredient delta-9-tetrahydrocannabinol (THC), has been associated with negative health outcomes, including cannabinoid-induced hyperemesis and cannabis-induced psychosis. Cannabis use is associated with drugged driving and increased risk of accidents. This is relevant to the workplace as a majority of workers drive as part of their employment [14].

Cognitive risks have also been associated with chronic cannabis use, including impaired learning and executive function. High potency THC compounds have been associated with greater psychiatric and neurological risks, including diminution of gray matter, particularly in adolescent early onset users whose brains are still maturing.

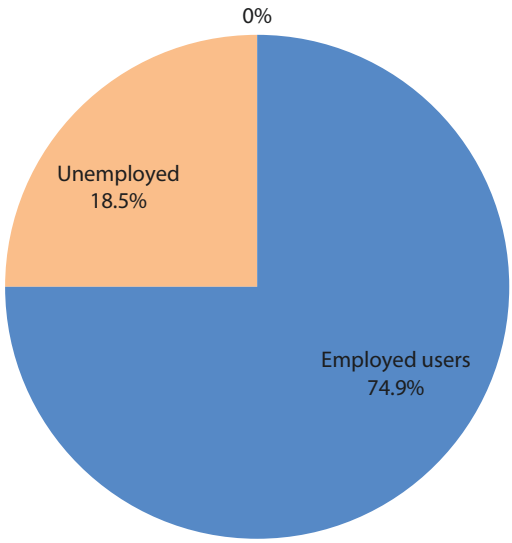
51.2 Drug Prevention in the Workplace

In the United States, drug testing to promote workplace safety and deter drug use is regulated by various governmental agencies at the federal, state, and municipal levels. And some employers' insurance carriers require specific drug testing programs. Different protocols exist for various industries and agencies; however, certain elements are consistent. Some companies require testing of every employee, others require preemployment testing only, and still others require periodic testing for employees holding safety-sensitive positions. Particularly after an accident, most employers require testing for potential drug or alcohol use. With the legalization of medical and recreational marijuana in many states, this has created another layer of complexity. The consequences of verifiable illicit drug/alcohol use in the workplace range from disciplinary action, referral to treatment, suspension, or employment termination.

The era of drug use prevention (other than alcohol) in the workplace began in the United States in the 1980s with the establishment of the Drug-Free Workplace Program**,** Executive Order #12564 [12]. This paralleled the drug epidemic permeating industrial settings and contributed to several highly publicized fatal accidents in which several employees tested positive for marijuana. As a result, in 1986 the US Federal Government issued Executive Order #12564:

> The Federal Government, as the largest employer in the nation, can and should show the way towards achieving drug-free workplaces through a program designed to offer drug users a helping hand and, at the same time, demonstrating to drug users and potential drug users that drugs will not be tolerated in the Federal workplace….

The Executive Order mandated that most Federal agencies, under the purview of the Executive Department, required the following: employees must refrain from illicit drug use, agencies implement and develop Employee Assistance Programs (EAPs), and they establish standard drug testing policies and procedures. The focus of the drug-free workplace was to eliminate illicit drug use of heroin, cocaine, amphetamines, marijuana, and 1, 1-phenylcyclohexyl (PCP). This panel became known as the National Institute on Drug Abuse-5 (NIDA-5). However, because alcohol was and is the primary drug problem in the industrial setting, both in the United States and worldwide, the Omnibus Transportation Employee Testing Act of 1991 included alcohol. According to the Division of Workplace Programs of the Substance Abuse and Mental Health Services Administration (SAMHSA) in the United States, the majority of active illicit drug/alcohol users are employed full-time and constitute two-thirds or more of the adult population [15]. The 2013 SAMHSA National Survey on Drug Use and Health reported that 68.9% of the estimated 22.4 million illicit drug users, age 18 or older, were employed full or part-time, while upward of 75% of adult binge and heavy alcohol drinkers were employed [24]. And in 2018, the number of users that were employed full-time rose to nearly 75% [7, 14].



The majority of current drug users are employed (current users of illicit drugs, ages 18 and over). (Source: National Survey on Drug Use and Health: National Findings)

While illicit drugs were the main impetus for establishing the drug-free workplace regulation in the 1980s in the United States, prescribed medications, especially opioids, became a growing issue, ravaging all regions of the United States. The resulting restrictions on prescribed opioids beginning in 2016 and becoming even more stringent in 2018 have created a shift to the utilization of heroin, illicit fentanyl, and other synthetic opioids (Centers for Disease Control). In 2017, the Centers for Disease Control (CDC) reported that over 70,200 drug overdose deaths involved opioids, and the primary driver was attributed to synthetic opioids (illicit fentanyl and analogues). Unintentional overdoses in the US workplace due to nonmedical use of drugs and alcohol increased over 25% each year from 2012 to 2017. The challenges employers face in this climate have resulted in far-reaching consequences beyond the scope of this chapter. It is worth noting that on January 1, 2018, the Federal Department of Transportation (DOT) added four additional drugs for screening: hydrocodone, hydromorphone, oxycodone, and oxymorphone.

US legislation established the designation of "Medical Review Officer" (MRO) [3, 20] in the 1980s specifically for the evaluation of "questionable" drug test results. A limited number of professional organizations offer courses to provide clinical training in the review and analysis of drug test results and a formal certification of MRO. The Medical Review Officer Certification Council (MROCC) promotes and preserves the highest quality of standards among MROs and their team members by setting standards, defining MRO competencies, promoting a Code of Ethics, offering certification examinations, and providing publications and educational activities. The role of the MRO in assessing safety in the workplace with prescribed medications, specifically opioids, continues to be extremely challenging.

Many companies that operate internationally have established EAPs designed to help them address safety and productivity issues by providing various services to behaviorally effected employees in order to alleviate and resolve issues interfering with their job performance. The Employee Assistance Professionals Association lists several national and regional EAP associations and organizations at www.EAPASSN.org.

51.3 Drug Testing in the United States Workplace

Workplace drug testing in the United States is highly structured and is intended to foster workplace safety standards and creates a healthy work environment [2, 6]. Tests are generally administered in a nonmedical setting, where body fluids, most commonly urine, are collected and analyzed. The sample passes through a rigorous and well-documented "chain of custody" process. The frequency, type, and drugs tested for typically depend on the industry and various government regulatory agencies involved. Companies

and organizations with US government contracts must be compliant with regulations regarding drug use in the workplace.

Drug testing is most common in settings where employees perform hazardous or safety-related tasks: such as operation of heavy equipment; transportation of passengers, medical, and surgical procedures; operation of nuclear power plants, public safety, and law enforcement. Every branch of the military has a specific program for drug testing of its service members.

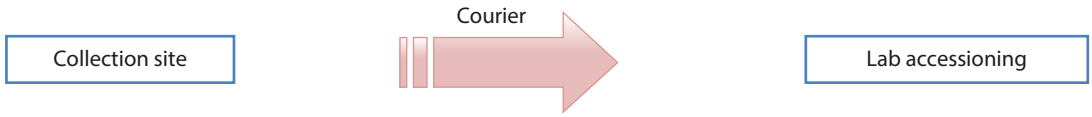
There are several instances that will initiate an order for a drug test. Some of these include preemployment, after an accident/incident, impaired performance on the job, observed use of drugs or alcohol, random assignment, voluntary, follow-up to treatment, and return to work. Continued monitoring and random drug testing may be instituted as part of an employee's recovery plan and often in conjunction with a medical professional.

Interpreting drug test results is more nuanced than a simple "positive" or "negative" if a valid result is to be obtained. Individuals may test positive if they are prescribed an opioid pain medication, for example. If a specimen is compromised or adulterated, either intentionally or inadvertently, an erroneous result report is likely to occur. For this reason, it is advisable that a qualified MRO be available to certify the results obtained. It must be noted that while MRO protocols are quite rigorous to assess sample adulteration, Internet search engines and individual initiative offer an ever-growing abundance of information on specimen tampering. Laboratories provide testing for validity markers (i.e., temperature, pH, and specific gravity) in order to assess for adulteration.

Medically prescribed drugs do not necessarily result in impairment or risk of accident on the job. Therefore, the focus in the United States as it relates to drug testing has been on substance use prevention and education. New synthetic drugs (e.g., synthetic cannabinoids, synthetic stimulants, etc.) that are continually emerging are not included on a standard drug test and pose a challenge to employers.

Random drug testing is mandated by many regulatory agencies in order to accurately assess whether or not an employee is using alcohol or illicit drugs. Employee identifications are typically generated in a random fashion, and the employee must report for a drug test within 24–48 hours at a location determined by the employer. After the specimen is collected, it may be analyzed on site immediately or may be shipped via overnight express to a centralized laboratory. Samples are usually "split" in the event there is a need to repeat and further analyze the specimen. For example, an employee may dispute the result at which time the MRO would intervene and review the results report or potentially request a retest in order to validate the findings.

Though specimen testing is largely via urine sample, other testing matrices may be utilized, such as blood, saliva, and hair. Regardless of the specimen collected, all must follow a rigorous protocol in order to balance the following: the employee's right to privacy, monitoring for specimen tampering, adherence to the process in the "chain of custody," and ensuring a valid and secure results report.

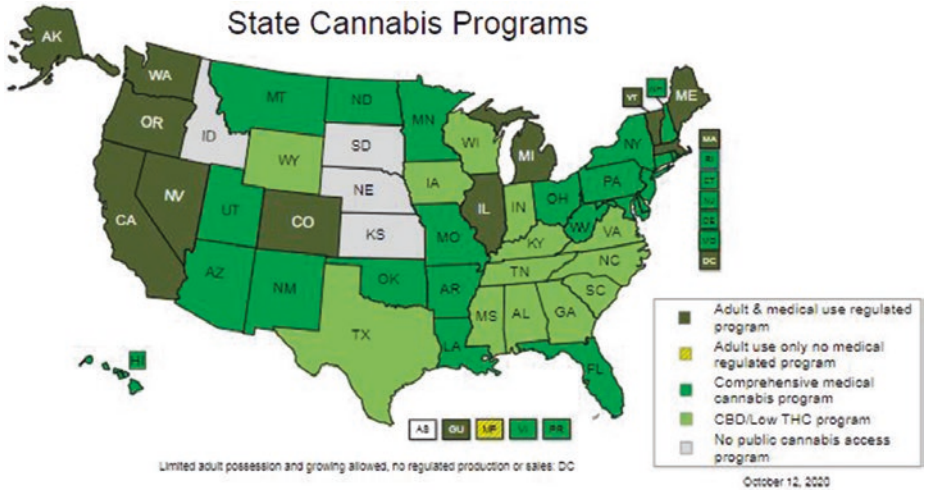


Components of specimen collection

- Employee's right to privacy
- Chain of custody
- Federal custody and control form (CCF)
- Integrity, security, and identification
- Temperature recording
- Tamper-evident bottle seal

Employees testing "positive" with an unexpected result are sometimes suspended from work until the results are reviewed and verified by the MRO. The specimen integrity, chain of command, potential shipping delay, or ambiguous result may require further investigation. Assessing the employee's use of over-the-counter (OTC) medications is also critical, as some of these products interfere with the laboratory testing, causing a false-positive result. In this case, the MRO must carefully review, assess, and interpret the results report for further clarification. Depending on the sensitivity and specificity of the drug testing methodology, foodstuffs like poppy seeds may also generate a false-positive result for opiates. For this reason, workplace testing in the United States has established cutoff levels for opiates above the levels generally triggered by poppy seed ingestion.

Similarly, a policy to raise the marijuana cutoff level has been instituted to address the issue of second-hand smoke or "passive inhalation" when in the presence of an individual smoking marijuana. However, with the legalization of medical and recreational marijuana in many states across the United States, many challenges continue to manifest. State laws and employer policies are highly variable, and the issue of impairment on the job must be addressed. That said, the DOT has not waivered or modified their drug testing program, even though the Department of Justice (DOJ) has issued guidelines for prosecutors in states that have enacted laws authorizing the use of medical or recreational marijuana. Currently, MROs are prohibited from verifying a DOT drug test as "negative" based upon a physician recommending an employee use of "medical marijuana." For more detailed information on this topic, visit the US Department of Transportation website for the full manuscript and current ruling posted 2019 (USDOT/documents/medical-marijuana.pdf).



Current state. Approved Marijuana status, August 2018. (Source: DEA)

While federal mandates for safety-sensitive jobs are clearly defined, the decision-making for private employers is extremely challenging as it relates to marijuana use. And according to the National Safety Council Report (February 2019 [19]), roughly 15 million employed individuals are struggling with some degree of substance misuse disorder. The top two substances are alcohol and cannabis, followed by opioid pain medications, benzodiazepines, and many other illicit drugs.

With the October 2018 legalization of cannabis in Canada, the Occupational and Environmental Medical Association of Canada (OEMAC) issued a position statement in September 2018 stating that "current evidence indicates cannabis is the most commonly encountered agent in workplace drug testing in Canada and, second to alcohol, the most prevalent substance implicated in driving under the influence." The document concludes that use of cannabis can lead to impairment, that motor vehicle or equipment operation is not advisable, that workplace drug and alcohol policies be updated, and that additional research and education are needed [21].

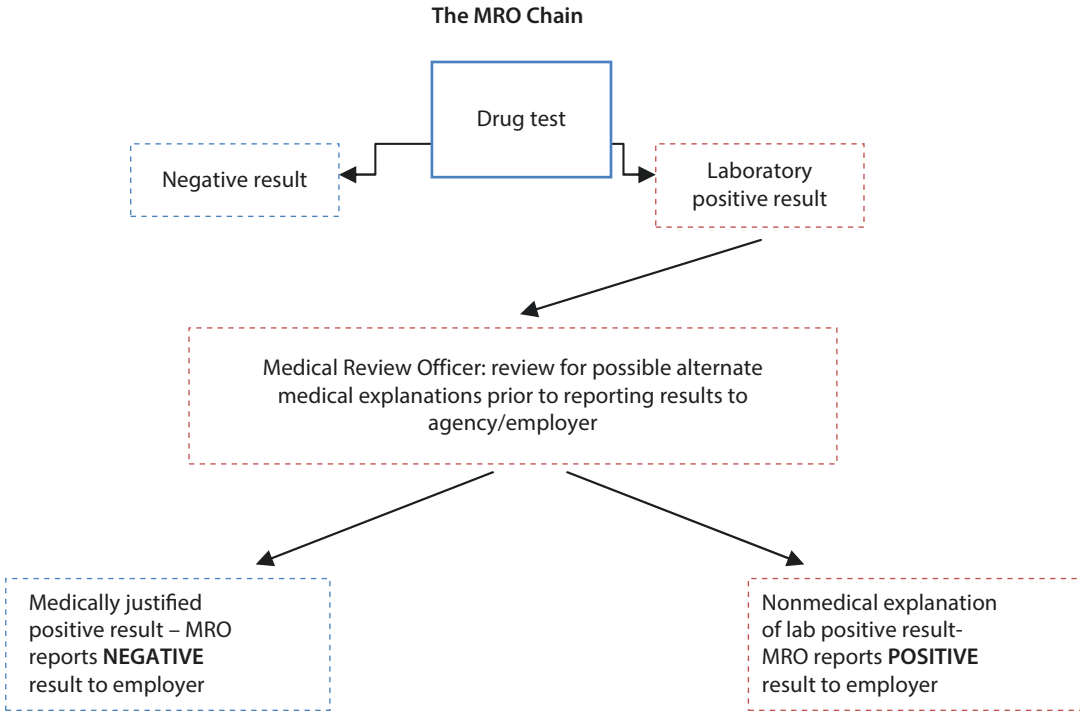
Some US states, including California, Massachusetts, and Nevada, have seen double-digit increases in the number of employees who test positive for marijuana. The complexity of this changing landscape has forced several private companies (in several states that have legalized medical and recreational cannabis use) to drop marijuana from their drug testing profile [13, 23].

Another significant challenge that is not captured by the NIDA-5 testing panel is the ever-growing issue of "designer drugs," now globally referred to as novel psychoactive substances (NPS). In 2008, synthetic cannabinoids (e.g., K2, spice, etc.) and synthetic stimulants were just emerging in the United States. Continued modification of these substances and creations of new products (e.g., illicit fentanyl and other synthetic opioids) have made it nearly impossible for a basic drug test to detect use [18]. Impairment on the job without the objective evidence from a drug test has created yet another dilemma for MRO recommendations and employer risks.

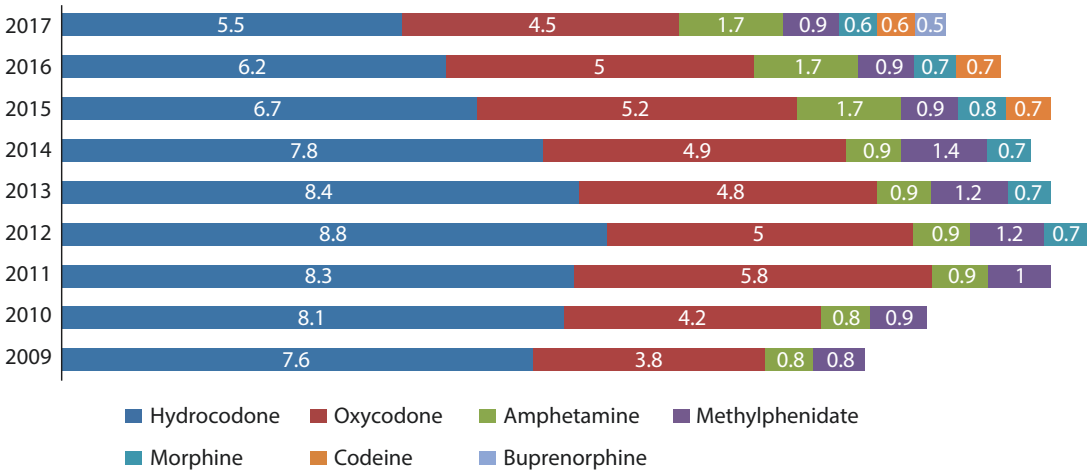
Over the last 5 years beginning in 2014, illicit fentanyl and fentanyl analogues have created severe risks in health-hazard exposure. The National Institute for Occupational Safety and Health's (NIOSH) 2018 guidance is available for reference, providing an in-depth review on preventing occupational exposure to these potentially lethal products [13].

Nonetheless, drug testing remains crucial for effective identification, intervention, and monitoring in the workplace. This medical test produces a results report that provides objective data that may be used for nullification purposes and also provides a platform to monitor effectiveness of treatment after an SUD has been diagnosed in the individual. The MRO designation was partly established so employees would not be denied necessary prescribed medications in overzealous attempts to extinguish illicit drug use.

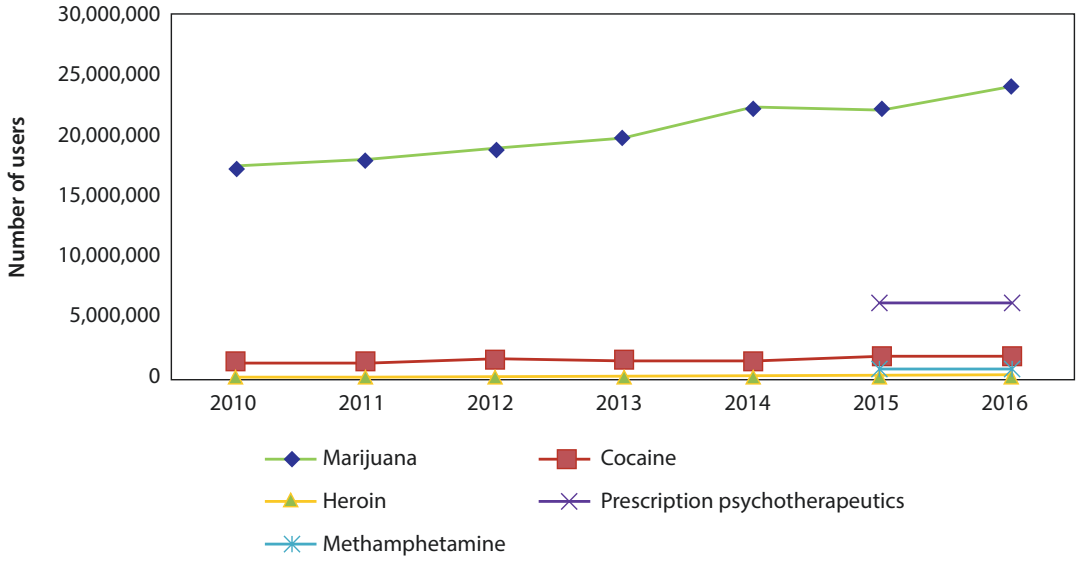
The following graphic illustrates the MRO decision tree and laboratory analysis:



The MRO chain



Top controlled prescription drugs sold to domestic retail level purchasers in billions of dosage units, 2009–2017. (Source: Automation of Reports and Consolidated Orders Systems, DEA)



Number of past month, nonmedical users of psychotherapeutic drugs compared to other select drugs of abuse, 2010–2016. (Source: Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health)

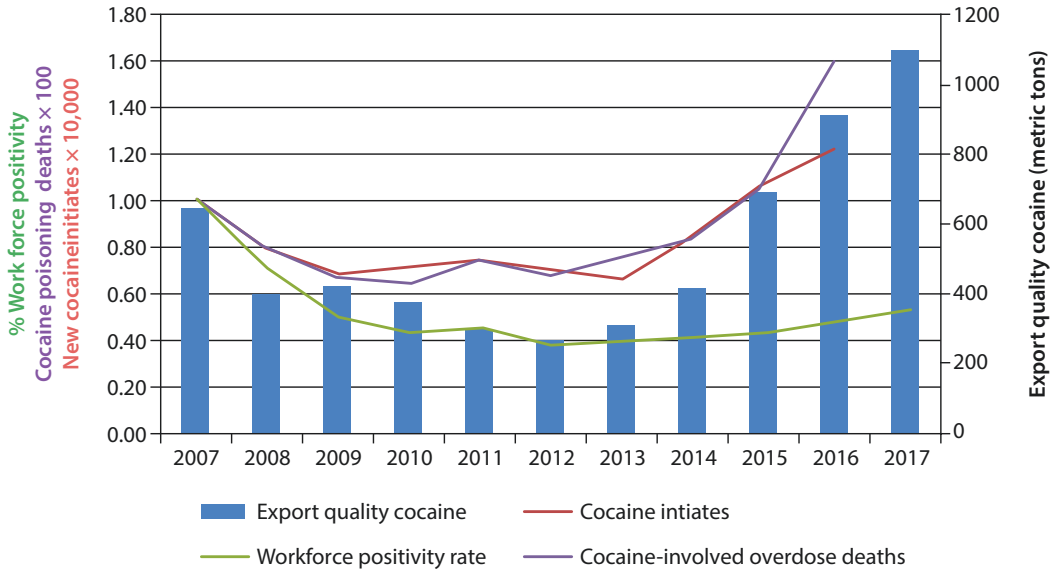
Though opioid-prescribing regulations and restrictions continue to tighten in the United States, they remain an issue for employees that use pain medications appropriately (with a valid physician prescription). Differentiating between appropriate use, misuse, abuse, addiction, and drug diversion in the workplace is crucial so that legitimate pain management is not confused with inappropriate use that results in negative health consequences and/or safety risks in the workplace. In these circumstances, when an employee's drug test indicates a "positive" opioid detection, the MRO must notify the employee and request a copy of the physician's prescription, to include a clinical diagnosis for treatment. Typically, the MRO will instruct the employee to cease work and immediately report to the supervisor. If the employee supplies the information to support medication use, the MRO will review the documents and notify the employer that the individual is medically cleared to return to work as long as no documented issues with performance or behavior have been observed.

Opioids, even when used for appropriate pain management, may potentially lead to workplace accidents, performance problems, and other medical, psychological, and behavioral problems. Side effects associated with opioid treatment include drowsiness, inattentiveness, impaired judgment, poor hand/eye coordination, tolerance and dose escalation, physical dependence, loss of function, perception of emotional pain as physical pain, and hyperalgesia (continual increases in dosage resulting in escalation of pain and the perception of pain).

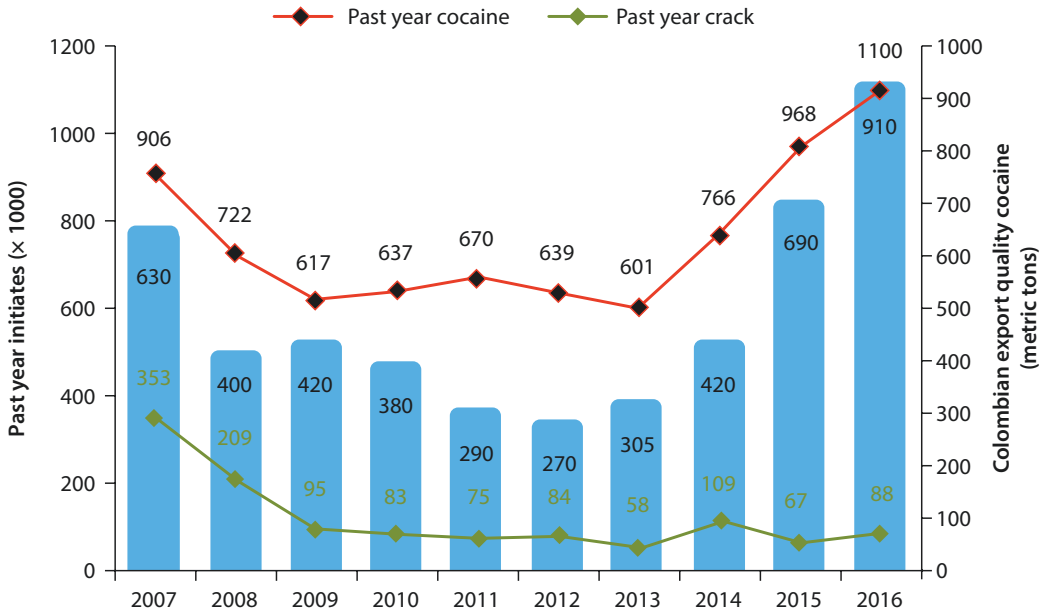
To date, there continues to be an issue of establishing set protocols for appropriate use of prescription medications as it relates to proper assessment of workplace performance. An individual's right to privacy is a significant factor. In the United States, the Americans with Disabilities Act (ADA) became law in 1990 to prohibit discrimination against individuals suffering from a disability in the workplace, schools, transportation, and all public and private areas that are open to the general public [17]. Several amendments to the civil rights law have been made over the years to guarantee civil rights protection for both public and private employers (more than 15 employees). Two recent settlements serve as a reminder that employers must be prudent when assessing cases that involve employees prescribed medication use and their ability to perform job duties.

MRO courses such as those presented by the Medical Review Officer Certification Council

(MROCC) provide clinical training on opioid medications and the potential of negative consequences such as intoxication, addiction, and overdose, as well as information on several other medications and substances of abuse, including stimulants like amphetamine, methamphetamine, and cocaine that are widely used and misused in the workplace. The latest Federal DEA data published in 2018 reports a significant escalation of coca production, cocaine trafficking, and imports have reached an all-time high in the United States [26]. As supply rises and prices fall, access and use increase [18].

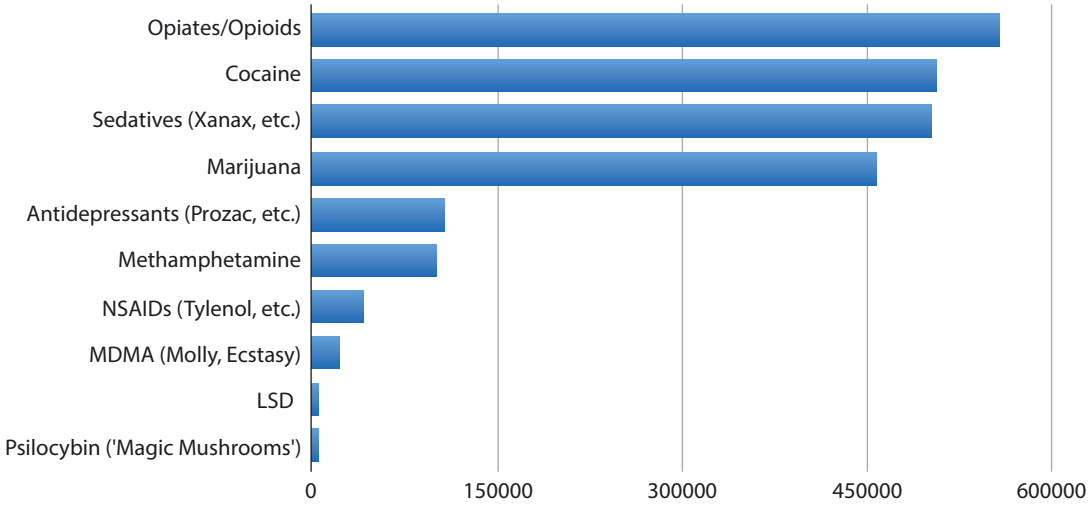


U.S. cocaine indicators and Colombia export quality cocaine production, based on 2007 value, 2007–2017. (Source: DEA National Forensic Laboratory Information System, August 2017)

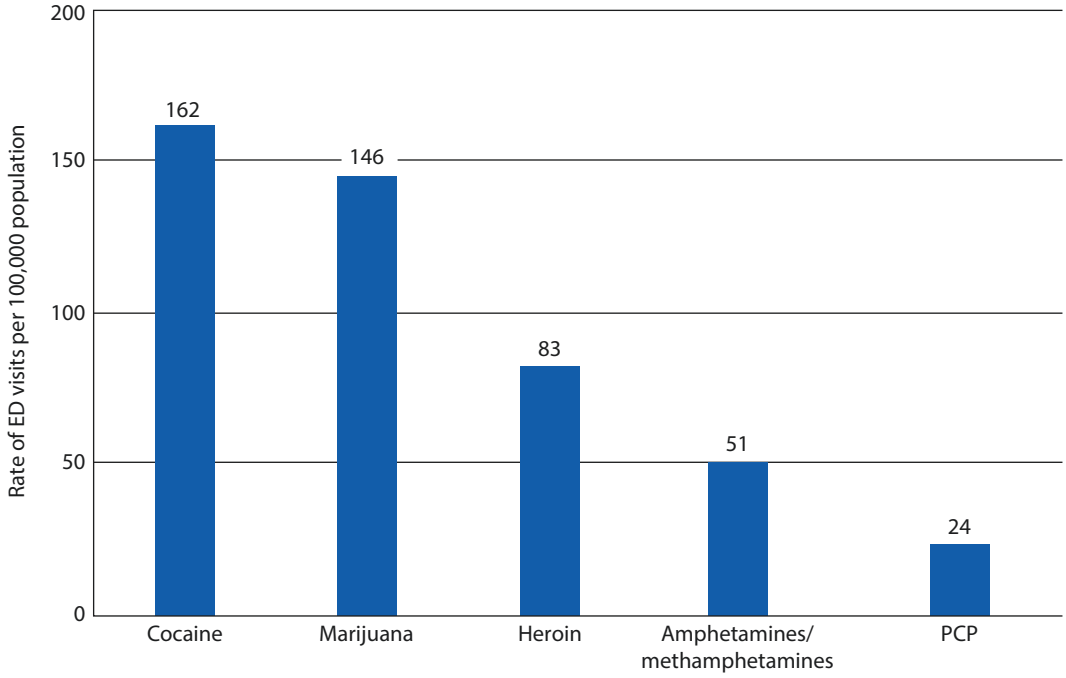


Past year cocaine initiates and export quality cocaine production. (Source: National Survey on Drug Use and Health and United States Government)

By definition in the Diagnostic and Statistical Manual of Mental Disorder's fifth Edition (DSM-V), SUD can affect workplace functioning due to dependence, abuse, intoxication, delirium, withdrawal, induction of psychotic disorder with hallucination or delusions, induced mood disorder, and many other negative consequences. And there are many adverse events that may require immediate medical attention whether or not the substance is legal (such as alcohol), prescribed by a physician, or obtained illegally. This potential for an adverse drug reaction is further heightened when multiple drugs/substances are ingested.



Emergency Department Admissions (2011). (Source: DEA.org)



Source: DAWN data, 2011

51.4 Alcohol Testing

The relationship between blood alcohol concentration (BAC) and accident risk is well established. The US National Transportation Safety Board (NTSB) is currently campaigning to reduce the BAC limits for all drivers.

For other substances like opioids and amphetamines, discerning impairment and accident risk is not well defined and can be extremely challenging for an MRO to assess. Even in cases where an employee has a legitimate prescription and qualifying diagnosis, dosage and impairment are not linear and clearly defined, as is the case with alcohol consumption.

Levels of alcohol intoxication

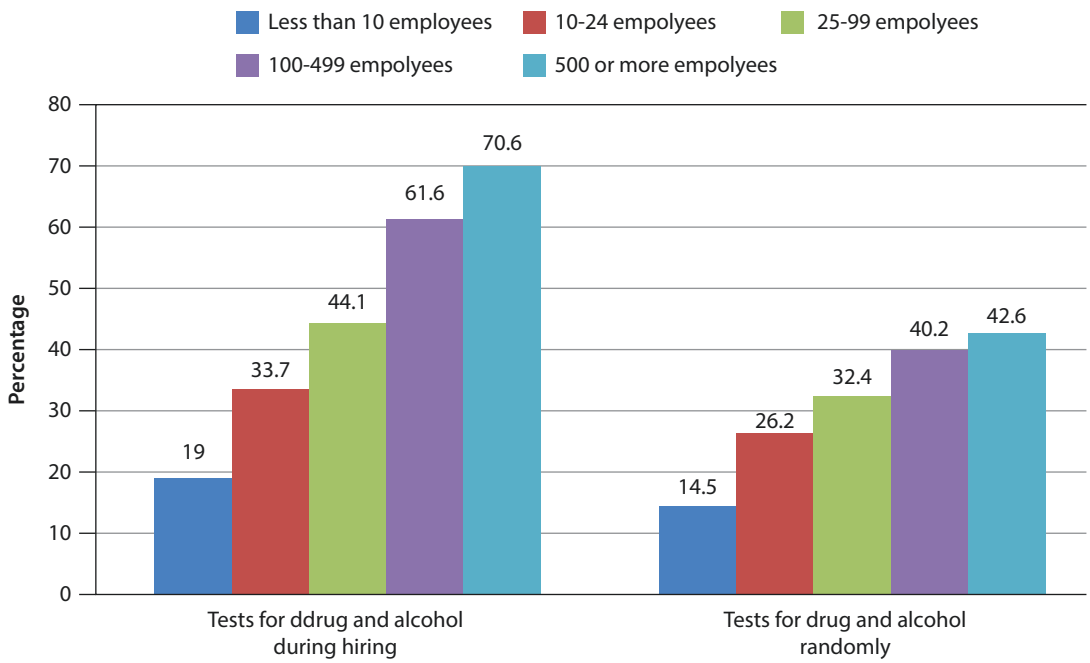
Blood alcohol concentration (BAC)	Percent of drivers too intoxicated to drive	Increased risk of accident
0.02% Restraint/ awareness	5%	^1
0.04% Comprehension	15%	1×
0.06% Judgment	35%	2×
0.08% Muscle control	65%	4×
0.10% Coordination	100%	8×
0.20% Equilibrium/ sleep		65×
0.30% Stupor		600×
0.40% Coma		
0.50% Death		

Because alcohol is rapidly metabolized, it is detectable only for approximately 6–8 hours when utilizing urine as the medium for drug testing. However, alcohol metabolites are present in the urine for up to 72 hours as ethyl glucuronide (EtG) and ethyl sulfate (EtS). The standard NIDA-5 does not include tests for these metabolites. In the event the MRO deems necessary, tests for EtG and EtS are available.

Identification of SUD in the workplace requires appropriate training and professional evaluation. As emphasized by Dr. Wesley H. Clark, former Director of the Center for Substance Abuse Treatment (CSAT) and faculty member of the now-discontinued ASAM MRO course, a positive toxicology report or an adverse drug reaction does not necessarily indicate substance misuse, abuse, or a diagnosis of SUD. Research has indicated there is a spectrum of substance use ranging from "I Like….I Want….I NEED." The DSM-V defines addiction as disease resulting in a pathological state with characteristic signs and symptoms.

Over time, morphological changes in the brain progress and impair rational thinking and decision-making. Predictable and often catastrophic consequences result when SUD is left untreated. It is characterized by the compulsive desire for the substance (or behavior known as *process* addiction), a loss of control when exposed, and continued use despite negative consequences. Though many individuals use alcohol and other substances and engage in unhealthy behaviors in the workplace, it is worth stating that only approximately 10% of those exposed actually progress to a diagnosis of SUD and require intensive treatment before returning to work.

Drug testing in the workplace is an essential component of a comprehensive workplace program. It provides objective evidence to accurately assess alcohol and drug consumption. Unfortunately, implementation in US industry is quite variable.



Type of drug and alcohol testing program, age 18–64. (Source: Worker Substance Use and Workplace Policies and Programs, 2007 NSDUH)

Treatment for SUD will assist those afflicted personally and professionally and foster a healthy workplace environment. Studies prepared by the Division of Workplace Programs of SAMHSA have shown that individuals' physical and mental health improve significantly during and after treatment, resulting in a major reduction in health care utilization. Recognizing that SUD is a disease has benefits for the employer when the employee is referred to treatment and is willing to accept and engage the process. If the employee successfully completes initial treatment, the employer is able to retain a trained, experienced employee and eliminate the cost of recruiting and training a new employee. And with continued treatment and monitoring, the employee provides a positive example for other fellow employees who may be suffering in silence.

51.5 Drug Testing in the European Workplace

In Europe and other countries, drug testing in the workplace is far less standardized and much more controversial than the United States. Varied social norms and cultural trends must be balanced with the need for safety in the workplace. National legislation varies widely in terms of the following: the employees' rights and obligations for being subject to testing, the conditions under which testing takes place, whether specimen collection is "observed," processed, and transported. Many other challenges exist when legislation and protocols are not clearly defined, for example, the need and availability of a qualified individual to interpret drug test results and the process of how these results are communicated to employer and employee. Further complicating the matter is that amounts of allowable intake of alcohol and other substances in the workplace setting vary widely.

Without consistent regulations and policies, it is difficult to create a standardized drug use prevention in the workplace program in Europe (and other countries), although efforts are underway to address this gap. Some countries have no specialized programs, while others have limited programs, but attitudes are beginning to change. In fact, the UK and several Scandinavian countries have developed comprehensive workplace drug testing policies and programs. Corral, Duran, and Isusi [9] examined the types of regulations in place

across a wide swath of the European countries in their report, "Use of Alcohol and Drugs at the Workplace," for the European Foundation for the Improvement of Living and Working Conditions (Eurofound). As in the United States, drug testing is mandated by a variety of governmental regulatory agencies and industries, but in many of these countries, employees have a much "louder voice" than is acceptable in the United States.

A sampling of study results cited in the European Foundation for the Improvement of Living and Working Conditions [11] document are listed below:

(a) There is a cultural tolerance of alcohol use (and sometimes other substances) in the workplace that varies from country to country. This approach is diametrically opposed to the United States where the model is a zero-tolerance policy.
(b) A majority of employers and employees do not agree with the use of alcohol and drugs in the workplace; however, cultural views on alcohol consumption and various substances are less rigid than the United States, so protocols for implementing policies are quite difficult to enforce and are highly variable.
(c) The cultural stance on alcohol and drug use in the workplace has grown more conservative over the years and has been addressed in a variety of studies. The Swedish Construction Federation reported that it was no longer socially acceptable to consume drugs in the workplace, a stark contrast to attitudes in the construction industry 40 years prior.
(d) In Portugal, there has been a growing awareness of the consequences of alcohol and drug use in the workplace. In early 2010, 90% of Portuguese enterprises had concerns related to employees' general health problems, increased incidence of sick leave and short-term absenteeism, reduced performance levels, labor conflicts, and an unsettled work environment.
(e) One Italian study reported that employees addicted to drugs/alcohol had more than double the rate of absenteeism compared to employees that did not use these substances [16].
(f) In Austria, alcohol-dependent employees took sick leave 16 times more frequently and reported "feeling sick" 2.5 times more often than those employees who were not alcohol dependent.

Other European studies investigating the use of alcohol and drugs in the workplace demonstrated that their use negatively impacted work performance, attitude, and morale and contributed to workplace accidents resulting in harm to a fellow employee. A 2008 Latvian report indicated that there were substantial economic losses and a damaged public image when accidents occurred in the workplace. As community members continued to discuss these incidences, the employer's reputation declined.

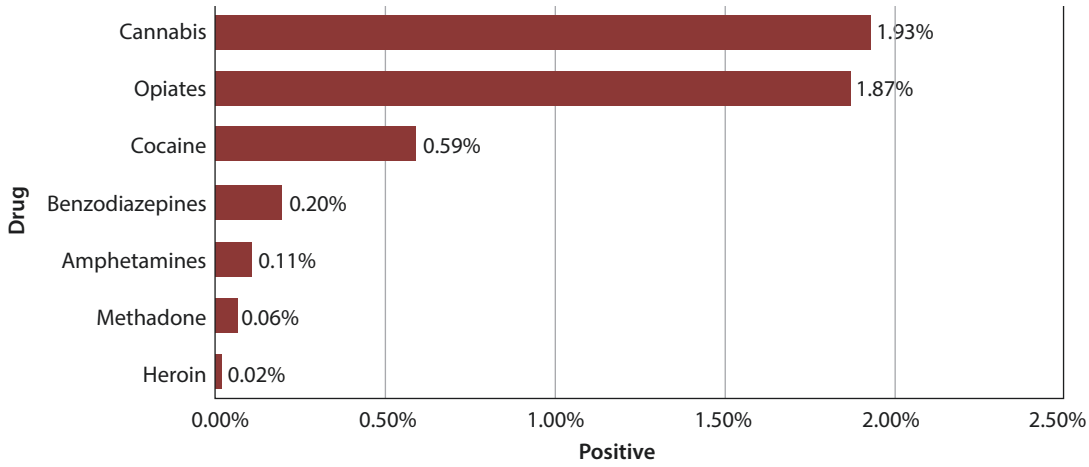
Other studies and reports have documented significant economic costs of substance misuse in the workplace. In Norway, alcohol-related illness accounted for substantial financial losses in millions of euros. And in the early 2010 period, Austrian alcohol use accounted for 1.5–2.5% of total payroll costs. The Austrian Federal Economic Chamber (*Wirtschaftskammer Osterreich*, www.wko.at) stated in this same era that a worker with alcohol and drug problems performed at roughly 75% of potential. Considering this information and more gathered since that time, European employers are closely examining the need for a new approach to strictly limit the use of alcohol and other substances in the workplace.

Unfortunately, there is often a delayed recognition of an employees' excessive consumption of alcohol/other drugs in the workplace. A German study indicated the delayed response time was nearly 10 years for men and 2–5 years for women. And more often than not, at this point, the employee was terminated. In contrast, the approach in the United States for first-time offenders is a strategy of intervention, treatment, continued monitoring, and reintegration into the workplace.

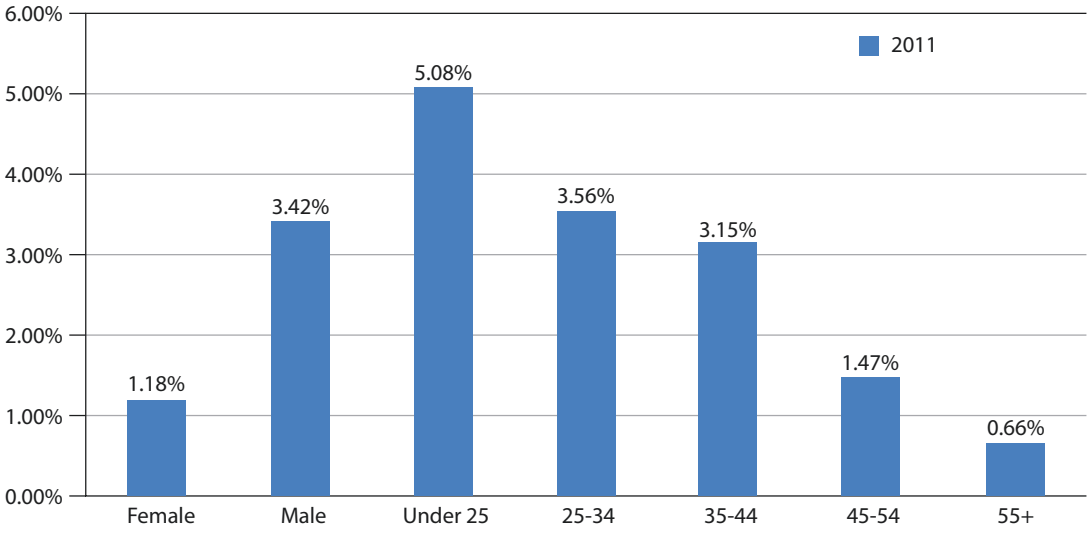
The European Workplace Drug Testing Society (www.EWDTS.org) works to examine issues relating to workplace drug testing and organizes annual conferences, providing an opportunity for all stakeholders to share ideas

and discuss best-practice approaches. EWDTS' mission statement is in part "….to ensure that drug testing in Europe is performed in a standard and legal manner…." The website provides brief summaries of workplace drug testing in various countries [27].

Though there is no centralized statistical information source in Europe and surrounding countries, the European Monitoring Centre for Drugs and Drug Addiction [4] reported that cocaine consumption was second to cannabis. A slightly different conclusion on drug prevalence in the UK workplace by drug testing provider Concateno [8] reported cannabis was the most frequently consumed, closely followed by opioids. The report also discussed the fact that patterns of drug use change with age. For instance, cannabis use appears to decrease with age, while the use of opioids increases. Amphetamines, methamphetamine, and the stimulant class as a whole have been and continue to be a growing problem.



UK drug prevalence within the workplace 2007–2011



UK workplace drug prevalence demographic for 2011

In France, the National Research and Safety Institute for the Prevention of Occupational Accidents and Diseases in the workplace has a program to train employers and supervisors to identify employees of concern and assist them in actionable plan forward. The German Centre for Addiction Issues commissioned an expert report on the practice of company-based drug prevention, and in 2006, it was debuted by policy makers, health insurers, and other social partners.

Several European nations have recognized that alcohol and drug use represents a severe problem for a significant percentage of the working population. National estimates indicate that 5–20% of workers are impaired by substance use, and particular work settings such as construction, transportation, and farming are at greater risk. Alcohol and drug consumption in the workplace often results in negative consequences such as a higher incidence of sick leave, reduced productivity, impaired performance, and avoidable accidents. Because the United States has more consistent national polices in workplace testing, comprehensive data is available to assess interventions, rehabilitation, and workplace reentry. Unfortunately, this type of information is lacking in the European countries.

Most European countries have some general legislation and agreements in place to prohibit or regulate the consumption of alcohol and other substances in the workplace, but there is considerable diversity regarding implementation and legal enforcement. In Germany, Belgium, and Denmark, "collective social agreements" are implemented in lieu of pure coercive measures. Until national labor codes and statutes are collectively agreed upon, many interventions are loosely labeled as "disciplinary," and corrective actions are taken to merely limit the use of alcohol and drugs in the workplace. However, companies that operate in multiple nations are forced to institute more formal drug-prevention and drug-interventional policies. International airlines and shipping firms illustrate this example.

European studies appear to place more emphasis on work-related reasons for alcohol and substance use, including strenuous physical work, poor working conditions, low job satisfaction, personal issues, relationship challenges, and lack of recognition of employees' rights. The intention appears to focus on what leads to substance use rather than flatly banning use and consumption in the workplace. Additionally, European cultures generally have a more tolerant view of alcohol use during the workday. Until the 1970s, this sentiment was more pervasive in the United States, and it was not unusual for a businessmen of the time to engage in a "three-martini lunch." But for the past several decades, the emphasis in the United States is for a drug-free workplace and zero-tolerance policy. Several recent reports indicate that European nations are changing their views and positions on alcohol/drug consumption in the workplace. As the economy globalizes, further study is needed to determine the most effective workplace programs to mitigate accidents and provide healthy and safe working environments. There is certainly a vested interest on behalf of employer groups to ensure productivity and safety.

51.6 Employee Assistance Programs

The key to an effective workplace program is a comprehensive Employee Assistance Program (EAP) [22]. Identification of the behaviorally impaired employee due to alcohol or substance misuse and/or abuse provides an opportunity for evaluation and referral to appropriate treatment, as opposed to a sudden disciplinary termination. The American Society of Addiction Medicine (ASAM) assessment and patient placement criteria [1] are most effective for such evaluation and referral. Although companies in the United States are not required to have workplace EAPs and treatment programs, many do because of insurance and liability risks. SAMHSA studies and reports have established that these programs result in excellent benefits, both economic and social. It has been shown that treatment averts many negative outcomes, saves money in overall health care costs, and reduces accident risk in the workplace.

EAPs for alcohol-use disorder gained prominence after World War II, largely due to the influence of Alcoholics Anonymous (AA), which was established in the 1930s. Individuals influential in the AA movement, such as Marty Mann, who helped found the National Committee for Education on Alcoholism (now known as the National Council on Alcoholism and Drug Dependence (NCADD)), and Dr. Ruth Fox, who helped form the New York Society of Alcoholism, were among the guiding forces behind the formation of the American Society of Addiction Medicine (ASAM).

ASAM [5] has developed a very clear clinical definition of the disease of addiction:

> Addiction is a primary, chronic disease of the brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social, and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.
>
> Addiction is characterized by an inability to consistently abstain, impairment in behavioral control, continual craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

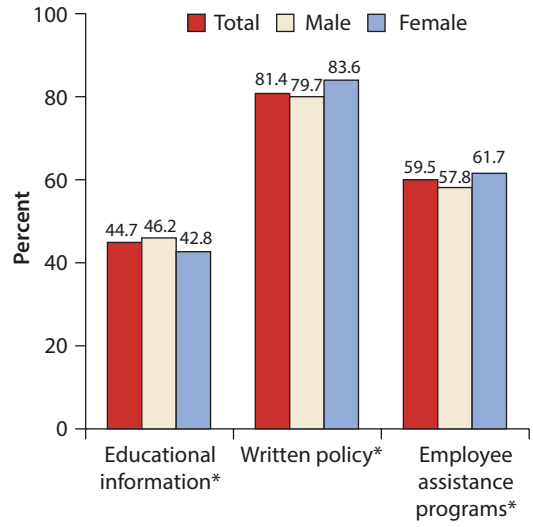
The 4 Cs of Addiction:

- *C*raving
- Loss of *C*ontrol
- *C*ompulsive Use
- *C*ontinued Use Despite Harm

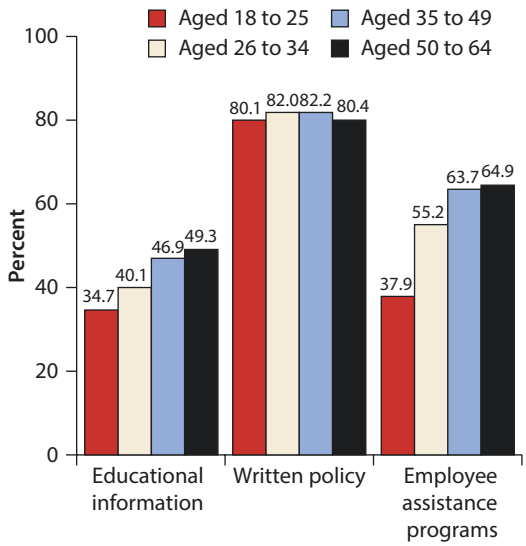
That said, some employees use narcotic pain medication under the care of a physician with a valid prescription. Differentiating appropriate use and potential misuse, abuse, addiction, or diversion in the workplace is crucial so that legitimate pain management is not confused with misuse. Evaluation and selection of an appropriate laboratory for drug testing are essential. In addition, it is necessary to engage a highly qualified MRO to interpret the drug test results in order to clarify false positives or negatives and to ensure that appropriate reporting and assessment take place.

EAPs may be funded by employers, employee benefit organizations, or unions and are often provided at no cost to the employee. They are designed to provide short-term counseling for a variety of personal issues, including legal, financial, relationship challenges, life events, and substance use disorders (SUD) – all of which may affect workplace performance. For issues that cannot be resolved quickly, referrals and other resources are provided. One might compare the services provided by an EAP to that of an ambulance – get to the patient quickly, stabilize the condition, and transfer to a facility for further evaluation and care if necessary. Confidentiality of an employee's visit with a counselor is required, as the session content cannot ethically be reported to the employer for any reason.

EAPs are available internationally. The Employee Assistance Professionals Association is a worldwide association (www.EAPASSN.org), and there are other national organizations focused in Europe, Canada, Australia, the UK, Ireland, and the Asia Pacific Region.



Workplace provides educational information, written policy, or employee assistance program concerning drug or alcohol use among full-time workers aged 18–64, by gender: annual averages, 2008–2012. *Difference between male and females is significant at the .05 level. (Source: SAMHSA, Center for Behavioral Health Statistics and quality, National Surveys on Drug Use and Health (NSDUHs), 2008–2010 (revised March 2012), and 2011–2012)



Workplace provides educational information, written policy, or employee assistance program concerning drug or alcohol use among full-time workers aged 18–64, by gender: annual averages, 2008–2012. (Source: SAMHSA, Center for Behavioral Health Statistics and quality, National Surveys on Drug Use and Health (NSDUHs), 2008–2010 (revised March 2012), and 2011–2012)

EAPs typically have a strong component of the recognition, referral, and treatment of substance misuse and abuse. Some large programs may engage Substance Abuse Professionals (SAPs) who have specialized training to identify potential drug problems and provide referral to treatment. They may also identify practitioners who enable employees to abuse drugs, misuse their medications, or divert for sale and profit. As many employer benefits include a prescription drug plan for the employee, there is a vested interest in containing unnecessary costs.

Many times, the EAP will play a role in monitoring the return to work process for employees suffering from SUD. This outcome is "best-case scenario" and benefits both the employer and employee. Monitoring with objective markers such as random drug testing, assuring the employee is attending psychotherapy sessions, and encouraging utilization of a 12-Step program are some of the ways the employee can be supported toward successful outcomes.

51.7 Summary

In reviewing the topic of alcohol and substance use in the workplace, drug testing, and management, it is clear there is no uniform approach. When considering the topic from an international prospective, cultural norms and views further vary the landscape of management approaches.

The United States has a well-defined and structured approach, including strict discipline, mandates, treatment, rehabilitation, and drug test monitoring prior to reentry into the workplace. In the European countries, the approach is less rigid and focuses more on the reasons why employees ingest alcohol/substances in the workplace, which appears to engage an approach of prevention and rehabilitation without placing the employee immediately at risk of consequence and potential job loss.

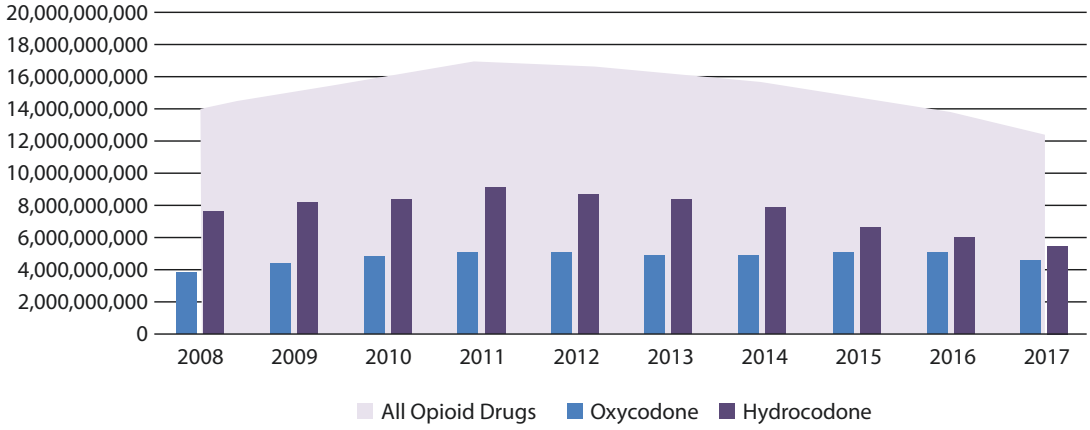
EAPs offer benefits to both employers and employees. For the employer, they provide an avenue for maintaining productivity, reducing absenteeism and workplace accidents, and retaining experienced and seasoned employees. For the employee, an EAP provides a lifeline in the event of serious life challenges and, in the event of a developing substance use disorder, a structured path with a compassionate and medically proven venue for treatment and continued monitoring.

Glossary

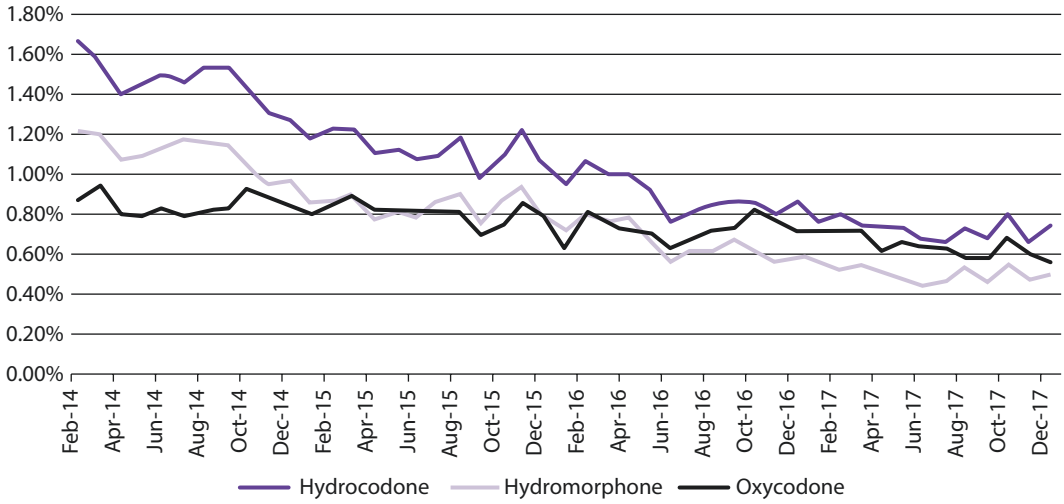
AA Alcoholics Anonymous
ASAM American Society of Addiction Medicine
CSAT Center for Substance Abuse Treatment, SAMHSA (USA)
DAWN Drug Abuse Warning Network (USA)
DOJ Department of Justice (USA)
DOT Department of Transportation (USA)
EAPA Employee Assistance Professionals Association
EMCDDA European Monitoring Centre for Drugs and Drug Addiction
EAP Employee Assistance Program
MRO Medical Review Officer
MROCC Medical Review Officer Certification Council

NCADD National Council on Alcoholism and Drug Dependence (USA)
NIDA National Institute on Drug Abuse (USA)
NIOSH National Institute for Occupational Safety and Health (USA)
NSDUH National Survey on Drug Use and Health (USA)
OTC Over-the-counter, that is, medications available without a prescription
SAMHSA Substance Abuse and Mental Health Services Administration (USA)
SAP Substance Abuse Professional

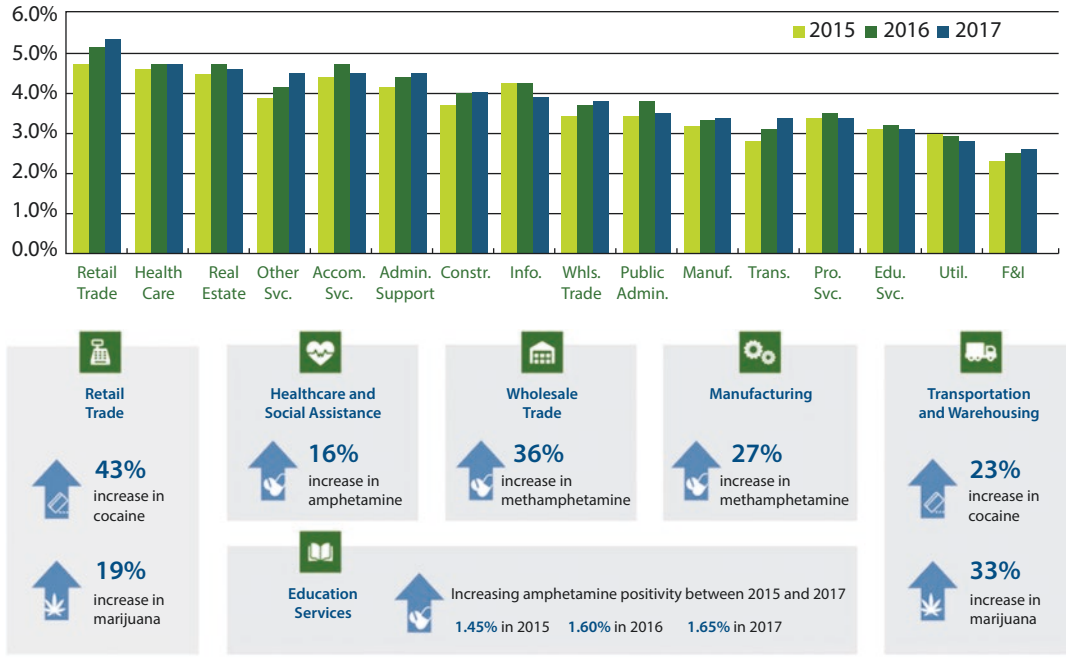
Appendix: Additional Graphics (U.S.) and Other Data



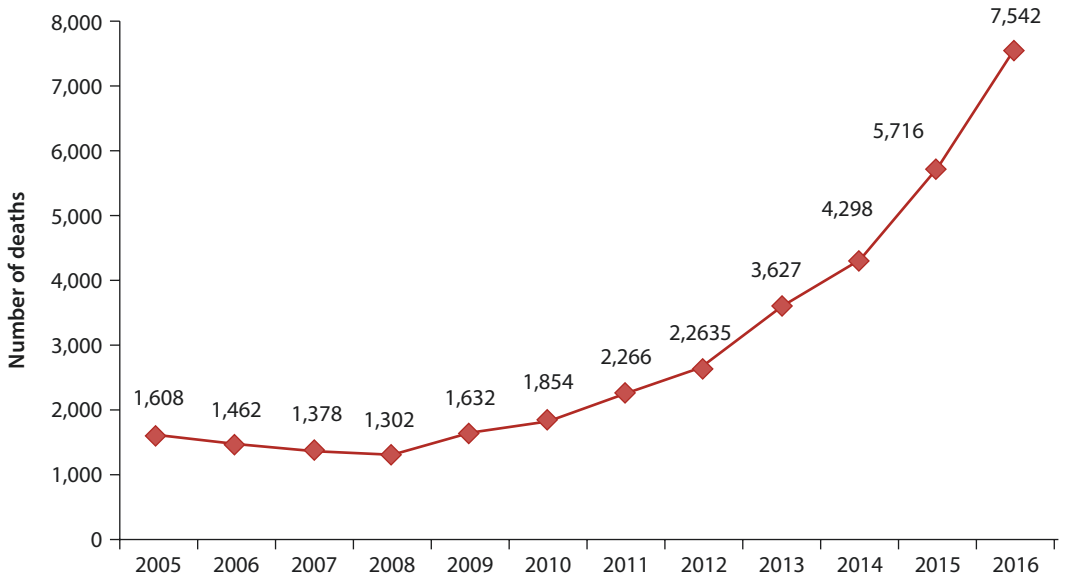
All opioid CPDs compared to the number of hydrocodone and oxycodone prescription drugs sold to retail level purchasers in billions of dosage units, 2008–2017. (Source: DEA)



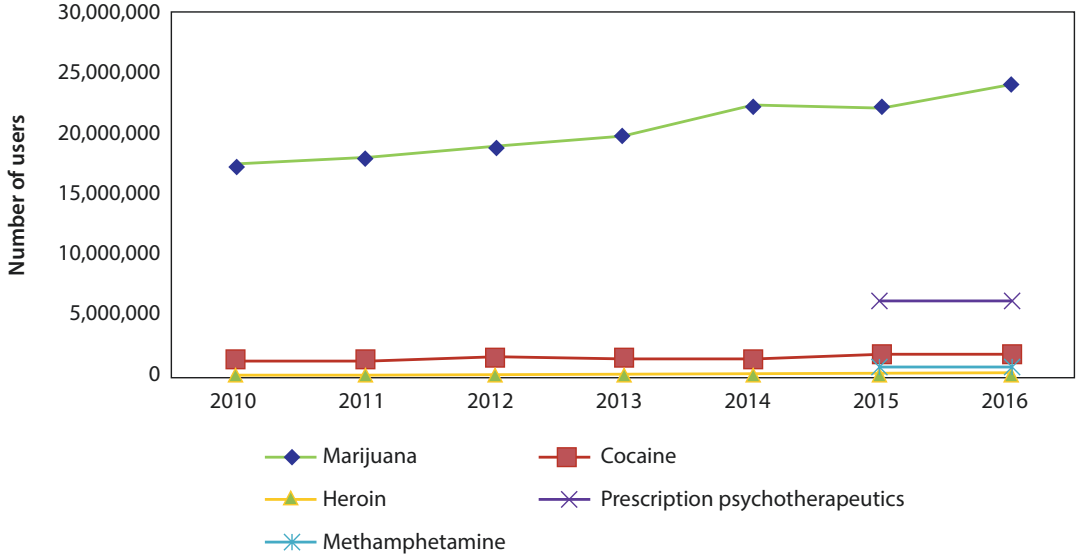
Workplace positive drug tests for select prescription drugs. (Source: Office of National Drug Policy/Quest Diagnostics Drug Testing Index)



Drug positivity rates by industry sector. (Source: Quest Diagnostics Drug Testing Index™, 2018)



Psychostimulant-involved drug poisoning deaths, 2005–2016. (Source: National Center for Health Statistics/Centers for Disease Control and Prevention)



Number of past month, nonmedical users of psychotherapeutic drugs compared to other select drugs of abuse, 2010–2016. (Source: Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health)

Supplemental Table 2D
Estimated numbers[a,b] and age-adjusted rates per 100,000 population of drug poisoning-related emergency department visits by selected substances — United States, January 1–September 30, 2016

	All drug poisonings[c]		All opioid poisonings[d]		Heroin poisonings[e]		Methadone poisonings[f]		Poisonings by other opioids[g]		Cocaine poisonings[h]		Methamphetamine poisonings[i]	
Socio-demographic characteristics	Rate[j]	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE
All visits	174.4	266	41.9	1.51	25.0	1.27	1.2	0.07	16.1	0.34	3.2	0.11	5.3	0.15
Sex														
Male	166.0	3.10	51.6	2.02	34.7	1.74	1.3	0.08	16.1	0.42	4.1	0.17	6.2	0.22
Female	182.8	2.52	32.1	1.07	15.2	0.85	1.1	0.08	16.1	0.36	2.3	0.11	4.3	0.15
Age Groups														
0–14	136.2	5.89	3.9	0.27	[k]	[k]	[k]	[k]	3.8	0.26	1.0	0.12	4.2	0.30
15–19	311.0	9.85	25.9	1.49	11.1	1.05	[k]	[k]	14.8	0.83	2.2	0.27	8.4	0.59
20–24	279.5	12.13	96.7	7.44	71.9	6.50	1.1	0.20	24.4	1.42	5.1	0.45	12.0	0.83
25–34	259.0	12.86	107.3	8.90	79.5	7.64	2.3	0.31	26.6	1.56	6.5	0.46	10.4	0.63
35–44	179.7	7.23	55.9	4.12	33.8	3.33	2.0	0.21	20.7	1.04	4.9	0.37	6.1	0.40
45–54	145.4	5.22	38.8	2.46	17.6	1.79	1.6	0.19	20.1	0.92	4.0	0.38	3.0	0.29
55–64	106.0	3.36	26.0	1.37	7.4	0.74	1.6	0.23	17.3	0.80	2.1	0.23	1.3	0.17
≥65	87.7	2.44	13.0	0.60	1.0	0.15	0.5	0.09	11.6	0.56	0.5	0.08	0.4	0.07
US. census region of residence														
Northeast	205.0	9.26	76.3	6.41	57.6	5.49	1.7	0.22	17.7	1.07	4.0	0.33	2.4	0.20
Midwest	198.0	6.42	52.6	3.68	35.1	3.05	1.0	0.13	17.0	0.81	3.7	0.30	6.1	0.38
South	159.6	3.83	30.6	1.77	14.6	1.48	0.9	0.08	15.5	0.49	3.5	0.18	5.1	0.22
West	155.8	3.36	26.1	1.06	9.5	0.70	1.4	0.15	15.5	0.52	1.5	0.14	6.9	0.35

Source: Annual Surveillance Report of Drug-Related Risks and Outcomes. U.S. CDC National Center for Injury Prevention and Control (2018)

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Harm-Reduction Interventions

52

Dagmar Hedrich and Richard Lionel Hartnoll

Contents

Abstract

The goal of harm reduction is to reduce both the individual and societal harms of drug use through knowledge-based interventions that change risks, risk behaviours and risk settings. This chapter describes the main harm-reduction interventions implemented in many countries around the world, synthesises evidence on their effectiveness and risks and summarises key lessons learned. The focus is on illegal drugs, especially opioids and the central nervous system stimulants. The interventions covered are opioid substitution treatment; needle and syringe programmes; supervised drug consumption facilities; drug overdose prevention; outreach, peer education and health promotion; testing, vaccination and treatment of drug-related infectious diseases; and interventions for stimulant users. Key themes stressed include the following: that harm reduction does not replace the need for treatment but adds to the capacity to respond effectively to the wide range of health and social challenges raised by drug use; that the scientific evidence shows that harm-reduction interventions are effective in terms of their stated goals, as long as they are implemented appropriately within their contextual settings,

D. Hedrich (✉) · R. L. Hartnoll
European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal
e-mail: dagmar.hedrich@emcdda.europa.eu

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and that single interventions are far more effective when implemented together as part of a broader public health policy, including steps to facilitate healthier living and safer social environments.

Keywords

Risk behaviour · Harm reduction · Needle syringe programme · Overdose prevention Naloxone · Supervised drug consumption Outreach · Peer education · HIV · Hepatitis C Combination intervention

52.1 Introduction

The goal of harm reduction is to reduce individual and societal harms of drug use through policies and interventions that change risks, risk behaviours and risk settings. Harm reduction is based on the concept of harmful drug use and does not assume that drug use per se is harmful. It is a pragmatic approach that aims to reduce harmful correlates and consequences of drug use through a package of evidence-based, targeted interventions tailored to local settings and needs.

Drug-related harm refers both to individual consequences, such as dependence, overdoses or infectious diseases, as well as to social, economic and public health harms to the community (crime, healthcare costs and high HIV prevalence). The underlying public health paradigm is broader than individual-centred treatment and involves balancing individual and societal needs.

Harm reduction as a policy started to gain acceptance in Europe with the emergence of HIV/AIDS amongst drug injectors in the mid-1980s and is now a major pillar of drug policy in all EU member states [38]. Globally it is supported by at least 87 countries [90] and promoted by the WHO, United Nations and European Union as a key element of a comprehensive approach.

Harm reduction entails a coordinated response from a range of actors, including treatment, prevention, public health, law enforcement, community groups and local authorities [21, 74, 79, 100]. It goes beyond interventions for individuals by stressing enabling environments to enhance protective factors, reduce harms and promote public health.

Harm reduction incorporates an important ethical dimension concerning human rights, equality of access to services, respect for privacy and confidentiality and efforts to counteract social exclusion and stigma [79].

Much drug-related harm is linked to heavy consumption of opioids, the central nervous system (CNS) stimulants or multiple drug combinations, including alcohol and other CNS depressants. There is a strong relationship between drug injecting and more severe levels of harm, though problems can arise with other routes of administration. Heavy drug use is often strongly correlated with unsafe sexual practices, including unprotected sex, multiple partners and sometimes selling sex for money or drugs.

Risk behaviours occur within a wider social context. Structural factors such as the policy and legislative framework can generate risk environments that increase social exclusion, deter help seeking for fear of arrest or exacerbate the spread of infectious diseases [17, 75, 80]. The diversity of settings implies diversity of risks and responses [34].

This chapter describes the major harm-reduction interventions, synthesises evidence on their effectiveness and summarises key lessons learned. It draws on a wide range of sources from research and practice, including scientific reviews, evidence-based guidelines and practical manuals. The interventions covered are the following:

- Opioid substitution treatment
- Needle and syringe programmes
- Supervised drug consumption facilities
- Overdose prevention interventions
- Outreach, peer education and health promotion
- Testing, vaccination and treatment of infectious diseases
- Interventions for stimulant use

The focus is on illegal drugs, especially opioids and the central nervous system stimulants. Harm-reduction approaches have been applied to other drugs including alcohol, cannabis and tobacco and to other user groups such as young recreational drug users [79, 83].

52.2 Interventions

52.2.1 Opioid Substitution Treatment

Other chapters in this textbook cover opioid substitution treatment (OST) as treatment for opioid dependence. In this section, the emphasis is on OST for reducing individual and social harms associated with illicit opioid use. Methadone is the main drug employed, though buprenorphine has become more common following the 1990s. In some European countries and Canada, heroin-assisted treatment is provided to long-term heroin dependent individuals who have not responded well on methadone [64, 91]. Whilst naltrexone, an opioid receptor antagonist, has also been researched as treatment for relapse prevention, its effectiveness is limited by poor adherence, and maintenance with methadone or buprenorphine remains the preferred treatment [18]. OST is usually combined with psychosocial treatment, counselling and other health and social services.

Within a harm-reduction paradigm, OST consists of the (usually long term) prescription of opioid agonists to prevent withdrawal symptoms and craving, enabling users to lead more stable lives and reduce illicit heroin use, risk behaviour and criminal activity. Apart from reduced illicit heroin use, which has been demonstrated in numerous studies (see Chap. 10 in this textbook), specific harm-reduction outcomes that are sought include reductions in prevalence and frequency of drug injecting, prevalence and frequency of sharing drug using paraphernalia, incidence and prevalence of infectious diseases (especially HIV and hepatitis C), rates of drug-related mortality (especially overdoses) [70] and rates of drug-related crime. Reductions in high-risk sexual behaviours, as well as improvements in health and social functioning, are also the objectives.

Reviews of multiple studies with robust designs all found strong evidence that OST is effective in reducing self-reported prevalence and frequency of injecting, sharing of injecting equipment and injecting risk behaviour scores [30, 44, 49, 50, 53]. The same reviews found clear, consistent evidence that OST in community settings is effective in reducing HIV transmission, especially amongst those in continuous treatment and when dosages are adequate [26]; for example, MacArthur [49] estimated that OST is associated with a 54% reduction in risk of HIV infection amongst people who inject drugs.

The effectiveness of OST in reducing HCV transmission has been harder to determine. This is probably because HCV is more easily transmitted through injecting risk behaviours and because baseline prevalence levels of HCV in drug-injecting populations are often high. However, a recent systematic review [73] found that OST is associated with a reduced risk of HCV acquisition, which is strengthened in studies assessing OST and needle and syringe programme (NSP) in combination. There is accumulating evidence on the impact of combining these prevention interventions on hepatitis elimination (e.g., [63, 67, 97]), and a recent global mathematical model [39] underlines the importance of bringing harm-reduction services up to scale, highlighting their key role in prevention.

There is long-standing, strong evidence that OST reduces substantially the risk of overdose mortality, as long as doses are sufficient and continuity of treatment is maintained [16, 43, 52].

There is clear and consistent evidence from many studies that criminal activity, arrest and incarceration rates decline markedly after patients enter OST and that this effect is stronger the longer they remain in treatment [62]. This is particularly true of drug-related criminal activity such as drug-dealing and acquisitive crime. Where sufficient coverage of the opioid-using population is achieved, decreases in drug-related crime at the individual level are reflected in reduced levels of crime at community level [62].

A systematic review of 21 studies conducted in prison settings concluded that the benefits of OST provided in prison are similar to those obtained in community settings [36]. OST was significantly associated with reduced heroin use, injecting and syringe-sharing in prison if doses were adequate. Prerelease OST was significantly associated with increased treatment entry and retention after release if arrangements existed to continue treatment. For other outcomes, associations with prerelease OST were weaker. Whilst some post-release reductions in heroin use were observed, evidence regarding crime and re-incarceration was equivocal. Due to lack of studies, there was insufficient evidence concerning HIV/HCV incidence, either in prison or post release. Disruption of OST continuity, especially due to brief periods of imprisonment, was associated with very significant increases in HCV incidence [19]. In a national prospective, observational study in England prison-based opioid substitution therapy was associated with a 75% reduction in all-cause mortality and an 85% reduction in fatal drug-related poisoning in the first month after release [51]. In a meta-analysis and systematic review by Moore et al. [59], opioid substitution treatment with methadone provided during incarceration was found to be effective in reducing post-incarceration illicit opioid use and injecting.

Benefits of OST that have been clearly established include reduced illicit heroin use, injecting and risk behaviours, reduced overdose mortality and criminal activity and reduced HIV and HCV incidence – especially in combination with high-scale NSP. There is also evidence that OST facilitates improved adherence to HIV treatment [65] and leads to reductions in high-risk sexual behaviours [30].

In prison settings, OST presents an opportunity to recruit problem opioid users into treatment, to reduce illicit opioid use and risk behaviours in prison, and potentially to minimise overdose risks on release [22]. If liaison with community-based programmes exists, prison OST facilitates continuity of treatment and longer-term benefits can be achieved. For prisoners in OST before imprisonment, prison OST provides treatment continuity, especially important for drug users who are incarcerated for short periods. A population-based retrospective cohort study amongst Canadian convicted offenders documents that the adherence to OST had a positive impact not only on overdose deaths but also on other causes of mortality after release [84].

There are also limitations. OST is suitable neither for users of non-opioid drugs nor for drug users who have only recently started to use opioids, even though during the early stages of use they may be at particular risk of becoming infected (especially with HCV) through using another person's paraphernalia. Even in countries with high levels of OST provision, coverage of the total opioid-dependent population rarely exceeds 60% [24, 25]. Whilst other treatment modalities meet some of the shortfall, there remain important populations of problematic drug users who do not come for treatment or who do not fare well in treatment. As described above, other approaches need to be pursued alongside or in combination with OST to optimise its effects.

Specific risks of OST include increased mortality risk during induction into treatment and immediately after leaving treatment, which should be dealt with by both public health and clinical mitigation strategies [89]. Methadone overdoses can occur in association with careless overprescribing or use of illicit methadone from diversion or thefts. A different challenge arises from the accumulation of ageing, long-term patients on OST, many with multiple comorbidities. A harm-reduction approach not only includes encouraging OST clients to become drug free when they can but also accepts that for some this is not possible.

Several important lessons learned should be stressed. Adequate doses are essential. Whilst individual dosage levels vary, positive outcomes are mostly achieved when average programmed methadone dosages are in the 60–120 mg range [26, 102]. Continuity too is vital, accompanied by appropriate socio-psychological support and health education input.

52.2.2 Needle and Syringe Programmes

A needle and syringe programme (NSP) is a specialised service, offered by low-threshold drugs- and health agencies including through outreach, and that consists of distributing syringes, needles and other sterile injecting equipment to people who inject drugs. These agencies are usually located close to areas where drug injecting is prevalent and form part of a wider network of local services. Their primary objective is to facilitate more hygienic injecting practices and reduce sharing or reuse of needles, syringes and other items in order to prevent drug-use-related complications, especially the transmission of HIV and HCV. Most needle and syringe service providers also offer equipment for safer non-injecting use of drugs.

NSPs often serve as important contact points for drug users who have little contact with treatment or other health services. Thus, a supplementary objective is to deliver health promotion and facilitate access to healthcare, including entry to OST or other treatment. They routinely distribute condoms and offer advice on safer sex. They may also provide counselling and testing for infectious diseases and sexually transmitted infections (STIs), as well as vaccination for hepatitis B and basic healthcare. In some countries, NSPs are mainly implemented through national networks of pharmacies. In other settings pharmacy-based programmes and vending machines supplement specialised NSPs. In some countries, NSPs have been established in prisons.

A broad body of evidence indicates that NSPs are effective, as part of a multicomponent set of responses, in limiting the transmission of bloodborne infections, without increasing the prevalence or frequency of injecting [2, 13, 66, 95]. There are methodological difficulties in separating the impact of NSPs from the influence of other interventions and local contextual factors, which means that rigorous scientific studies of the effectiveness of NSPs as a single intervention are limited. Evidence from systematic reviews of NSPs across a range of settings and countries indicates that they are effective in reducing self-reported risk behaviours associated with injecting [50] and in reducing the transmission of HIV amongst people who inject drugs [2]. A recent systematic review [73] found greater heterogeneity between studies and weaker evidence for impact of NSP on HCV acquisition. High NSP coverage (defined as regular attendance at an NSP or all injections being covered by a new needle/syringe) was associated with a reduction in the risk of HCV acquisition in studies in Europe, whilst the effect was not clear for studies conducted in North America. The lack of evidence from US studies can be attributed to a mixture of confounding, differences in injecting patterns, potential selection bias and misclassification of exposure [73]. There is also evidence that NSPs and other harm-reduction interventions are cost-effective [101].

Benefits of NSPs, when implemented appropriately and at sufficient scale, include important reductions in injecting risk behaviours and HIV transmission. In combination with opioid substitution treatment, they make a significant contribution to reducing not only HIV but also HCV transmission. There is no evidence that the establishment of NSPs encourages non-injectors to start injecting or that injection frequency increases amongst attenders [79]. There were no reports of adverse events involving syringes in studies of prison-based NSPs.

Important lessons have been learned over the past three decades. It is essential to aim for full coverage of clients' injecting needs. Restrictions on the number of needles and syringes distributed, or insistence on returning used equipment, can be counter-productive, especially for high-frequency injectors such as cocaine users, since this can facilitate reuse and sharing. The underlying principle should be at least 100% coverage of each injection and distribution according to need rather than one-for-one exchange. It is also important to achieve wide coverage of local populations of drug injectors. Many NSPs allow secondary distribution, where clients distribute clean needles and syringes to partners or peers. Mobile units and outreach are valuable to further extend coverage.

Injecting equipment should take account of local context and the type and preparation of drugs

injected. Injectors in different settings often have preferences for certain types or sizes of equipment. Apart from needles and syringes, NSPs should provide other injecting-related items, including alcohol swabs, sterile water, filters, mixing vessels (e.g., spoons or "cookers") and acidifiers to assist with dissolving the substance to be injected [21].

Health promotion activities among people who use drugs should address viral infections such as HIV and hepatitis B and C, that is, how they are transmitted and how they can be avoided, practical advice on hygiene and safer injecting, as well as information on STIs and reducing sexual risks. They should also include provision of condoms, information on health and social services and, when appropriate, referral to drug treatment. Whilst staff can encourage clients to consider entering treatment or changing to safer routes of administration, this should not be linked to pressure such as implied withdrawal of services. Since NSPs come in contact with out-of-treatment drug injectors, it is valuable if they can carry out on-site counselling, testing and monitoring of HIV, viral hepatitis, STIs and TB, as well as vaccination for hepatitis B. Some NSPs also provide basic healthcare (e.g., wound dressing) or train clients in overdose prevention and management, including giving out naloxone. Testing and behaviour change counselling are essential not only for those who are seropositive but also for those who test negative since it is important to avoid complacency (see Sect. 52.2.6 in this chapter).

Reuse of injection equipment for administering injections to more than one person or introducing the syringe in a shared repository of drugs, reuse of syringe barrels or of the whole syringe and informal cleaning have been identified by WHO [105] as high-risk practices. To increase one-time use of injection equipment in medical settings, WHO issue a recommendation for the use of syringes with a reuse prevention feature. Research on low dead space syringes (LDSS) suggests that they reduce the amount of blood remaining in the syringe after completely pushing down the plunger – and subsequently, after rinsing with water, HIV viral burden may be reduced by a factor of 1000 compared to high dead space syringes [106]. A model described LDSS as a potential powerful HIV prevention strategy, and recent real-life data from the UK show an association between exclusive LDSS use with lower prevalence of HCV amongst people who had started injecting recently, suggesting LDSS use may be protective against HCV [96]. However, there is a risk that promoting LDSS may appear to accept sharing, in contradiction to the clear message that syringes should never be reused or shared.

Safe disposal of used equipment is important. NSPs can facilitate safe disposal by receiving used syringes or by providing puncture-resistant disposal containers to clients. However, if carrying used needles and syringes is a criminal offence or may be used as evidence of drug use, clients may be reluctant to bring used equipment back.

Accessibility and acceptability to target populations are important. This means setting up NSPs in locations with easy access and a minimum of bureaucratic entry requirements. Opening hours should include evenings and weekends. Staff should be positive and sympathetic.

NSPs are mostly implemented in urban settings with a higher prevalence of injecting. In smaller towns and rural settings, a pharmacy-based model may be more appropriate. Apart from (free) distribution through NSPs, needles and syringes can be purchased at pharmacies in many countries, though various formal or informal restrictions can discourage people from using this option, and even a low price may be a disincentive for low-income populations.

The distribution of non-injecting paraphernalia such as safer smoking kits is among the main harm-reduction measures suggested for people who smoke heroin, crack cocaine or methamphetamine (crystal) [82]. A pilot study by Pizzey and Hunt [72] suggested that distributing foil and smoking materials from needle and syringe programmes helps to promote transitions from heroin injecting to chasing. An online survey amongst managers of 80 NSPs in Canada showed that efforts to reduce harm of non-injecting routes of administration are increasing. A majority of programmes educated clients on reducing risks

associated with sharing crack cocaine smoking equipment and most of them also distributed equipment (crack pipes). The most common reasons for not distributing safer smoking equipment were not enough funding and lack of client demand [93].

Despite clear evidence on the benefits of NSPs, opposition from local policymakers, professionals and community groups can limit the possibilities of establishing an effective network of NSPs. Thus, a process of consultation with relevant local bodies is essential. Careful planning and co-ordination with local health and treatment services are important to establish clear procedures for referral links. Agreement needs to be reached with justice and police officials to avoid counter-productive interventions.

52.2.3 Supervised Drug Consumption Facilities

Drug consumption rooms (DCRs) are professionally supervised healthcare facilities where drug users can use drugs in safer and more hygienic conditions [37]. DCRs seek to attract hard-to-reach populations of drug users, especially marginalised groups and those who use drugs on the streets or in other risky and unhygienic conditions. They aim to reduce morbidity and mortality by providing a safe environment for more hygienic drug use and by training clients in safer drug use. At the same time, they seek to reduce public drug use and to improve public amenity in areas surrounding urban drug markets. A further aim is to promote access to social, health and drug treatment facilities [42]. Since 1986, more than 150 DCRs have been set up in 10 European countries as well as in Canada, Australia and Mexico [24, 25]. They are highly targeted services addressing specific local problems within a wider network of services, and access is typically restricted to registered service users. They usually operate as an integrated part of low-threshold facilities for drug users or the homeless, though some are stand-alone units. Most target drug injectors, though increasingly also cover users who inhale or smoke drugs. At times, their establishment has been controversial due to concerns that they may encourage drug use, delay treatment entry or aggravate problems of local drug markets, and initiatives to establish DCRs have been prevented by political intervention.

Evidence shows that DCRs succeed in reaching their target populations and achieve immediate improvements in terms of better hygiene and safer use for clients who use the services. There is consistent evidence that DCR use is associated with self-reported reductions in injecting risk behaviour such as syringe sharing as well as reductions in improperly discarded syringes, so DCRs are also likely to be beneficial in reducing drug use in public and related problems of public disorder. Studies on overdose-related morbidity and mortality suggest a protective effect of DCRs [37, 42]. Regarding transmission of HIV and HCV, due to a lack of robust studies and methodological problems such as isolating the effect of DCRs from other interventions or low coverage of the risk population, there is insufficient evidence either to support or discount the effectiveness of DCRs [3, 50].

Benefits of DCRs include improvements in safe, hygienic drug use, especially amongst regular clients, increased access to health and social services and reduced public drug use and associated nuisance. The availability of safer injecting facilities does not increase drug use or frequency of injecting; it facilitates rather than delays treatment entry, and does not result in higher rates of local drug-related crime.

DCRs have mostly been established in specific urban settings with problems of public drug use and overdose or where there are subpopulations of drug users with limited possibilities of hygienic injection (e.g., homeless, living in insecure accommodation or shelters). As with NSPs, consultation with local key actors is essential to minimise community resistance or counter-productive police responses.

52.2.4 Overdose Prevention

Large increases in opioid overdose deaths in the USA and Canada over the last decade

raised alarm about the overprescribing of strong opioids and the significantly increased presence of fentanyl (a highly potent opioid) in the illicit heroin market [54, 85], trends not observed in Europe. However, although rising overdose deaths often trigger concern, efforts to develop interventions specifically targeted at reducing overdose deaths have historically emerged more slowly than responses to other drug-related problems like dependence, crime or HIV/AIDS.

As noted above, effective drug treatment, in particular OST, significantly reduces overdose mortality, and DCRs can contribute at local level if capacity is sufficient. A more specific and promising approach to reducing opioid overdose deaths is offered by community-based overdose prevention programmes that include peer naloxone distribution.

Naloxone is an opioid-antagonist used in medical emergencies to reverse respiratory depression caused by opioid overdose. It has no effect on non-opioid drug overdoses and has a high safety margin. It is available in injectable form and also as an intranasal spray since 2015.

The aim of naloxone distribution programmes is to increase the availability of effective medication in places where overdoses are more likely to occur. Overdose is common amongst opioid users, and most overdoses happen in the presence of a witness, often in the users' home. Many people who die from opioid overdose fail to receive proper medical attention because witnesses (often other drug users) do not recognise the seriousness of the situation, delay, or do not call emergency services for fear of police involvement.

Peer naloxone distribution programmes work by training drug users and other likely first responders (e.g., peers, families), as well as frontline services such as healthcare providers, staff in homeless shelters and, in some cases, police officers, on how to recognise and respond to an overdose, including administration of naloxone, until emergency medical help is obtained. Naloxone is distributed to trained participants, to be at hand if they witness an overdose.

While local naloxone projects started in the USA and Europe in the 1990s [92], they have only recently been scaled up in some locations. Given the dramatic rates of fatal opioid overdoses in the USA and Canada, federal, state and local governments have prioritised increased access to naloxone and overdose education, and naloxone distribution programmes are implemented as a harm-reduction strategy. Nationwide take-home naloxone programmes exist in European countries with high rates of drug-related deaths (including the UK, Norway and Denmark).

A study covering the first 8 years of naloxone provision by community-based organisations across the USA documented that over 150,000 laypersons had been trained and 26,463 overdoses reversed [99]. A systematic review of 21 studies reporting outcomes of take-home naloxone programmes found evidence that educational and training interventions, complemented by naloxone distribution, may decrease overdose-related mortality and that opioid-dependent patients and their peers involved in such programmes improve their knowledge on the correct use of naloxone and management of witnessed overdoses [57]. A meta-analysis of pooled data from four studies on bystander naloxone administration and from five studies on overdose education programmes [29] confirmed an association of naloxone programmes with increased odds of recovery and improved knowledge of overdose recognition and management in nonclinical settings. Furthermore, naloxone distribution was found to be cost-effective [12]. In a pre-post evaluation of a national naloxone programme (Scotland), brief training and standardised naloxone supply for individuals at risk of opioid overdose in prison were effective in reducing by 36% the proportion of opioid-related deaths occurring in the 4 weeks following release from prison [5]. A recent study in the USA analysed whether different laws affecting the accessibility of naloxone correlated with the number of overdoses and deaths [1]. The researchers found that only laws allowing widest access via direct dispensing by pharmacists appeared to be useful in reducing opioid-related fatalities, but noted an increase in

non-fatal overdoses in communities where access to naloxone is improved.

Benefits include substantial reductions in opioid overdose deaths, if sufficient coverage of risk populations can be achieved. Giving people, who are likely to witness an overdose, access to naloxone is recommended by WHO in guidelines on community management of overdose and as a component of a comprehensive package of services for people who use drugs. The introduction of naloxone nasal sprays promises to ease the administration of naloxone and improves safety through avoidance of needlestick injuries when treating a population at high risk of blood-borne infections.

Raising overdose risk awareness and increasing response skills amongst professionals in contact with drug users, and disseminating overdose risk information to users, their peers and families constitute an other important part of a comprehensive programme to reduce overdose mortality. Counselling on overdose risk should be a key component of prison release or treatment discharge protocols. Crisis intervention and counselling at hospital emergency rooms following admission for overdose have been tried in some countries.

Since in the USA a significant proportion of drug overdose deaths are associated with prescription opioids and sedatives, prescription monitoring and co-prescribing of naloxone to long-term pain patients have been suggested among various responses to curb the epidemic of overdose deaths [11].

52.2.5 Outreach, Peer Education and Health Promotion

Community-based outreach aims to facilitate improvements in health and reductions in risks and harms for individuals and groups who are not effectively reached by fixed-site services or through traditional health education channels [76]. It seeks to achieve this through identifying and contacting target groups of drug users in different community settings in order to deliver in situ interventions to hard-to-reach populations as well as to provide a contact point for increasing access to a range of other services. Depending on circumstances, interventions may include dissemination of information on drug- and sex-related harms and risk behaviours; provision of advice and counselling on individual behaviour change; distribution of prevention and safer use materials such as sterile injecting equipment, condoms and lubricants; overdose prevention training, including take-home naloxone distribution; and measures to facilitate access to healthcare, social services and drug treatment. The focus may be on individual risk reduction, or it may also include attempts to change social norms concerning risk behaviours amongst the target populations concerned.

Outreach projects may operate from a standalone base, but they are often attached to other community health and social services such as NSPs, street-level low-threshold services, treatment centres, etc. Target groups may include homeless, migrant or minority group users with limited access to services, street users, sex workers, chaotic stimulant and multiple drug users or more private, closed groups.

Different models of outreach have been described [60, 76, 77, 78]. Some are based on professional youth or community health workers, others originated from ethnographic research involving indigenous leaders to target risk networks and individuals, others have focussed on promoting peer-driven outreach, whilst others have developed out of advocacy or self-help organisations. Some concentrate more on the individual level (e.g., information and awareness raising, referral or support for change), whilst others give greater emphasis to a network approach involving peer education and modification of peer norms or empowerment of vulnerable groups.

Reviews of studies of outreach interventions to prevent HIV infection conclude that outreach is an effective strategy for reaching hard-to-reach, hidden populations of people who inject drugs, enabling them to reduce their risk behaviours and increase protective behaviours [50, 60, 88].

Studies of network approaches suggest that, given guidance and nominal incentives, injecting drug users can play a more extensive role in community outreach efforts than the traditional model allows. New models of care, developed in the context of viral hepatitis elimination, show that referrals made by peer outreach teams or using specialised liaison nurses help to engage with homeless individuals with multiple comorbidities and help undiagnosed people who inject drugs to access voluntary testing [33, 46].

Outreach is a flexible and effective component of local harm-reduction strategies. It is essential that outreach workers can establish rapport with target populations and gain acceptance as trusted and knowledgeable sources of information and advice. It is vital to ensure confidentiality and to communicate messages clearly. Outreach workers need adequate training, support and protection, especially in peer-driven interventions. This is helped by clear guidelines covering objectives, services offered, responsibilities and limits (personal, professional, legal, etc.). Concrete procedures with other local agencies are important to maximise the uptake of referrals. Drug users and user organisations should be actively involved as partners in planning and conducting outreach.

52.2.6 Testing, Vaccination and Treatment of Infectious Diseases

Public health guidelines recommend a comprehensive and integrated approach to preventing and treating infectious diseases amongst high-risk populations with focus on the individual's overall health and social conditions. This section highlights key points for practitioners and managers involved in harm-reduction interventions for people who use drugs. Innovative technologies are influencing algorithms for diagnosing infections, and new highly effective treatments have led to rapid changes regarding hepatitis C. Extensive, up-to-date information on public health policy, scientific evidence and clinical practice can be found in reviews and guidelines by public health institutions (e.g., ECDC, CDC and WHO) [8, 20, 21, 22, 104].

Recommended core measures include provider-initiated offer of voluntary, confidential screening for HIV, hepatitis B and C, common STDs and TB; vaccination for hepatitis A and B, and where clinically indicated for tetanus, influenza and pneumococcus (HIV positive) and antiviral treatment for HIV and hepatitis C; as well as treatment for STDs and TB [21]. Care should be taken about potential medication interactions, including methadone, especially in the treatment of people with co-infections.

Many people who inject drugs may be unaware that they are infected. Accessible testing in settings where people who use drugs are reached offers an opportunity to provide information and health education and to identify cases for vaccination or treatment. Knowledge of sero-status provides an informed basis for discussing changes in drug use and sexual behaviour with clients and has been found to be associated with positive behaviour changes [20].

Access to and uptake of testing and treatment of infectious diseases and STIs can be increased through on-site screening at services for drug users (drug treatment centres, NSPs or DCRs). Rapid testing techniques now allow this in diverse contexts, including low-threshold services and outreach. Where possible, treatment should take place at the same sites to improve uptake. If not possible, then active referral pathways to public health facilities should be established.

Screening programmes for infectious diseases need to be tailored to clients' life situations and be highly accessible and quick. Thus, the use of point-of-care rapid tests is common. For HIV antibodies, inexpensive enzyme immunoassays using unprocessed blood (finger stick) or oral fluid specimens provide results within 20 minutes. HIV self-testing (HIVST) is recommended by WHO for reaching as-yet undiagnosed populations. Rapid HIV testing kits for home use are approved in the USA and other countries and are available from major pharmacies; some harm-reduction agencies include HIVST kits amongst a range of prevention materials.

When positive, rapid tests require laboratory confirmation with serum or plasma. Delays between first test and confirmation (and treatment start) often cause loss to follow-up. New technical devices (platforms) allow detection and quantification of HIV nucleic acid and HCV viral load at the point of care using unprocessed whole blood specimens. Mechanisms linking those infected to treatment need to be established; as infections can be asymptomatic, starting treatment may not be a priority from the client's perspective. Whilst testing has already moved towards point of care, a new approach to prevent loss to follow-up is to combine diagnosis and start of antiviral treatment in the same visit.

Testing can also provide opportunities to encourage partners to be tested and to participate in changes needed to reduce risks. Periodic health checks and monitoring of seronegative individuals, as well as those successfully treated, help to reinforce protective behaviours and identify reinfection. It also contributes to monitoring programme effectiveness.

52.2.6.1 Agenda 2030 for Sustainable Development

Target 3 of the agenda for global development (SDG 2030) aims at ending the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases by 2030. Recent advances in the treatment of hepatitis C led WHO to add the elimination of viral hepatitis as a public health threat by 2030 as an additional goal.

Antiretroviral treatment (ART) is a highly effective treatment for HIV and reduces viral load amongst those who adhere to it to undetectable levels. A policy of universal test and treat – making ART available to all HIV-infected persons regardless of CD4 count – is recommended by WHO since 2014. Earliest ART initiation results in successful treatment outcomes amongst PWID with no increase in self-reported risk behaviour. Early diagnosis and engagement in OST should be promoted whilst enhancing care for those with advanced HIV disease and history of imprisonment [61].

New hepatitis C treatments with combinations of drugs called direct-acting antivirals (DAAs) achieve high cure rates even amongst active PWID – in terms of a sustained virologic response (SVR) – with few side effects and after treatment periods of 12 weeks or less. Treating HIV and HCV in those infected not only benefits individuals but has an important preventive effect since it reduces infectivity and thus the risk of transmission to others [100].

Recommendations by the European Association for the Study of the Liver (EASL) on treatment of hepatitis C [68] recommend prioritising groups with high risk of transmission – including active PWID and people in prison, for viral hepatitis treatment as a way to significantly decrease incidence. As reinfection can occur amongst those who remain involved in high-risk practices, maintaining an offer of high-scale harm-reduction measures alongside treatment of infection is essential. This includes education and support to reduce risks, access to clean injecting equipment, effective treatment of drug dependence and reducing stigma related to drug use and infection. For populations exposed to high-risk drug use environments, DCRs can complement other measures. Active PWID are not eligible for direct-acting antiviral treatment in some health systems, and research on how to overcome further client- or provider-related barriers to treatment initiation is needed [98].

For those uninfected, taking ART as preventive measure (pre-exposure prophylaxis PrEP) has been shown to be effective in men who have sex with men (MSM) and heterosexually active men and women [8, 41]. A randomised controlled trial of tenofovir covering over 2400 PWID in Bangkok showed a 49% reduction in HIV incidence related to PrEP over placebo. Based on these findings, the US Centers for Disease Control and Prevention (CDC) recommend PrEP be considered 'as one of several prevention options for persons at very high risk for HIV acquisition through the injection of illicit drugs' [7]. PWID may still be largely unaware of PrEP, but recent studies show that they are interested in taking it [4, 86].

Universal vaccination of children for hepatitis B and vaccination campaigns targeting high-risk groups mean that hepatitis B should become increasingly rare. Meanwhile, it is valuable to continue screening for HBV and, where appropriate, offer vaccination using the Accelerated Schedule [103].

STIs increase the risk of sexual transmission of HIV [9]. Thus, identification and treatment of common STIs is one of the principles of HIV prevention strategies amongst sexually active individuals, especially in high-risk populations.

Investment in prevention, scaling up harm-reduction interventions for PWID, remains a crucial priority for halting the HIV and HCV epidemics [39, 47].

52.2.7 Interventions for Stimulant Use

After alcohol and tobacco, amphetamine-type substances and cocaine are the most prevalent substances used worldwide. It is estimated that one in five to seven recent stimulant users develop a problematic consumption pattern [15, 69]. Apart from dependence, harms especially associated with chronic stimulant use include cardiovascular and cerebrovascular diseases; pulmonary damage; mental health problems such as acute psychotic episodes, depression and anxiety; chaotic behaviour, including higher rates of needle sharing associated with intensive, high-frequency injection; and sexual behaviours that increase transmission risks of HIV and STIs. In high cocaine prevalence areas, significant numbers of acute cocaine episodes ('overamping' [1]) are seen by medical emergency services, and deaths involving cocaine (injected or smoked) and psychostimulants have increased in the USA in recent years [40].

The likelihood of harm varies according to context. For example, crack cocaine is more common amongst highly marginalised groups and is associated with elevated levels of HIV transmission risk, especially for women who trade sex for money or drugs [23, 56]. Crack is sometimes injected as well as smoked, adding a further risk dimension [81]. Transmission of HCV may occur through sharing crack pipes via oral sores and cracked lips [27, 55]. Methamphetamine use, especially by men who have sex with men (MSM), is associated with high levels of sexual risk behaviour [87]. 'Chemsex', the intentional combination of sex with the use of certain psychoactive drugs amongst MSM can bear high risks of infection transmission, and concerns small subgroups of MSM who typically present further risk factors [94]. High levels of cocaine use may also be found amongst socially integrated users who sniff rather than inject or smoke the drug. Whilst health risks are lower, they still remain, especially through sexual risk behaviour and sharing straws (HCV). The social networks and economic resources of socially integrated cocaine users may enable them to resolve problems without contacting services [14]. For the most part, problem stimulant use is associated with lower socioeconomic status and a range of social and legal problems, in addition to a variety of psychiatric comorbidities [31].

Harm-reduction interventions for stimulant users include safer smoking equipment (pipes and foil), outreach and peer-driven programmes, sexual risk reduction education, information campaigns including web-based dissemination, assertive community treatment, environments to reduce anxiety and increase control over use in a non-rushed environment, such as supervised consumption facilities, as well as various innovative approaches based on alternative medicine [71].

There are few high-quality scientific studies of interventions to reduce specifically the harms of CNS stimulants. Systematic reviews on treatment for psychostimulants indicate that the addition of

[1]The term 'overamping' is used to describe the variety of negative of uncomfortable physical and psychological effects; can include paranoia, increased heart rate, discomfort, violence, anxiety, sweating and other experiences – See: https://harmreduction.org/issues/overdose-prevention/overview/stimulant-overamping-basics/what-is-overamping/

psychosocial treatment such as contingency management, cognitive behavioural therapy, motivational interviewing and others may offer modest improvements compared to treatment as usual (usually characterised by group counselling or case management), probably reducing the dropout rate and increasing the longest period of abstinence [58]. Retention rates in treatment tend to be low, reducing the potential for systematic efforts to reduce risk behaviours.

A systematic review addressing pharmacotherapy for cocaine use [10] found no evidence of effectiveness of any class of drug in increasing abstinence, reducing use or improving treatment retention rates. There were some indications that particular drugs may be beneficial, such as sertraline to maintain abstinence, antipsychotics to improve treatment retention and psychostimulants and anti-depressants to increase abstinence in comorbid opioid users. Work on a cocaine vaccine progresses slowly and is still in early stages of optimising vaccine formulations to improve efficacy [45].

A review of whether substitution with medications that have psychostimulant effect is effective for treating patients with cocaine dependence [6] assessed nine CNS stimulants (bupropion, dexamphetamine, lisdexamfetamine, methylphenidate, modafinil, mazindol, methamphetamine, mixed amphetamine salts and selegiline) and found mixed results, suggesting research to further evaluate the approach in combination with behavioural and psychosocial input to stabilise drug use and lifestyle.

NSPs are an effective intervention to reduce injecting-related risks for injecting stimulant users as well as opioid users. However, as noted earlier, people who inject stimulants inject frequently and need a plentiful supply of sterile syringes and needles. Given the chaotic lifestyle, frenetic drug-using behaviours and disturbed sleep patterns often seen in compulsive stimulant injectors, providing adequate coverage of injecting needs, potentially for up to 24 hours per day, is a challenge for any service. Mobile units and syringe dispensing machines can help extend coverage in terms of times and places.

Most DCRs were initially established for heroin injectors and often did not admit cocaine injectors or smokers but have increasingly adapted to client needs by setting up separate rooms for those who smoke or inhale drugs. This has proved to be feasible, attracting important subgroups such as crack-using sex workers, and appears to provide benefits similar to those that obtain for heroin users [35, 82].

It has been suggested that traditional harm-reduction services fail to reach problem stimulant users due to opiate-centred services and social barriers to young or female users [31]. Thus, greater emphasis needs to be placed on outreach and peer education approaches (see Sect. 52.2.5), especially for younger users. In response to the risks associated with smoking crack, some programmes in the USA, Brazil, Canada and France have developed ‘crack kits’ [82]. These include a Pyrex Tube, rubber mouthpieces, filters, lip balm, sterile compresses, chewing gum for salivation and condoms. Initial results suggest that sharing of crack pipes decreased dramatically, whilst crack users reduced injecting and more often smoked cocaine [48]. However, crack kits are controversial and rarely funded.

Regarding crack, there is some evidence that the severity of mental health harms associated with cocaine is related more to the intensity and context of use than to the specific form of cocaine used [32]. Harm-reduction measures aimed at safer, more controlled, less intensive use of cocaine together with steps to stabilise the social situation may help to decrease mental health problems.

Other approaches include acupuncture as an adjunct to treatment to reduce craving, though a systematic review of controlled trials found no evidence of effectiveness [28], or providing accessible and flexible walk-in calming environments to reduce agitation and anxiety levels. Advice, counselling and treatment services for socially integrated users may be more attractive if separated from services for opioid users and

drug injectors and if they operate at appropriate hours, for example, evenings.

Interventions for less intensive users include information dissemination on managing mental health risks or on stimulant use via flyers, websites, personal messaging via mobile phones or "pill testing" in nightlife settings [31, 82].

Patterns of stimulant use and risks can vary greatly from one setting to another. For example, in some former Soviet Union republics, home production of stimulants is associated with specific and highly risky patterns of drug consumption [31], and in the UK, groin injection of crack cocaine raises special challenges [81]. In some settings, women are particularly at risk. This means that interventions need to be thoughtfully planned to take account of local circumstances and vulnerable groups. This should include critical reflection on whether any unintended negative effects might arise. Whilst there is much room for innovative development of harm-reduction responses, it should be stressed that all interventions for stimulant users need to give high priority to sexual risks as well as to drug-related risks.

52.3 Conclusion

This chapter has provided an overview of interventions that contribute to reducing drug-related harms. Above and beyond any particular intervention, it must be emphasised that single interventions are far more effective when implemented together as part of a broader package, including policies to facilitate enabling environments that foster healthier and safer living.

Harm reduction does not replace the need for treatment but adds to our capacity to respond effectively to the wide range of health and social challenges raised by drug use. Apart from skills in dealing with individual clients, practitioners need an understanding of the social, community and public health settings within which drug use and drug-related harms arise, as well as an awareness of how social responses can have unintended consequences. Willingness and ability to co-operate within a local network of agencies and listen to the concerns of drug users themselves is essential. This involves a broad vision of drug use, harms and responses and willingness to think outside of traditional individual psychiatric and social casework paradigms.

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Part V

Policies and Training in Addiction

Alexander Baldacchino and Barbara Broers

Policy and Training in Addiction: An Introduction

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Alexander M. Baldacchino and Barbara Broers

Content

Worldwide, around 271 million people (5.5% of the global population) aged 15–64 years, used illegal drugs at least once during 2017 [1]. These drugs predominantly include cannabinoids, opioids, cocaine and/or amphetamine-type stimulant (ATS) groups. Some 31 million people who use drugs suffer from drug use disorders (DUDs), meaning that their drug use is harmful to the point where they may need advice or treatment. Some 585,000 people are estimated to have died as a result of drug use in 2017. Opioids take a large share, accounting for 76% of deaths amongst people using drugs. About 11.3 million persons in 2017 have a recent history of intravenous drug use. This subgroup endures the greatest health risks with almost half of them living with Hepatitis C, 1.4 million living with HIV and one million living with both of these preventable conditions. The disability-adjusted life year (DALY) in 2017 attributable to illicit drug use was estimated to be 27.8 million. This was compared with tobacco use and alcohol use, accounting for 170.9 million and 85 million in the DALY [2].

Surveys on drug use amongst the general population show that the extent of drug use amongst young people remains higher than that amongst older people, although there are some exceptions associated with the traditional use of drugs, such as opium or khat. Most research suggests that adolescence (12 to 17 years old) is a critical risk period for the initiation of substance use and that substance use may peak amongst young people aged 18–25 years [1].

There have been steps taken at a global level to set strategies for response to the world drug problem. The Joint UN Ministerial Political Declaration and Plan of Action in 2014 [3] explicitly reaffirmed that DUD is a health problem with a need to further strengthen public health systems that are responsive to current and

A. M. Baldacchino (✉)
Population and Behavioural Science Division (Psychiatry and Addictions), University of St Andrews and NHS Fife, St Andrews, UK
e-mail: amb30@st-andrews.ac.uk

B. Broers
Unit for Dependencies, Division for Primary Care, Department for Community Medicine, Primary Care and Emergencies, Geneva University Hospitals, Geneva, Switzerland
e-mail: barbara.broers@unige.ch

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emerging drug-related problems. The adoption of target 3.5 of the Sustainable Development Goals [4] also reaffirms this vision of strengthening the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol.

The outcome document of the special session of the United Nations General Assembly on the World Drug Problem held in 2016 [5] contains more than 100 recommendations on promoting evidence-based prevention, care and other measures to address both supply and demand. Additionally, World Health Organization (WHO) and United Nation Office for Drug Control (UNODC) have developed close collaborations to support the implementation of development of comprehensive, integrated health-based approaches to drug policies that can reduce demand for illicit substances, relieve suffering and decrease drug- and alcohol-related harm to individuals, families, communities and societies [6].

In order to benefit optimally from the international covenants and policy environment, a series of consultations with the WHO technical focal points from all member states was conducted. With close collaboration with sister UN and other international drug policy agencies, a framework to strengthen public health responses to drug and alcohol problems was agreed. The underpinning principles behind this framework include interventions that are evidence based, adopt a life-course approach, promote multi-sectorial action and observe standard of care across a continuum which is gender and culture sensitive. The drivers behind this framework include an active engagement of civil society that has the voices of both service users and care providers that value the protection and promotion of equity and universal rights to access optimal treatment and harm reduction interventions.

The framework incorporates five overarching strategic domains:

1. *Governance:* This includes the adoption of evidence-based and cost-effective interventions as part of the universal health coverage benefit package; develop and update evidence-informed national substance use policies and associated legislation with a strong public health component in consultation with stakeholders from public, private, as well as civil society sectors; set up an inter-sectoral coordination mechanism to facilitate implementation and monitoring of evidence-based substance use policies and legislation and allocate specific budget allocations within the health and welfare sectors to address prevention, management, rehabilitation, recovery and monitoring and evaluation of drug- and alcohol-use problems; develop programmes offering alternatives to incarcerate illicit drug offenders.
2. *Health Sector Responses:* Integrate screening and brief interventions for substance-use disorders and management of overdose in primary health care and emergency rooms; develop and strengthen specialised services for holistic and integrated management of substance use disorders, including pharmacological and psychosocial interventions; introduce and/or rapidly scale up the comprehensive package of services for harm reduction; ensure availability of essential medicines in management of substance-use disorders; facilitate and promote establishment of self- help and mutual aid groups and develop/strengthen capacity to conduct and utilise implementation research.
3. *Promotion and Prevention:* Embed universal substance-use prevention programmes in the broader health policies and strategies based on rigorous local needs and resource assessments and design and implement age-specific substance use prevention programmes in community, education and work place settings.
4. *Monitoring and Surveillance:* Identify a standard set of comparable core indicators to monitor the substance use situation including for inclusion in the existing surveys and develop a system for national substance use monitoring and surveillance system to collect and report core set of indicators using standardised data collection tools and methodologies.

5. *International and Regional Cooperation:* Promote active sharing of information and evidence between professionals and civil society organisations from countries of the region at national and international policy forums on substance use.

The second edition of this ISAM Textbook reflects the increasing importance of the interplay amongst policy, legal, quality and other governance-led standards within the field of addiction medicine as summarised by the above framework. The quality standards will be discussed by Marica Ferri et al. from the EMCDDA with ethical and legal aspects addressed by Ambros Uchtenhagen. Evidence-based policy can only be delivered if the appropriate methodologies are established. This will be addressed separately by Robin Room and Ambros Uchtenhagen.

However, one aspect that as yet has not been fully developed in the above framework is the global recognition to increase and improve our addiction medicine workforce. The framework recognises the need to develop capacity of personnel in health and social welfare sector for substance-use prevention, treatment, care and rehabilitation through integrating the component in preservice and in-service teaching/ training and as a part of continuing professional education/recertification processes. This is the International Society of Addiction Medicine's core mission and involves the long-term commitment from relevant stakeholders to improve undergraduate addiction medicine training and postgraduate specialisation in addiction medicine. This is most relevant to the future medical workforce who will increasingly be treating complex cases with multi-morbidities (mental and physical) directly or indirectly related to polydrug misuse and/or multiple dependencies (pharmacological and behavioural). Additionally, this is as equally relevant to other clinicians working in the field of addiction medicine who, with the medical workforce, are increasingly encouraged to work within an environment that encourages shared decision and multidisciplinary teamwork.

Training in addiction medicine needs to be both knowledge and competence based, especially when one reaches postgraduate/specialisation stage of the professional career [7]. This has been shown to influence positively the clinical, educational, information and research governance requirements to complex interventions. The result will be a competent and confident workforce that enables and sustains delivery of efficacious and effective health sector and culturally sensitive and non-stigmatising responses. Further challenges faced with establishing such a competitive-based informed learning environment are discussed by Nady el-Guebaly et al., Steve Gust et al., Christine Goodair et al. and Cor de Jong et al. separately addressing some of the solutions.

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Good Practice and Quality Standards

54

Marica Ferri and Paul Griffiths

Contents

Abstract

The present chapter is aimed at enabling the readers to understand the methods and the available tools to ascertain whether an evidence-based recommendation is appropriate for real-world patients in specific contexts. In times of a wide availability of real-time information on potentially anything, it is crucial to develop an individual capacity for critical assessment of scientific literature including strategies to search for updated and reliable sources of evidence. The methods, the processes, and the practical meaning of the most popular tools for the promotion of quality are presented with links to current projects and free-of-cost resources for professionals. The ultimate goal of evidence-based medicine is to provide patients with the best possible interventions. To reach this goal, knowledge has to be translated into practice. Guidelines and standards are popular instruments to disseminate and implement evidence-based recommendations. Nevertheless, to implement them into specific contexts, some decisions are needed. The chapter includes a description of the main approaches used to adapt or adopt guidelines and standards.

Quality is never an accident. It is always the result of intelligent effort. There must be the will to produce a superior thing. —John Ruskin

M. Ferri (✉) · P. Griffiths
EMCDDA, Lisbon, Portugal
e-mail: marica.ferri@emcdda.europa.eu

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54.1 Introduction

The promotion of quality of health and social interventions and the exchange of good practices are recognized as an important strategy both to improve the effectiveness of drug-related interventions and to ensure the efficient use of limited resources. Guidelines and standards, in particular, are among the most frequently used tools for the promotion of quality through the translation of knowledge into the daily practice of treatment of drug addiction. But publishing new guidelines and standards is not always needed; often the existing good-quality guidance documents can be adapted to suit a specific national or local context.

New disciplines focusing on methods for successful knowledge transfer to action, such as implementation science, translational science, and knowledge mobilization, have emerged. A common recommendation to successful implementation is the promotion of participation among all the stakeholders, starting with medical doctors and health professionals and including decision makers, patients and their families, and the public in general. It is therefore important that the professionals in the treatment of drug addiction are familiar with the terminology and the methods of quality promotion, as these are increasingly part of their daily activity.

The contents of the evidence base change rapidly, as new studies contribute to new results. This is why it is important to master the methods to ascertain whether a recommendation is appropriate for real-world patients in specific contexts. It becomes crucial to develop an individual capacity for critical assessment and to know where to search for updated and reliable sources of evidence. This chapter seeks to address these concerns. It describes the evolution from evidence base to implementation and provides details on the terminology and references for further reading. The methods, processes, and the practical meaning of the most popular tools for the promotion of quality are also presented here with links to current projects and free-of-cost resources for professionals, researchers, and patients. In particular, it details how time and resources can be saved by *adapting* or *adopting* already published evidence-based guidelines to specific needs and contexts. The current initiatives for the development of quality standards in drug addiction treatment at international and at the national level are described and compared, and for each of them, the links for free downloading of documents are included. To complement the information on implementation, the chapter includes also a description and references to some recent initiatives in the medical field, in which the participation of drug addiction treatment professionals is crucial but still not sufficient. All these initiatives are studying strategies to effectively communicate with decision makers and patients. In addition, two examples of the use of standards are compared more in-depth: one case as part of an accreditation system, and the other as support for implementation and the measuring of quality criteria.

54.2 From Knowledge to Implementation

54.2.1 Knowledge Translation into Practice: From Evidence to Change

The overall aim of good practice sharing and standards development is the achievement of improvement in the quality of treatment. Quality is not an abstract concept but rather an umbrella definition for a series of measurable achievements in the health and well-being of the treated patients.

"*Primum non nocere*" – first of all, do not harm –, the phrase attributed to the Hippocratic Oath, reminds us that the first aim of a health intervention is to avoid harm. And it is exactly with this intention that the pioneers of the evidence-based medicine called the attention on the discrepancies between research results and medical practice, which would have cost human lives [11]. According to their claims, the timely application to the practice of the results from clinical research would have saved many lives and reduced subsequent costs to society [16]. For example, randomized controlled trials proving the effectiveness of systemic glucocorticosteroids administered to pregnant women at risk of preterm delivery to reduce respiratory distress syndrome in newborn

babies were available already in the 1970s, but it took almost 20 years before this intervention became common practice [39].

The possible effect of the delay in the adoption of this practice was that a significant number of premature babies probably suffered and possibly died and needed more expensive treatment than was necessary [38].

The movement for the systematic collection of scientific results for dissemination outside the restricted circles of researchers and academics became known worldwide at the beginning of the 1990s [41] and was boosted by the foundation of the Cochrane Collaboration, an international organization aimed at helping "healthcare providers, policy-makers, patients, their advocates and carers, make well-informed decisions about health care, by preparing, updating, and promoting the accessibility of Cochrane Reviews" [10].

In 1998, an editorial group specifically devoted to the study of interventions for drugs and alcohol-related problems was founded with its base in Rome [13], and since then around 70 reviews on prevention, treatment, and harm reduction have been published and systematically updated.

The availability of good quality research on the effectiveness of treatment for drug problems has dramatically increased over the last years, even though important gaps remain to be bridged with evidence [47]. The availability of studies and systematic reviews nurtured the production of clinical guidelines as a major tool for the dissemination and application of evidence in practice.

For example, a survey for the identification of treatment guidelines in Europe identified more than 140 sets of guidelines for the treatment of drug addiction [18]. Nevertheless, the practical effects of such a massive effort to produce clinical guidelines were not clear. When measured, the impact on the quality of treatment seemed not impressive. Some surveys performed in the medical field, not specifically in the drug addiction one, showed that clinical guidelines are applied to practice in only 50–70% of day-to-day decisions, and the main reason given for not applying them is that they are of limited relevance to patients and healthcare staff [36]. Moreover, in a debate promoted by the British Medical Journal about the effectiveness of guidelines [23], it was pointed out that to ensure clinical guidelines have an impact on actual care and practice, activities beyond the mere production and dissemination should be instigated [21].

This type of considerations along with the need to reduce cost and improve quality and outcomes must be at the base of the evolution toward the *knowledge translation into practice* approach [5]. Moving from the concept of evidence to that of knowledge expands an idea already present in the definition of evidence-based medicine. The practice of evidence-based medicine integrates clinical expertise with the best available evidence from systematic research, explained David Sackett [41]. "Without clinical expertise, practice risks becoming tyrannized by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient" reinforced. Probably "knowledge" is a better term to put together evidence with expertise. *Knowledge translation* has been defined as a "dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically sound application of knowledge to improve health, provide more effective health services and products, and strengthen the health care system" [9]. Knowledge translation is not the only term that has been used to name this tendency toward the practical use of knowledge to improve practice. According to Straus et al. [45], more than 90 terms were identified in the literature. According to them, in Europe, preferences are for "implementation science" or "research utilization," whereas the terms "dissemination and diffusion," "research use," and "knowledge transfer and uptake" are more frequently preferred in the United States. The Canadian "knowledge translation" has been adapted by others, including the United States National Center for Dissemination of Disability Research and the World Health Organization (WHO).

The lowest common denominator among the above-described different terms is a move beyond the dissemination of knowledge into the actual use of it to transform practice. "Knowledge creation (i.e., primary research), knowledge distillation (i.e., the creation of systematic reviews and guidelines) and knowledge dissemination (i.e., appearances in journals and presentations) are not enough on their own

to ensure the use of knowledge in decision-making" [45].

A definition of the "best-practice" concept was recently developed by a group of European experts convened by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). In brief, best practice is the best application of the available evidence to current activities in the drug field. Several factors were identified as contributing to making an intervention qualify as "best practice." In summary, a best-practice intervention is based on the most robust scientific evidence available regarding what is known to be effective in producing successful outcomes, and it is tailored to the needs of those it addresses. Methods used will be transparent, reliable, and transferable and can be updated as the knowledge base develops. Concerning implementation, local contextual factors will be taken into account, and the intervention will be harmonized with other actions as a part of a comprehensive approach to drug problems. A best practice is closely linked to the concept of "evidence-based practice," and it requires the careful integration of both scientific knowledge and implementation expertise to appropriately adapt the intervention to the single individual and/or to a specific context. A best-practice intervention should provide better outcomes than other interventions and therefore also allow a rational allocation of resources [21].

There remain challenges associated with the promotion of best practice through guidelines, standards, and other similar tools. The first is to make sure that they are based on reliable scientific evidence and that they are regularly updated when new systematic reviews are published. The second is to make the best use of the currently existing guidelines. Finally, it is important to ensure that guidelines and standards are appropriately implemented.

54.2.2 Quality of Interventions: The Main Tools and Their Life Cycle

Clinical guidelines are the main instrument to disseminate evidence-based interventions via recommendations for practice that are based on a clear methodology for the appraisal, synthesis, and grading of the available evidence [12]. Evidence-based guidelines are produced by convening multidisciplinary groups of experts who systematically assess the quality of the available evidence and classify the recommendations according to the level of supporting evidence. The level of evidence is determined by a synthesis of relevant studies' design (systematic reviews), the number of participants studied, and the number of studies sharing the same results along with the overall measure of effect found by pooling the results of the studies. Each recommendation should be accompanied by an indication of its strength, which clarifies how and when this applies to the patients. Although the level of evidence influences the strength of a recommendation, there are conditions under which, even where there is a lack of evidence from studies, the appointed group of experts may attribute a high strength to some recommendations. This is the case for some interventions, such as hydration for hospital patients or blankets to prevent heat loss in trauma patients, that are supported by practical experience and do not need to be based on experimental evidence. Guidelines may, therefore, include a statement such as "we recommend that this intervention is offered to most patients, even though there are no studies which prove or refute the effects, and this recommendation is based only on expert opinion." In some milestone manuals for guidelines development, these are indicated as *good practice points* [44].

Another example is where patients cannot be directly studied for ethical reasons (such as exposing newborn babies to different drug therapies). In such cases, the recommendations can be based on the results of studies on other types of patients, by analogy. In practical terms, this system, which separates the level of evidence from strength of recommendations, produces two separate – but not completely independent – scores. In general, evidence-based guidelines are published by independent organizations that can assemble experts who are free from conflicts of interest and who represent different fields and professions. These groups generally involve as many stakeholders as necessary to ensure they

appropriately address all the different aspects of a question, including patients' preferences and practical concerns arising from the experience of the carers [18].

In 2000, a collaboration was established of people interested in addressing the shortcomings of the grading systems used in guideline development, "the grading of recommendations assessment, development, and evaluation" (GRADE) working group [26]. Over the years, this group has developed and continuously updated a common, sensible, and transparent approach to grading the quality of evidence and the strength of recommendations. This system has been adopted by several international organizations among which are the EMCDDA (the Best Practice Portal); the World Health Organization (WHO); Agency for Healthcare Research and Quality (AHRQ), United States; and the National Institute for Clinical Excellence (NICE) in the United Kingdom. The complete list of the organizations that have adopted GRADE can be found in its website (http://www.gradeworkinggroup.org/).

The evidence-based clinical guidelines are meant to facilitate the application of updated evidence to practice, and therefore, they are supposed to be timely revised. An indication of a specific date for revision should be stated clearly, and the choice of this date should be based on an assessment of the time in which new evidence is likely to be available.

This anticipation of a date for the availability of new evidence is in general possible because evidence-based clinical guidelines are based on systematic reviews of studies. These reviews are identified through structured "search strategies" based on a list of "clinical questions" that the guidelines should address. Based on those questions – which should be relevant to the patients and detailed enough to allow the appropriate search for the available evidence [42] – the methodologists search, identify, and select some systematic reviews of evidence. The latter are based on published and unpublished studies and should also identify – in ad hoc created registries [51] – the ongoing studies. Those registries collect information from the very beginning of the clinical studies and follow up each step until the publication. The entity (or the individual researcher) registering a clinical trial is requested to include a date of completion. Although these dates can be changed during the study period, they provide an idea when new results can be available.

Several tools have been developed to assess the quality dimensions in guidelines, one of them being the "appraisal of guidelines for research and evaluation" [1], which was created to address the issue of variability in guideline quality by assessing methodological rigor and transparency. The updated version, "AGREE II" (AGREE Next Steps Consortium [2]), is composed of six domains aimed at assessing whether or not the scope and purpose of the guidelines is clearly indicated; the stakeholders' involvement is sufficient to represent the views of the intended users; the process of development is rigorous; the presentation and text are clear; and the guidelines are fit for purpose and free from conflicts of interest.

Worldwide, there are currently several international inventories of guidelines that can be consulted to find relevant documents. Among those, the more important are the inventory maintained by the Guidelines International Network (http://www.g-i-n.net/library) containing over 6000 sets of guidelines for evidence-based healthcare (in multiple languages) and the National Guidelines Clearinghouse (http://www.guideline.gov/), an initiative of the Agency for Healthcare Research and Quality (AHRQ) in the United States, which publishes guidelines from any countries provided they are in English. The website of the National Guidelines Clearinghouse offers an automated function to compare different guidelines and obtain the synthesis of guidelines. The main aim of the inventories of guidelines is to avoid duplication of efforts making good quality guidelines available for adoption or adaptation in different contexts.

54.2.2.1 Adaptation of Guidelines to Everyday Practice Under Local Circumstances

Clinical guidelines can be elaborated and published at several levels: international, national, or local level. The World Health Organization, for

example, published guidelines and principles on the treatment of drug addiction [50].

Being a very resource-intensive activity, guidelines are in general commissioned to specialized national agencies that have the capacity for convening many stakeholders from all the involved parts and reduce the risks of conflicts of interest. Examples of agencies to develop clinical guidelines are the National Institute for Clinical Excellence in the United Kingdom; the Scottish Intercollegiate Guidelines Network; the Finnish STAKES, National Research and Development Centre for Welfare and Health; the French National Health Authority (HAS); the New Zealand Guideline Group (went in voluntary liquidation in 2012); the Canadian Task Force on Preventive Health Care; and many others. An indicative list of organizations that develop and publish guidelines is available on the website of the Guidelines International Network [25].

Guidelines that are published at a general level may require some further elaboration before they can be effectively applied to everyday practice. The translation of evidence-based recommendations into practice is the so-called implementation process.

Implementation activities can follow two general approaches mainly depending on the "distance" between the context where the guidelines were issued and that where they have to be implemented. In some cases, it is sufficient to *adopt* the guidelines through the development of protocols at the service level in which the guidelines' recommendations are broken down into actions and responsibilities, agreed by the healthcare personnel. This type of protocols (which can be also called *clinical pathways*) supplements clinical recommendations with hospital (or service)-specific details and, in some cases, can emend those recommendations which are considered not fitting with the local context [24]. These protocols can be disseminated in the realm of some peer-led educational activities, and they can include reminders and other initiatives aimed at reinforcing the application of recommendations in practice [7] (Table 54.1).

Table 54.1 Quality standards in the treatment of drug addiction

Title and year of publication	Supporting organization	Target groups	Structure of the standards	Web address
European Minimum Quality Standards (EQUS), 2012	European Commission	Professionals performing interventions; service directors and managers responsible for the functioning of their institutions and staff; and health authorities, planners, and policymakers who are mainly concerned with the drug demand reduction activities at the system and network levels	Structural standards of services Process standards at the service level Process standards of interventions Outcome standards at the system level	www.isgf.ch
Proposed continental minimum quality standards for the treatment of drug dependence, 2012	African Union [3]	Unspecified	14 principles of effective drug dependence treatment 15 standards for the treatment of drug dependence and 3 standards for evaluation and assessment	http://www.au.int/en/

Table 54.1 (continued)

Title and year of publication	Supporting organization	Target groups	Structure of the standards	Web address
Principles of drug dependence treatment, 2008	UNODC WHO [49]	https://www.unodc.org/docs/treatment/UNODC-WHO_2016_treatment_standards_E.pdf	9 principles: description and justification components Actions to promote each principle	http://www.who.int/substance_abuse/publications/principles_drug_dependence_treatment.pdf
National standards Service delivery for people with coexisting mental health and addiction, 2010	New Zealand Ministry of Health	This guidance document is aimed at all those who have an interest and responsibility for planning, funding, and providing mental health and addiction services including District Health Boards, non-governmental organizations and the Ministry of Health. The content will be of interest to staff working in services, consumers, and service users, carers, and others who have contact with these services	General principles Tips for mental health and addiction planners and funders Tips for mental health and addiction service managers and clinical leaders Suggested actions for local planning	http://www.health.govt.nz/publication/service-delivery-people-co-existing- mental-health-and-addiction-problems- integrated-solutions-2010
Principles of drug addiction treatment, 2012	National Institute for Drug Addiction (NIDA), USA	Unspecified	13 principles of effective treatment 22 frequently asked questions	http://www.drugabuse.gov/publications/term/33/Guidelines%20and%20Manuals
Alcohol dependence and harmful alcohol use quality standard, 2011	National Institute for Clinical Excellence (UK)	The public, health and social care professionals, commissioners, and service providers	13 statements and 13 quality measures for: structure process outcome	http://publications.nice.org.uk/alcohol-dependence-and-harmful-alcohol-use- quality-standard-qs11/list-of-statements
Quality standard for drug use disorders, 2012	National Institute for Clinical Excellence (UK)	The public, health and social care professionals, commissioners, and service providers	10 statements and quality measures for: structure process outcome	http://publications.nice.org.uk/quality-standard-for-drug-use-disorders-qs23
Quality framework for mental health services in Ireland, 2005	Mental Health Commission Ireland	Service users as well as the different nature and scale of organizations involved in service delivery	8 themes 24 standards 163 criteria	http://www.mhcirl.ie/Standards_Quality_Assurance/ Quality_Framework.pdf
Standards for integrated care pathways for mental health December 2007	NHS Quality Improvement Scotland	Local management, health staff at the service level	9 process standards 21 care assessment, planning, delivery, and outcome standards 16 condition-specific standards (only one relevant to drug addiction) 2 service improvement standards	http://www.healthcareimprovementscotland.org/programmes/mental_health/icps_for_mental_health/standards_for_integrated_care.aspx

In other cases, an *adaptation* process is put in place, where the source guidelines are further analyzed by a group of local experts who draft new contextual-wise recommendations. Customizing clinical practice guidelines to a particular context and involving local stakeholders and the end-users of the guideline in this process have been identified as ways to improve acceptance and adherence [27]. In general, but not necessarily, the *adaptation* occurs when (inter) national guidelines are to be applied at the local level. In this case, the adaptation process can consider more than one set of guidelines and imply a process similar to the one needed for drafting a new guideline. The major difference lies in the search for source documents that, in the case of an *adaptation*, focus on guidelines rather than on systematic reviews of evidence (and or primary studies) as in the case of development of a new guideline.

ADAPTE (www.Adapte.org) is an international organization of methodologists, researchers, guideline developers, and guideline implementers who aim to promote the development and use of clinical practice guidelines through the adaptation of existing guidelines. The organization created a resource toolkit that can be freely downloaded in the Guidelines International Network website (www.g-i-n.net).

Quality standards are becoming an increasingly popular tool for ensuring the quality of interventions in healthcare. In general terms, standards are principles and sets of rules about what to do and what to have [6] presented as voluntary to many potential adopters. According to one of the most known organizations for standards development, a standard is a document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines, or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context [28]. Typically, the standards proposed in the health field refer to content issues, processes, or structural (formal) aspects of quality assurance, such as environment and staffing composition.

Quality standards can be developed by private sector organizations as it is the case for the International Standards Organization [29]; national private, nonprofit organizations like the American National Standards Institute (ANSI); the Association Franc¸aise de Normalisations (AFNOR); and the British Standards Institute (BSI). The great majority of these organizations have been founded at the beginning of the twentieth century and some after the Second World War. Standards can also be developed by international governmental organizations like the United Nations, the Organization for Economic Co-operation and Development, and the European Union. Standards are a good way to propose harmonization, especially by those organizations whose members are sovereign states that cannot be obliged to follow some rules [6]. Nevertheless, there are also several national organizations, especially in the health field, which develop quality standards. In the case of these organizations, quality standards are intended as sets of rules based on evidence and used to implement the interventions recommended in clinical guidelines. The standards which are developed by the National Institute of Clinical Evidence in the United Kingdom, for example, are typically composed of a general statement and a measure that can be used to assess the quality of care or service provider specified in the statement. "The quality statements are clear, measurable and concise and describe high-priority areas for quality improvement. They are aspirational (they describe high-quality care or service provision) but achievable" [34].

Several international organizations are undertaking standards development for health interventions in drug demand reduction.

The European Commission financed a study on the Development of a European Union Framework for minimum quality standards and benchmarks in drug demand reduction (EQUS) [43], proposing a set of 22 quality standards for treatment (the study included also 33 standards for prevention and 16 for harm reduction).

According to the background paper of this project, in the medical sciences, quality standards are determined by different stakeholders: health authorities, insurance companies, service providers, professionals, and patients. Each of these

professional categories brings different goals, interests, and priorities that need to be reflected in the standards in the light of the underlying scientific evidence. The project, whose lead investigator was Ambros Uchtenaghen [48], divided the quality standards into three dimensions:

1. *Structural quality*, for example, standards relating to the physical environment, staff, training, etc.
2. *Process quality*, for example, standards relating to the process of an intervention, diagnostic assessment
3. *Outcome quality and economic quality*, for example, standards to measure the cost-benefit ratio

The *structural standards for services* cover areas like the physical accessibility of treatment services (which need to be located in places easily reached by public transport) or the environment where the treatment takes place, which should be adequate (to allow privacy during consultations) and safe. Another important aspect is the need for a documented diagnosis as a basis for treatment choice. Staff education and composition are also mentioned in terms of ensuring the presence of medical and nursing staff along with psychologists or social workers and multidisciplinarity with at least three professions represented.

The *process standards at the service level* included the assessment of substance use history, diagnosis, and treatment history along with the somatic and the social status for each patient including an assessment of the psychiatric conditions.

Each patient should be provided with information on the treatment options available and should be provided with a treatment plan tailored to his/her individual needs.

Treatment plans, assessments, changes, unexpected events, and any relevant information should be recorded and kept confidential. Each treatment service should promote cooperation with other agencies and services to ensure an appropriate response to the needs of their patients (whenever a service is not equipped to deal with all needs of a given patient, another appropriate service is at hand for referral) and should ensure continuous education for the staff members.

The *outcome standards proposed at the system level* included the goals of health and social stabilization of patients and the reduction of illegal or non-prescribed psychotropic substances. Monitoring included the level of utilization (each service should provide information on the number of slots or bed utilized) and the ratio of discharges occurred as planned or for different reasons.

Internal and external evaluation of services was also proposed as a standard.

Beyond the list of proposed standards, the project-added value lies in the process adopted to consult the stakeholders and to identify several levels of standards. Namely, the stakeholders were interviewed by rounds of Internet-based consultations about the level of implementation status and acceptability of the proposed standards in their respective countries. Through this strategy, it was possible to identify a long list of standards and grade them by priority of implementation. The European Minimum Quality Standards (EQUS) study also included a review of existing quality standards already implemented at the national level, involving experts from 24 European countries. Concerning drug treatment processes, the standards most frequently reported as already implemented were in the areas of client data confidentiality and assessment of clients' drug use history, whereas the standards concerned with routine cooperation with other services, and those focusing on continuous staff training, were less often implemented. In the area of treatment outcomes, the two types of the standard most frequently reported as implemented were those with goals linked to health improvement and reduced substance use. Among the standards less likely to be applied were those focusing on external evaluation and monitoring client discharge; problems related to the implementation of these standards were reported.

This approach may allow the participating countries to set their own goals and to pace their achievement according to their own capacity and

priorities. This process would also be greatly facilitated by the existence of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), a decentralized agency whose aim is to provide sound and comparable information on drugs in Europe. Thanks to its impartiality and comprehensiveness of information, EMCDDA can support the countries volunteering for the adoption of the quality standards in setting their goals and measuring their successes.

In September 2015, the Council of the European Union adopted Council conclusions on the implementation of minimum quality standards in drug demand reduction in the EU. The list of 16 standards was the result of an initiative of the Italian Presidency that, taking over the priority of defining quality standards based on the project EQUS, set by the Greek Presidency, convened a group of European experts. The expert group cross-analyzed different sets of international standards, comparing them against the principles of the European Drugs Strategy.

These standards represent a minimum benchmark of quality for interventions in: drug use prevention, risk and harm reduction, treatment, social integration, and rehabilitation. Although non-binding for national governments, the document represents the political will of EU countries to address demand reduction interventions with an evidence-based approach. These guidelines have been drawn up in the context of Action 9 of the EU Action Plan on Drugs (2013–2016) (Table 54.2).

In general terms, it can be observed that the existing standards (at their different level of implementation) seem to be triggered by several reasons: the harmonization of the existing services, the translation in practice of the evidence-based guidelines, the consistency between policy decisions and service provision, and the need to measure the results of interventions. These reasons are diversely reflected in the initiatives mentioned mainly about the level, where the standards are proposed. The life cycle of quality standards depends on the supporting evidence, but not completely. When it comes to human rights or general safety measures, the relevant principles are imperishable.

Clinical pathways are structured, multidisciplinary plans of care designed to support the implementation of clinical guidelines and protocols. In the recent past, it was considered that this definition was variedly interpreted by different stakeholders until a recent systematic review [31] clarified the concept.

The clinical pathways are essential to the translation of evidence-based guidelines at the service level. They are meant to "detail essential steps in care of patients with a specific clinical problem" and sequence "the actions of a multidisciplinary team" [14]. In clarifying which actions should be undertaken to practice evidence-based recommendations, clinical pathways "facilitate translation of national guidelines into local protocols" [8] and allow continuous improvement by monitoring and evaluating variances.

Clinical pathways are commonly adopted in the United States, where, in 2003, it was reported that almost 80% of the hospitals used this tool [31]. Evidence supports the adoption of clinical pathways at the hospital level for the reduction of

Table 54.2 Processes for the adaptation of guidelines at the local level

Document	Process	Professionals' involvement	Output	Definition
Guidelines (national or international)	Adoption	Service personnel	Service protocol/ clinical pathway	A comprehensive set of rigid criteria outlining the management steps for a single clinical condition or aspects of the organization (http://www.openclinical.org/guidelines.html#gandp)
Guidelines	Adaptation	Stakeholders	Locally adapted guidelines	The local adaptation of national guidelines has been proposed as a way of increasing the benefit of local ownership while maintaining scientific validity [30]

in-hospital complications (such as infections, bleeding, and pneumonia), improved documentation, and possibly a reduction in the length of stay [40]. An experience of integrated clinical pathways in mental health has been reported in Scotland, where the National Health Service (NHS) Scotland is taking a national approach to improving the quality and safety of mental health services. The program started with the publication of national standards by NHS Quality Improvement Scotland (NHS QIS), setting out the framework for development at the local level.

The emphasis of development and implementation of the ICPs lies with local NHS boards to ensure they are developed with local ownership and to meet the needs of the local population. However, to ensure accreditation by NHS QIS, the local ICPs must incorporate the national standards and evidence improvement to the quality of care provided [17]. In Belgium, there is the European Association for the development of clinical pathways (http://www.e-p-a.org/about-epa/index.html). Among the objectives of this organization, there is the setup of an international network for pooling know-how on clinical pathways and the promotion and fostering of international cooperation between healthcare researchers, managers, and healthcare providers from European countries and the wider international community. The association has a journal that publishes research results on the development of clinical pathways.

54.2.3 Participation: A Key for Successful Implementation

Two core elements underlie all the instruments for quality improvement mentioned above (evidence-based clinical guidelines, quality standards, and clinical pathways): (i) the evidence base and (ii) stakeholders' consensus. The last three decades have been devoted to define and share a valid methodology for the identification assessment and synthesis of the available evidence. This activity successfully brought to a general understanding of the terminology and the sources of correct information. Nowadays the role of evidence to base decisions is widely recognized, and the access to good quality sources of evidence is increasingly available.

The new challenge seems to lie on the promotion of an authentic participatory implementation of evidence-based interventions.

The same pioneers of the evidence-based medicine are now exploring strategies to communicating and involving two crucial stakeholders: the decision makers and the patients (this latter category includes also family members, civil society organizations, community representatives [15]). Projects like SUPPORT, financed by the European Commission's 6th Framework Programme [32], and the most recent DECIDE [46], co-funded by the European Commission under the Seventh Framework Programme, are both aimed at supporting decision makers in the use of evidence.

SUPPORT targets policymakers as a diverse group that includes cabinet members (e.g., Ministers of Health or Finance), elected officials (e.g., chairs of legislative committees), senior civil servants (e.g., directors of primary healthcare programs), and high-level political appointees (e.g., heads of government agencies). In spite of being aware of the differences that can exist among the countries due to the different political systems, the leading project managers of SUPPORT state that what all the decision makers have in common is the authority to make or influence decisions directly. The project encompasses several tools for boosting evidence-based decision making in various settings including low- and middle-income countries and high-income countries. As the other mentioned project, DECIDE, also SUPPORT, sought strategies for the involvement of the public in evidence-based decision making [35]. In particular, DECIDE, whose target is Europe, is composed of eight work packages, three of which are devoted to identifying best strategies to communicate with specific target groups such as health professionals, policymakers and managers, and patients and public.

The two projects have similar objectives though following different approaches: DECIDE focuses on guidelines and recommendations,

while SUPPORT aims to support policy-relevant reviews and trials. DECIDE on the other hand is developing tools that will help policymakers to decide about, say, whether to pay for particular healthcare innovation in their region. Additionally, it is developing tools to make understanding the research information that forms the basis for guideline recommendations easier for a wide audience, including policymakers and the public. To some extent, DECIDE builds on the work of SUPPORT.

Even though these projects are important, quite often the exercise of knowledge translation brings to the appreciation of huge gaps in knowledge, gaps that are difficult to fill with methods for gathering consensus and taking decisions in the lack of evidence. The only possible way forward to fill those gaps is to propose new studies to find answers. These new studies should rely on mixed methods to get sound evidence from several sources and, of course, to be based on the priorities of the end-users of the answers they should provide, such as the patients [33]. In the United Kingdom, Sir Iain Chalmers, one of the founders of the Cochrane Collaboration, has undertaken a new initiative for the proactive involvement of patients in the setting of research priorities through the James Lind Alliance initiative (Petit-Zeman S FAU – Cowan and Cowan [2]). The James Lind Alliance brings together patients, carers, and clinicians to identify and prioritize the uncertainties, or "unanswered questions," about the effects of treatments, which they agree are most important, and makes the list of research questions public and available for researchers and research funders. Not always is the area of addiction represented in these initiatives. The main linkages are granted by the Cochrane Group on Drugs and Alcohol and by the European Monitoring Centre for Drugs and Drug Addiction which is working in partnership to bring the typical problems of this field in the broader perspective of knowledge translation.

Some of the characteristics of the drug addiction field can be shared by other medical conditions. For example, the behavioral component calls for research that cannot be only based on experimental studies. An important aspect of knowledge can be found in long-term observational studies, and in some cases, they require qualitative analysis which is more difficult to be systematically retrieved with the typical search strategies adopted in systematic reviews and even more difficult to be assessed for quality and included in the meta-analysis [22]. Nevertheless, there are some added values in the drug addiction field which compensate for those extra efforts. The impact of interventions on public health and security makes drug addiction an important point on every political agenda and needs to be based on the best available evidence.

54.2.3.1 Implementation Strategies

In recent years, it became clear that implementation is key to effective evidence-based interventions. Particular attention has been paid to the identification of strategies to implement interventions in specific contexts and for specific targets. The implementation of evidence-based interventions can be particularly challenging in the case of drug-related interventions for a number of reasons: (i) these interventions involve not only health but also social and policy elements; (ii) some drug-related interventions are highly controversial, as is the case with drug consumption rooms, for example, and (iii) they involve all relevant communities.

For these reasons, it is helpful to consider the lessons learnt in other fields, that is, not only in health but also in education, social work, and so on [20]. For example, Powell et al. (2015) consulted experts through a DELPHI consultation and identified 73 strategies for implementing interventions in education [4]. The list of actions and strategies proposed by the experts included:

- Obtaining funding
- Using train-the-trainer strategies
- Creating new teams
- Obtaining formal commitments
- Changing physical structure and equipment
- Developing tools and processes for the monitoring of quality
- Promoting ongoing consultation
- Using data experts
- Working with educational institutions

A prerequisite for implementation is the setting of objectives and measurable outcomes; tools such as Support and DECIDE, mentioned above, support this exercise. Another important aspect to consider is that the process of implementation can be also assessed through dimensions such as the implementation climate in an organization; the degree to which an evidence-based practice is adopted over time; the level of fidelity with which an intervention is implemented by staff; or the costs of an implementation process [4].

The deeper reflection on the importance of implementation resulted in the establishment of several initiatives and collaborations around the world. Examples include the Society for implementation research collaboration (SIRC http://societyforimplementationresearchcollaboration.org) and the European Implementation Collaborative (https://implementation.eu/). These initiatives are devoted to improve the implementation of evidence-based interventions by facilitating communication and collaboration between implementation research teams, researchers, and community providers. They hold conferences and develop tools and materials to facilitate implementation. A large number of aspects are covered in these resources, some of which are developed by other researchers and made available on institutional websites. Topics covered span from measuring the fidelity of implementation to dimensions needed for effective changes, decision-making tools, and evaluation tools.

54.2.3.2 Training Initiatives

The training of professionals is a central element for the implementation of good quality interventions. Training sessions can address behavior change as well as skills to deliver specific interventions. A recent example of training for professionals is the Universal Prevention Curriculum, which was adapted to the European context through a European-funded project (UPC-ADAPT).

Many European countries offer training programs for intervention providers. These range from specialist university programs, as it is the case in Germany and Czechia, to specific courses offered in many countries as part of the university curricula for health or social welfare degrees.

54.2.4 Examples of Frameworks for Quality Standards

Several evidence-based guidelines, issued at the international and national levels, are currently available for the treatment of drug addiction, in particular for the combined pharmacological and psychological approaches to opioid dependence. Quality standards are also becoming widely available, and combined also with training initiatives for professionals. As the majority of quality standards have been developed in the context of prevention, the first training initiatives target prevention professionals [19].

Two examples of national quality standards for drug addiction treatment in Europe can be drawn from Czechia and the United Kingdom.

In Czechia, the implementation of quality standards for the treatment of drug addiction dates back to 1995 for an initiative of the Interdepartmental National Drug Commission (now Government Council for Drug Policy Coordination). Called minimal standards, these were adopted by the Association of Non-Governmental Organizations (ANO) for Addiction Prevention and Treatment for evaluating the quality of member organizations and newly established facilities. After further elaboration occurred in the subsequent 4 years, those standards became the basis for a certification process, which recognizes that a specific service provider is in line with predefined quality standards. Since 2004, the adherence to quality standards has been assessed by specifically trained external evaluators. The current process for the certification of treatment providers was kicked off in 2005, and it included a transition period to allow the treatment provider services to start the certification process. After that period, certification became a prerequisite for applying for state grant programs. The overall aim of the certification process was the improvement of the quality of the network of services including a cost-effective

administration of public funds. With the certification process came the integration of drug addiction services into the medical and social national system.

The underlying principles are as follows: (i) voluntariness – certification is not required to provide drug services but only to apply for public funds; (ii) transparency – the evaluation process is carried out according to published criteria; and (iii) objectivity – the actual evaluation of quality is performed by an independent agency who appoints trained evaluators, and the facility providers can point out any possible conflict of interest.

The standards are at the base of the certification and accreditation process. The core activity of the certification process includes that a group of trained assessors visit the service providers to collect relevant information. Active participants in this process are the facilities requesting the certificate of quality (those wishing to apply for public funds); the certification agency (an independent institution that arranges on-site examinations, communication between the parties of the certification processes, and training of certificators); the certification team carrying out on-site examinations (composed by at least three trained certificators); the Certification Board of the Government Council for Drug Policy Coordination (deciding about certification request results and validity of certification ranging from 1 to 4 years); and the Executive Board of the Government Council for Drug Policy Coordination – to which the facilities can address their complaints about, for example, the composition of the certification team. Before the certification can start, the agency and the requesting facility have to agree on the date and the composition of the team of assessors. Subsequently, several previously identified employees and clients are interviewed with semi-structured questionnaires. The on-site examination, in general, lasts 1 day, at the end of which the team of assessors drafts a report with a proposal for certification or suggestions for improvement. The report is shared with the interested facility, which is allowed to comment in writing.

The report is therefore completed and forwarded by the certification agency to the Certification Board of the Government Council for Drug Policy for the final decision.

Overall the process takes around 2 months, and the facilities requesting certification have 15 days to contest the results.

In the United Kingdom, the National Institute for Clinical Excellence (NICE) publishes evidence-based clinical guidelines for many different medical disciplines including drug addiction. Sets of quality standards are derived from the best available evidence such as NICE guidance and other evidence sources accredited. They are developed in collaboration with NHS and social care professionals, their partners, and service users. The standards consider issues like evidence of effectiveness and cost-effectiveness, people's experience, safety, equality, and cost impact. The quality standards are considered central to supporting the government's vision for an NHS and social care system focused on delivering the best possible outcomes for people who use services [37]. This act clarifies that the Secretary of State "must have regard to the quality standards prepared by NICE." The care system should consider those standards in planning and delivering services to secure continuous improvement in quality. NICE quality standards do not provide service specifications but rather define priority areas for quality improvement. Nevertheless, those standards are the basis to ensure that the providers of health and adult social care in England meet the standards of quality and safety required by the Care Quality Commission.

The standards developed by NICE are typically composed of a general statement complemented by a measure. These quality measures are drafted only after the quality statement wording has been agreed and addresses the structure of care or services, process of care or service provision, and, if appropriate, outcome of care or service provision. The majority of measures refer to process and are expressed as a numerator and denominator to define a proportion, in which the numerator is a subset of the denominator popula-

tion. For example, for the standard "People who inject drugs have access to needle and syringe programmes in accordance with NICE guidance," there is a measure at the structure level, which is "Evidence of local arrangements to ensure people who inject drugs have access to needle and syringe programmes in accordance with NICE guidance," complemented by a measure of outcome: (i) proportion of people who inject drugs who access needle and syringe programs, wherein the numerator is the number of people who access needle and syringe programs and the denominator is the estimated prevalence of injecting drug users and (ii) incidence of blood-borne viruses among people who inject drugs.

To clarify the implications of the standard, a breakdown of meanings of the standard for each stakeholder is included: service providers ensure systems are in place for people who inject drugs to have access to needle and syringe programs in accordance with NICE guidance; needle and syringe program staff ensure people who inject drugs have access to needle and syringe programs in accordance with NICE guidance; commissioners ensure they commission services for people who inject drugs to have access to needle and syringe programs in accordance with NICE guidance; and people who inject drugs have access to needle and syringe programs that are nearby, have suitable opening hours, and provide injecting equipment and advice on reducing the risk of harm. The standards include also that the sources of data be considered in the measurement. Furthermore, at NICE, there is an implementation team to support key audiences and organizations to maximize the uptake of guidance and quality standards. The team assesses the aids and barriers to implementation and provides practical support tools for commissioning, service improvement and audit, education, and learning. The team prepares reports on the uptake of guidance that are used to inform the development of the quality standard. The implementation team collaborates with national bodies and local organizations, through local implementation consultants, to support the use of quality standards and to facilitate shared learning. Overall, the process to produce standards at the National Institute for Clinical Excellence lasts indicatively for 42 weeks.

These two examples suggest the possibility of different approaches to the use of quality standards. In the Czech experience, the development of the standards represents an initial effort, whereas the actual focus seems to lie on the certification and accreditation process including several levels of training and a "learning by experience" process. Furthermore, the entire experience initiated around 20 years ago has been conceived and developed specifically in the treatment of drug addiction.

On the other hand, the National Institute for Clinical Evidence has created, along with the Department of Health and other key partners, a core library of topics for quality standard development in health-related topics, among which alcohol dependence and drug use were included. In this case, the focus seems to be on the development itself of the standards which *translate the evidence-based guidelines* into general statements and measures of outcomes at the system level including the indication of the sources of data to be used for the assessment of the implementation. Furthermore, NICE offers the support of an implementation team to enhance local adoption initiatives.

54.3 Conclusion

Quality of intervention is entrenched to the evidence base, and in the last 20 years, important progress has been made in the availability of good quality systematic reviews of effectiveness in the field of drug addiction treatment. Nevertheless, important gaps in knowledge still exist and need to be addressed by further investment in research. To ensure that research answers concrete problems arising from the daily experience of those affected by the drug problems at several levels, it is crucial that the end-users of research results – such as practitioners, patients, and decision makers – are involved in the selection of priority for investigation.

Currently, the attention seems to be focused on how to better communicate evidence to policymakers, patients, and the general public. The achievement and maintenance of quality in the treatment of drug addiction need the participation of all the stakeholders. The agencies providing data to assess the current situation and set the future goals, the decision-makers at the system level, and those managing the local, regional, and national services, have to collaborate with the practitioners to offer the best possible treatment to the drug users. The drug users, the families, and the public have to proactively be involved in any decision and should be able to speak out their needs and problems.

The tools to translate evidence into the quality of treatment have to be understandable by all the relevant stakeholders to empower them in a reiterative process of testing and learning lessons.

Quality is a continuous process where each new achievement has to be seen as a step toward new goals.

Glossary

Accreditation is the process by which an institution delivering a service is independently assessed for quality against some predefined criteria. Accreditation requires a set of minimum standards, which are set by the accrediting body.

Benchmarking is the process of comparing service processes and performance metrics to best practices from other services. Dimensions typically measured are quality, time, and cost.

Clinical pathways are structured, multidisciplinary plans of care designed to support the implementation of clinical guidelines and protocols.

Guidance is a general term that covers documents such as guidelines and quality standards.

Guidelines are "statements that include recommendations intended to optimise patient care that is informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (Institute of Medicine 2011). They are designed to assist carers' and clients' decisions about appropriate interventions in specific circumstances.

Protocols in general, are documents that specify the procedures to follow to perform some tasks, typically those used to conduct a study or to implement some guidelines at the individual service level.

Standards and quality standards are principles and sets of rules based on evidence [6], which are used to implement the interventions recommended in guidelines. They can refer to content issues, processes, or structural (formal) aspects of quality assurance, such as environment and staffing composition. In some cases, standards are legally binding.

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The United Nations Drug Conventions: Evidence on Effects and Impact

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Robin Room

Contents

Abstract

The three international drug treaties cover many psychoactive substances ("drugs"), although not tobacco (now under a separate treaty) or alcohol. They include a penal regime to enforce the limitation of use to medical or scientific purposes, a trade regime concerning drugs for medical use, and a planning scheme to ensure adequate supplies of medical opiates. The system, initiated in 1912, had shifted its main focus by the time of the 1988 treaty to combating the illicit markets, which accompany a prohibitory system. The place of the drug treaties in the United Nations system and the bodies which make up the system are briefly characterised. Nearly every country has signed each treaty, though often with reservations. The option this opens up of denouncing and re-acceding with reservations has also been successfully used by Bolivia concerning coca leaves. The system has assured access to pain medication in most high-income countries, but not in much of the world, where the system's emphasis on law enforcement has often indirectly but effectively cut off supplies. In terms of controlling legal medical markets, the system has had mixed success. But the

R. Room (✉)
Centre for Alcohol Policy Research, La Trobe University, Bundoora, VIC, Australia

Centre for Social Research on Alcohol & Drugs, Department of Public Health Sciences, Stockholm University, Stockholm, Sweden
e-mail: r.room@latrobe.edu.au

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system has mostly failed in cutting off the illicit drug trade. In a system that has been committed to a prohibitory approach, there are recent signs of change, particularly in the Americas; the legalisation of cannabis in Canada and much of the USA poses a new challenge to the status quo in the international system.

Keywords

Drug treaties · Cannabis · Opioids
Medication supply · Legalisation
Prohibition effects

55.1 Introduction

The United Nations drug control system is organised around three international treaties: the Single Convention on Narcotic Drugs of 1961, as amended by a Protocol of 1972; the Convention on Psychotropic Substances of 1971; and the UN Convention against Trafficking in Narcotic Drugs and Psychotropic Substances of 1988. Their texts, and the official commentaries on them, are conveniently available online: https://www.unodc.org/unodc/treaties/index.html

The treaties, of course, do not cover the whole range of psychoactive substances. There is a separate treaty on tobacco, the Framework Convention on Tobacco Control of 2003, negotiated under the auspices of the World Health Organization (WHO), and an International Convention against Doping in Sport (many of the substances covered by it are psychoactive), which was adopted in 2005 under the auspices of UNESCO. Notably absent from the list of substances under international control is alcohol, although it was actually the subject of the first international drug treaty, controlling "trade spirits" in colonial Africa, negotiated in 1889 but now in abeyance [8]. The 2012 WHO Expert Committee on Drug Dependence briefly discussed whether alcohol would qualify for listing under the UN drug conventions, but though this was referred for consideration at a future Expert Committee meeting [30:16], as of 2019 this has not occurred.

From the perspective of the inherent harmfulness of different psychoactive substances (e.g. [19]), what is included and excluded in the three "drug treaties" is not easily defensible, except as reflecting the vagaries of history. But despite the ongoing convergence in scientific thinking about psychoactive substances [10], it is still true that discussions of international drug control which take account of the whole range of drugs and their regulation are rare (for an exception, see [7]).

In this chapter, however, attention remains focused on the three UN drug treaties. We consider the intended functions of the treaties, the institutional arrangements for their implementation, and what evidence is available on effects and impact of the system. A brief discussion of potential future developments is also included.

55.2 Intended Functions of the Treaties

The treaties have three main functions: as a penal regime to enforce limitation of use of scheduled substances to medical or scientific purposes; as a specialised trade treaty, controlling international trade in psychoactive substances for medical use; and as a central planning scheme to ensure adequate supplies, particularly of opiates for medical use.

55.2.1 A Penal Regime to Enforce Drug Prohibition

The Single Convention, as its name conveys, replaced an array of treaties and protocols, which had accumulated since the first opium treaty, the Hague Convention of 1912. But the Single Convention went well beyond what was in the previous treaties, signalling a change in the system's orientation [9]. Whereas the prime concern of the previous treaties had been with regulating international trade in plant-derived drugs (opiates, cocaine and cannabis), the 1961 Convention introduced requirements that possession and

delivery, along with a wide variety of market-related actions concerning the drugs covered, be criminalised under a country's domestic laws [4]. What had been a system concerned primarily with controlling international movement of drugs became a system committed to enforcing prohibitions on nonmedical use of the drugs, with each country's criminal laws as means of enforcement. The international prohibition system, as it now exists, can thus be said to have begun with the 1961 treaty.

The 1971 treaty greatly expanded the scope of the system by including a wide range of synthetic substances, many of them with pharmaceutical uses. The market controls in the 1971 treaty are weaker than those in the 1961 treaty, reflecting the powerful influence of the pharmaceutical industry on the treaty negotiations [18]. The requirement concerning criminalisation under domestic law is more simply stated than in the 1961 treaty, requiring penalisation of "any action contrary to a law or regulation adopted in pursuance of its obligations under this Convention". Since the Convention requires a medical prescription to authorise use of a covered drug, any possession or use without a prescription should thus be criminalised.

The 1988 treaty, as its name reveals, represented a further shift in the system's focus, with more attention focused on combatting the illicit markets which had emerged as a by-product of the prohibition system, including, for the first time, controls on precursor chemicals used in the preparation of controlled drugs. But, in an effort to eliminate any remaining ambiguity, it also included a further provision on criminalisation at the level of the individual drug user: that a signatory country should "establish as a criminal offence under its domestic law, when committed intentionally, the possession, purchase or cultivation of narcotic drugs or psychotropic substances for personal consumption".

The system of treaties inaugurated by the 1961 Convention, then, has as a main goal the elimination or at least suppression of any nonmedical use of drugs, aiming to eliminate illicit markets in drugs by a five-pronged approach: (1) particularly for drugs covered by the 1961 treaty, by restriction of the supply of the drugs, limiting production to the estimated medical need for the drugs; (2) by a system of export and import permits, restricting legitimate trade in the drugs in accordance with a receiving country's wishes; (3) by requiring that most substances covered by the treaties be in a prescription system, as a way of confining availability to medical control and use; (4) by criminalising production, sale, and other market activities outside those permitted for drugs for medical use; and (5) by criminalising users for purchase or possession of drugs other than for medical purposes.

55.2.2 A Trading and Marketing Control Regime

The treaties also set up a trading and marketing regime, a special kind of trade treaty which aims more to structure and direct international trade, rather than the more usual main aim of trade treaties – to facilitate trade. Requiring that an import permit be issued by the receiving country before drugs can be shipped to it means that a country can control and indeed cut off the legal supply of a drug to its residents.

Although the drug treaty system was established before the formation of the current system of international trade treaties, it has served an informal function of protecting the substances under its jurisdiction from any trade disputes seeking to open up markets for controlled drugs. This contrasts with the situation for alcohol and tobacco [3, 21, 26].

55.2.3 A Central Planning Scheme to Supply Medical Needs

Particularly through the 1961 treaty and its predecessors, and particularly for opiates, the international system is intended to ensure that supplies of opium-derived drugs for medical use are available globally. Each signatory country is supposed to send to the International Narcotics Control Board (INCB) annual data on medical use of opioids and estimates of requirements for the next

year. There is a system of permits for countries to grow opium to meet the demands of the medicinal market (in the mid-2010s, around half the legal supply was grown in Tasmania – [14]). Particularly with respect to opium, the aim is to create a globally controlled system of cultivation, manufacture, and supply, which will ensure that medical needs, everywhere, for opioid medications are met.

55.3 Institutional Arrangements for Implementation of the Treaties

In the United Nations system, the drug treaties come under the jurisdiction of the UN's Economic and Social Council (ECOSOC), which serves as the final deciding body for issues, such as the scheduling of drugs under the treaties, and determines whether a conference should be called to consider amendments to the treaties. The political body governing the drug system is the Commission on Narcotic Drugs (CND), with 53 member states elected by ECOSOC, but with proceedings open to attendance by other UN member states. The CND meets annually for several days in March in Vienna, in proceedings including plenary sessions, a Committee of the Whole for the discussion of proposed resolutions, and committee meetings. Each year, the CND adopts resolutions following discussions which are often lengthy, since its decisions are customarily made by consensus.

The administrative body for the system is the UN Office on Drugs and Crime (UNODC), which has responsibility also for the two UN crime treaties (on transnational organised crime and against corruption). UNODC has a limited "regular budget" as part of the UN system, and relies, for 90% of its funding, on "voluntary contributions", mainly from governments. Since these contributions are usually earmarked for specific projects, donor countries have a large say in determining the directions of the UNODC's work. In 2012, UNODC had about 500 employees, spread around the world – a smaller number than the US Drug Enforcement Agency had posted outside the USA [25].

The International Narcotics Control Board (INCB) is a board consisting of 13 individual members elected by ECOSOC, 3 of them from a list of 5 nominated by the World Health Organization. They are supposed to serve as independent experts, not as representatives of any state; a unit within the UNODC serves as the INCB's secretariat. In addition to technical duties such as running the international market for opiate medications, the INCB has regarded itself as the "guardian of the treaties", issuing an annual detailed global report on the state of compliance as the INCB defines it [5].

The World Health Organization also has responsibilities, under the 1961 and 1971 treaties, for providing scientific and medical expertise, particularly concerning the classification and scheduling of psychoactive substances under the Conventions. According to the 1971 Convention, its assessments "shall be determinative as to medical and scientific matters". These responsibilities are primarily assigned to the Expert Committee on Drug Dependence, which is supposed to be constituted every 2 years for a process involving first pre-review and then 2 years later a detailed review concerning classification of particular substances. However, the meetings were less frequent in the decade of the 2000s, due to WHO's limited resources, but have become annual since 2014, with two meetings in 2018. Recognising that the present scheduling of many substances had not been re-examined in the light of scientific and other developments for many years, an Expert Committee meeting proposed that each scheduled substance be re-reviewed every 20 years; the first ECDD review ever on cannabis was conducted in late 2018 [17], recommending that cannabis be rescheduled under the treaties to legitimate medical use. The ECDD is also charged with tackling classification of the diverse category of new psychoactive substances, of which 750 have been reported to the system since 2009. Despite the increased frequency of meetings, resources remain inadequate for the tasks the ECDD system is assigned. An ECDD meeting has also pointed out that the language of the Conventions does not map easily onto current scientific language concerning drugs [30:16, 23–35].

Over a number of years, the drug treaty system and the WHO drifted apart. A signal of this has been the divergence between the CND and WHO's Expert Committee on scheduling of specific substances [1:213–214, 2:232]. Another signal of the division had been over the place of harm reduction in the treatment of drug problems. In public health in general, the reduction of harm is a central commitment and strategy, and as the global public health agency, WHO was necessarily committed to its promotion. However, prior to 2009 the USA had insisted that the concept and term "harm reduction" not be used in the work of the international treaty agencies. After 2009, relationships between UNODC and WHO improved again, including joint work on treatment guidelines [25]. But in general, the UNDCP has operated in substantial isolation from other UN bodies [2:237].

55.4 What Can Be Said About the Effects and Impact of the System?

One measure of the success of the system is its near-universality, in terms of formal adherence to the treaties. Each year's INCB report notes with some pride the tally of countries which are signed up to each treaty. The desire for universality triumphed in the case of Bolivia's denunciation and reaccession to the 1961 treaty, despite disapproval by the INCB and other guardians of the system. Bolivia took this route to add a reservation to the treaty, which would then allow Bolivians to chew coca leaves without contravening Bolivia's treaty commitments. Thwarted in an attempt to make this change by international consensus, Bolivia denounced (announced its withdrawal from) the treaty, proposing to reaccede with a reservation concerning coca-chewing if the reservation was accepted [23]. If one-third of countries acceding to the treaty had objected, Bolivia's reaccession would not have gone into effect. It is a mark of the system's commitment to universality that there were only a few objections, despite considerable displeasure expressed by the INCB and others about Bolivia's reservation.

A second measure is in terms of its success in ensuring access to pain medication. For developed countries, this is not generally a problem. But the WHO has estimated that 80% of the world's population lacks adequate access to effective pain medication [29]. Part of the problem, of course, is a lack of resources to procure or supply the medication. But another part is the indirect result of the treaty system. In consequence of the system's emphasis on law enforcement, decisions on importation of controlled drugs are often in the hands of police, who may choose to restrict or stop imports in order to impede diversion of the medicine to illicit markets. Reflecting concern about this, the WHO Expert Committee decided that ketamine, a cheap and relatively safe anaesthetic widely used in poor countries, should not be brought under the treaties. "Concerns were raised that if ketamine were placed under international control, this would adversely impact its availability and accessibility. This in turn would limit access to essential and emergency surgery, which would constitute a public-health crisis in countries where no affordable alternative anaesthetic is available. On this basis, the Expert Committee decided that bringing ketamine under international control is not appropriate" [30:9]. Reflecting a greater priority still being placed on the prohibition of nonmedical use than on the availability of needed medications, many national delegations and three regional groupings expressed concerns or regret about the WHO's decision at the May 2013 meeting of the CND [13:11], and China pressed again on this issue for two further years [2:232].

A third measure is in terms of success in controlling legal markets. Here the system can show some success, among mixed results. The pre-Single Convention system succeeded (aided by the Depression) in substantially reducing world consumption of opium in the years prior to World War II. The current system, however, has not impeded the substantial rise, in recent years, in prescribed use of opioids in North America, which accounts for the lion's share of global use of prescribed opioids. In general, the conclusion of Bruun et al. [8] remains true: the system's suc-

cesses tend to occur where "it has been the conduct of professions and private enterprise which has been influenced". Large firms and state-licensed professionals have something to gain from cooperation with a control system, and with such levers of influence drug control systems have had some successes, for instance, in getting chemical industries to control chemical precursors, and in changing doctors' prescribing patterns when drugs, such as the barbiturates, prove to be more dangerous than was thought. Nevertheless, the sharp rise in opioid use and deaths in the early twenty-first century, particularly in North America [11, 12], was to a substantial degree fuelled by prescribed medications; pharmaceutical firms and professionals involved were not sufficiently persuaded or deterred from profit-seeking by the control system. The lack of any trade disputes about drugs under the system's control, in an era when free-market ideology has been dominant, might also be regarded as an unheralded success for the system.

A fourth measure, of course, is the system's degree of success in eliminating or at least reducing illicit trade, markets, and use. Here the overall result must be viewed as a failure. In 1998, the UN system set a 10-year goal of "eliminating or significantly reducing the illicit cultivation of coca bush, the cannabis plant, and the opium poppy by the year 2008". The UNODC's 2014 Annual Report concluded "that overall the global situation … is generally stable" [27]. Twenty years after it was set, the goal of reducing illicit markets remained a vain hope.

55.5 Signs and Directions of Change

The failure of the international drug prohibition system in terms of its most public goal, of eliminating or minimising illicit markets, has been apparent for some decades. At national and subnational levels, there have been initiatives and experiments since the 1960s in moving in other directions, although these initiatives have been greatly hampered by the perceived necessity of operating within the constraints of the international system. Thus even the Dutch "coffee shop" system for quasi-legal retail sale of cannabis, the most far-reaching attempt prior to 2010 to move from an illicit to a regulated market, was handicapped by the "back door" problem – that cannabis which was sold under license at the front door had come in the back door illegally, since no way could be found to reconcile a legal wholesale supply with national obligations under the treaty [16].

But there have been signs of change in the 2010s, particularly in the Americas. A diverse array of Latin American countries have shown a growing impatience with the status quo and have been willing to push against the longstanding "Washington consensus" for the status quo on drug policies. First, several retired Latin American presidents, and then some sitting presidents, have expressed the need for new directions. The motivations have been diverse. In Mexico and Central America, the primary issue has been the carnage in their populations from a "war on drugs" aimed at cutting off the supply to the insatiable demand from northern neighbours. In Bolivia, as mentioned, legalisation of the folk custom of coca-leaf chewing has been a main concern. In countries like Uruguay, efforts to create a regulated legal cannabis market are aimed primarily at removing a main source of criminalisation of young people. With a report from the Organization of American States (OAS) exploring alternative scenarios for the future [20], these impulses at national levels took on a collective form in the region's intergovernmental agency.

At least as important have been the changes in North America, particularly concerning cannabis. In November 2012, votes on popular initiatives for regulated cannabis markets in Colorado and Washington began concrete processes of change likely to have lasting effects, no matter how the US federal government may position itself. At about the same time, trends in opinion polls among US adults for the first time showed a popular majority for legalising cannabis [28]. By the end of 2018, 9 US states had legalised commercial sales of cannabis for recreational use and 14 more had decriminalised possession [31]. Cannabis became legal throughout Canada on 17 October 2018, sold in some provinces in government stores [6]. Changes in the legal status of

cannabis do not, of course, deal with the drug problem as a whole. But, since three-quarters of the illicit drug users in the world use only cannabis, in numeric terms, such changes in the status of cannabis will have a large effect.

The direction and extent of any changes in the international drug treaties and control system are still unclear. The OAS report lays out some alternative scenarios for the future. Other recent reports have laid out options for change in the treaties and have discussed more and less likely scenarios [24], including a potential Framework Convention on Cannabis, which might supersede the handling of cannabis in the Single Convention [22]. But, at least in the short run, it is more likely that changes will be piecemeal and country-specific, rather than at the system level – whether involving changes made within the rules of the system, as in the case of Bolivia, or beyond the rules, as with cannabis buyers' clubs in Spain and other parts of Europe [15] and with the North American shifts on cannabis.

Key Points

- The international drug control system is nearly universal, but somewhat ossified and resistant to change.
- It classifies psychoactive drugs in terms of their potency and potential harm but provides for potential medical use of most controlled drugs. It does not deal with some drugs in wide use in Western societies, notably alcohol.
- It has not succeeded in its goal of eliminating illicit supply of drugs for nonmedical use. It succeeds in ensuring supplies for medical use in wealthy countries, but not in much of the world, where actions against the illicit market also cut off medical supplies. Particularly in North America, there has been an oversupply and overuse of medicinal opioids.
- The system's prohibition of nonmedicinal cannabis and restrictions on medicinal cannabis are under siege and increasingly ignored at national and subnational levels. The system has also been overwhelmed by the large number of "new psychoactive substances" for potential control. But there is, as yet, little appetite within the system for reform.

Clinical Relevance

In considering both patient drug use patterns and whether and what psychoactive medications to prescribe, a clinician needs to take into account the legal status of a substance. However, in terms of the drug's actions and utility, the clinician should look beyond the legal divisions between medications, illicit drugs, and legal substances like nicotine and alcohol.

There has been substantial overpromotion, in affluent societies, of psychoactive medications, particularly medicinal opioids, and clinicians need to exercise care in their prescription.

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56 Ethical and Legal Aspects of Interventions in Addiction Treatment

Ambros Uchtenhagen

Contents

Abstract

The United Nations (UN) conventions present the international legal framework; they urge member states to provide treatment and rehabilitation but prohibit consumption and possession of scheduled drugs. This creates problems for providing treatment and harm reduction programs to patients who are not or not yet ready to stop illicit drug use. Other international documents, notably from the World Health Organization and the United Nations Office on Drugs and Crime, are strongly in favor of agonist substitution treatment and harm reduction measures. Within this framework, national legislation has much room for diverse preferences; the International Narcotic Control Board regularly comments the national practices, as well as the European Monitoring Centre for Drugs and Drug Addiction for the EU member states. An international trend gradually prefers therapeutic measures over criminal sanctions for drug users.

The international ethical framework is set by the universal declaration and European convention on human rights, striking a balance between individual rights and societal interests. Less ambiguous guidance comes from medical ethics claiming the full range of patient's rights for addicted persons.

Note: Some of the material is based on earlier work of the author about ethical aspects of treatment and care in addiction [50–53].

A. Uchtenhagen (✉)
Swiss Research Foundation for Public Health and Addiction, Zurich University, Zurich, Switzerland
e-mail: ambros.uchtenhagen@isgf.uzh.ch

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The respective conduct codes for medical professions are regional or national and include procedures how to deal with ethical conflicts. Conflicting situations frequently occur, for example, around the principles of autonomy or of confidentiality.

An essential ethical element of treatment is its effectiveness and avoidance of harm, asking for scientific evaluation of therapeutic approaches, services, and systems. The ethical acceptability of agonist substitution treatment and of harm reduction measures is based on rigorous evidence of their effectiveness. Other aspects concern the limits of social acceptability of addictive behavior and the limits of what can be attained for an individual patient by therapeutic interventions; avoidance of harm often is the more immediate objective than full recovery. In a public health perspective, effects at population level rather than at individual level are a priority, aiming at good coverage of treatment needs by good accessibility and affordability of services.

56.1 Introduction

Addiction treatment is historically, and until present, guided by the basic understanding of addictive behavior. Interventions are shaped accordingly to prevailing paradigms explaining substance use and substance dependence. Legislation is a preferred instrument to limit consumption and addictive behavior, through preventive interventions as well as sanctions. The development of liberal societies caring for individual freedom and responsibility, less interference with lifestyles and personal choices, and the need for ethical standards in human behavior came to the forefront and resulted in various rules guiding interventions and therapist's conduct. This process in the area of addiction treatment has been taken at hand, but with persisting differences in orientation and a need for conflict management.

56.2 International Frameworks and National Diversities

56.2.1 Legal Aspects

56.2.1.1 The International Framework: The United Nations Conventions

The UN conventions of 1961, 1971, and 1988 have some implications for delivering addiction treatment.

The Single Convention urges "to take all practicable measures for the prevention of abuse of drugs and for the early identification, treatment, education, after-care, rehabilitation, and social reintegration of the persons involved." While this Article 38 does not indicate how treatment should be delivered, Resolution II declares that "one of the most effective methods of treatment for addiction is treatment in a hospital institution having a drug free atmosphere," and urges the provision of such facilities [56].

The Convention on Psychotropic Substances of 1971 [57] restricts the "use and possession of, substances in Schedules II, III and IV to medical and scientific purposes," thereby criminalizing patients in treatment who continue, sporadically or regularly, to use illicit drugs (schedules II, III, and IV include drugs such as barbiturates, benzodiazepines, and buprenorphine). Art. 7 states, for schedule I drugs, to "prohibit all use except for scientific and very limited medical purposes by duly authorized persons." What the limitations are is open to interpretation. Art. 9 requires "that substances in Schedules II, III and IV be supplied or dispensed for use by individuals pursuant to medical prescription only, except when individuals may lawfully obtain, use, dispense or administer such substances in the duly authorized exercise of therapeutic or scientific functions." Licensed pharmacists, however, may "supply, at their discretion and without prescription, for use for medical purposes by individuals in exceptional cases, small quantities, within limits to be defined by the Parties, of substances

in Schedules III and IV." Art. 20 urges to "take all practicable measures for the prevention of abuse of psychotropic substances and for the early identification, treatment, education, aftercare, rehabilitation and social reintegration of the persons involved." Also, treatment may be provided either as an alternative to conviction or punishment or, in addition to punishment, if abusers of psychotropic substances have committed such offences (Art. 22).

According to the 1988 Convention [58], preparatory acts for personal use of scheduled substances are criminal offences (Art. 3,2):

> Subject to its constitutional principles and the basic concepts of its legal system, each Party shall adopt such measures as may be necessary to establish as a criminal offence under its domestic law, when committed intentionally, the possession, purchase or cultivation of narcotic drugs or psychotropic substances for personal consumption contrary to the provisions of the 1961 Convention, the 1961 Convention as amended or the 1971 Convention.

Implicitly, this includes criminalization of use (no use without preparatory acts). The International Narcotic Control Board (INCB) was set up in 1968, with the main task to control and facilitate the implementation of the Single Convention at national level. The following conventions have revised and restated the functions of the Board.

In summary, the UN conventions urge the treatment and rehabilitation of drug abusers but prohibit the consumption of narcotics and psychotropic substances (including tranquilizers and sedatives), which creates problems for patients in treatment (continued use is often a reason to exclude patients from treatment) and even more problems for harm reduction approaches designed to diminish the medical risks of substance use (for persons in addiction treatment and outside of treatment). Agonist maintenance treatment is viewed critically by INCB as a potential source of diversion of narcotics to the illegal market [29]. However, the conventions allow diversion to treatment as an alternative to punishment.

56.2.1.2 Other International Frameworks

Some international documents are mentioned here with relevance to addiction treatment and specifically in regard to agonist maintenance treatment and harm reduction interventions. These evidence-based documents present strong recommendations which are not legally binding.

The World Health Organization (WHO) and the United Nations Office on Crime and Drugs (UNODC) published Principles of Drug Dependence Treatment in 2008. This chapter is in strong support of agonist maintenance treatment for opioid dependence: "Opioid agonist pharmacotherapy is one of the most effective treatment options for opioid dependence when methadone or buprenorphine are administered at an individualized dosage for a period of several months to years." The chapter also urges to implement legal frameworks, which guarantee protection from potential sanctions for those seeking treatment [69].

The UNODC, WHO, and United Nations Programme on HIV/AIDS (UNAIDS) "Technical Guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users," published in 2009, has a range of preventive measures (e.g., needle and syringe exchange programs) among its recommendations, thereby complementing the treatment recommendations [59].

In Europe, the EU Action Plan 2005–2008 [16] foresaw harm reduction measures as a specific action for the implementation of Objective 14 (prevention of health risks related to drug use) and Objective 15 (availability and access to harm reduction services). The implementation process and the available evidence on outcomes are presented in a monograph [41].

56.2.1.3 Diversity of National Legislation

At the national level, narcotic laws and policy guidelines mirror a diversity of principles, priorities, and preferences, even when countries have ratified the UN conventions. Treatment of

substance abuse is one of the essential elements, but how it is defined, for whom it is available, under which circumstances, and which approaches are officially accepted are all subject to major differences. One example is the national guidelines for substitution treatments of opiate dependence; an analysis of 28 national guidelines found a large variety of indication criteria and practices [53].

At present, the diversity of legislations and regulations is best documented in regard to Cannabis. The alternatives to prohibition, in the sense of the UN conventions, range from decriminalization of use and preparatory acts for personal use to a replacement of illicit markets by tolerated controlled markets without legalization, to partial or full legalization in analogy to alcohol and tobacco. *Decriminalization* means or preferring administrative instead of criminal sanctions, or no sanctions within age limits and allowed quantities. A *tolerated controlled market* is based on issuing licenses for production, marketing, and sale of cannabis products under specified conditions. Compliance with the conditions is controlled and licenses are withdrawn in case of non-compliance. License holders pay taxes for their profits. *Legalization* may be restricted for defined target groups (e.g., residents only, medical cannabis prescribed to patients suffering from specified conditions, adult members of cannabis social clubs). Legal availability of cannabis may be restricted with age limits, quantities allowed per time period, and Tetrahydrocannabinol (THC) content in order to prevent negative effects of use. Maximum prices apply in certain jurisdictions, in order to avoid a competitive illegal market with lower prices (overview in Uchtenhagen 2016).

An official source of information on problems with the implementation of the UN conventions is presented in the annual reports of the International Narcotic Control Board (INCB). The 2011 report includes, for example, information on unacceptable treatment problems, such as diversion of prescribed pain medications or allowing safe injection rooms ([29], p. 38). The setting up of the lack of aftercare is admonished (p. 59). On the other hand, large compulsory treatment centers are mentioned (p. 78), as well as detoxification, rehabilitation, and counseling services (p. 83); opiate substitution treatment (p. 51, 78); and needle/syringe exchange programs (p. 51), without indicating their acceptability and outcomes.

The 2018 report provides, in Chap. 1, recent developments in the use and regulation of the medical use of Cannabinoids and Cannabis, as well as recent changes in national legislation in regard of non-medical cannabis use (legalizing production, sale, possession, and consumption). Concerns are expressed about diversion of medical cannabis for non-medical use, weakening public awareness of risks resulting in facilitating legalization of non-medical cannabis. Chap. 2 provides information about the compliance with the treaties by national authorities in member states. Chap. 3 gives a detailed overview on the worldwide situation in the production and use of scheduled drugs worldwide, followed by Chap. 4 with recommendations (not legally binding) to governments and involved organizations.

A complete and updated collection of national drug laws and drug policies is presented by the European Monitoring Centre on Drugs and Drug Abuse (EMCDDA); it includes not only the EU member states but also acceding and candidate countries as well as neighboring and Central Asian countries [15]. The same source provides systematic information on treatment approaches and harm reduction approaches in these countries.

56.2.1.4 Sanctions

Use and possession of illegal drugs for personal use are prohibited in a range of countries. For Europe, an analysis of national practices is presented [14]. Only rarely, prison sentences are handed out in case of infraction. In other regions, imprisonment and compulsory treatment are more common, for example, in labor camps [67].

In some countries, drug possession is an offence, which may entail imprisonment or even capital punishment. A systematic overview is not available. In Islamic law, use of any drugs including alcohol is prohibited and sanctioned, but it also provides care for those suffering from medical conditions.

A high-level organization, the Global Commission for Drug Policy, strongly recommends to avoid criminal sanctions for the use of all scheduled drugs and the stigmatization of all substance users [21].

Agonist maintenance therapy is prohibited in Russia [37], while a growing number of countries support and expand this approach, replacing criminal sanctions.

56.2.2 Ethical Aspects

56.2.2.1 Ethical Basis of Interventions: Human Rights

The Universal Declaration of Human Rights [54] contains a number of relevant conditions, such as no discrimination (Art. 2), no degrading or inhuman treatment (Art. 5), and right of equal access to medical care and social services (Art. 25/1), but also that everyone has duties to the community (Art. 29/1) and that limitations of rights and freedom are admissible on the basis of "just requirements of morality, public order and the general welfare" (Art. 29/2).

In view of conflicts this may create, a recent initiative proposes the formulation of meta-rules, providing guidance on how to resolve conflicts in human rights [4].

The European Convention on Human Rights [7] further stipulates that a person's liberty may be deprived in case of lawful detention of alcoholics or drug addicts (Art. 5/1/e), with a right to appeal to a court (Art. 5/4).

In summary, these statements try to establish a balance between protecting the individual rights of the person and respecting the needs of society for public order, general welfare, and even morality. There is large room for interpretation, so that every society can decide on the compatibility of addictive behavior with the nature and extent of the above-mentioned requirements. Compulsory measures against persons with substance dependence may be admissible on the basis of national laws.

A step further is made in the EU, where the Commission has issued guidelines on the regulation of patient rights. A growing number of member states have adopted laws or regulations, granting patients the right to self-determination (no interventions without informed consent) and confidentiality [17]. Only exceptionally, involuntary interventions are allowed, for example in cases of criminal behavior or deficient power of judgment. This creates a new ethical dilemma in case of serious destructive behavior as a symptom of the patient's condition. It is argued that treating physicians in such a case have a responsibility to protect the patient from the negative consequences of behavior, even through involuntary intervention.

Again a new situation has been created with the UN Convention on the Rights of disabled persons (CRPD), in force since May 2008, ratified by 177 member states [55]. This convention grants all human rights to persons with any kind of disability, including psychiatric conditions and therefore also with substance use disorders. Some of the specific rights cover the freedom of accommodation, of mobility, of social participation, not easy to be reconciled with addictive behaviors. All signatories are obliged to send annually a report to the Secretary General on how these rights are implemented at the national level.

56.2.2.2 Ethical Basis of Interventions: Medical Ethics

Medical ethics apply only if and inasmuch as substance dependence is understood as a medical condition. This has been the official position of the leading medical organizations since decades (and brain research has identified it as a "brain disease," thereby giving it a biological basis) [33]. The substance-dependent person is a patient and should enjoy the status and all the rights of patients.

The current medical science defines substance dependence as a condition with diagnostic criteria, described in the generally acknowledged diagnostic systems, such as International Classification of Diseases ICD-10 of World Health Organization [68] and Diagnostic-Statistical Manual of Mental Disorders DSM-IV TR of the American Psychiatric Association [2]. The criteria include biological

symptoms (tolerance, withdrawal symptoms in case of discontinued use), psychological symptoms (craving, desire to reduce consumption), and behavioral symptoms (loss of control over consumption, consuming in spite of perceived negative consequences).

ICD-10 includes a diagnosis of harmful use (with negative health consequences of use), while DSM-IV includes a diagnosis of abuse. These conditions are also considered to be a medical condition inviting therapeutic interventions.

What are the consequences for the treatment of addiction? Examples of the general conduct codes are the Standards of Conduct of the American Medical Association [1] and the Good Medical Practice of the British General Medical Council [22]. Main issues are the patient's autonomy of decision, informed consent, dignity and confidentiality, nondiscriminatory beneficence, and non-maleficence, but also keeping up professional standards by continued education and networking with other services and colleagues in order to provide the best possible care. In addition, the American recommendations include a responsibility to seek change in official or legal requirements, which are contrary to the best interests of the patient. These codes usually acknowledge the occurrence of ethical conflicts and provide links for support in such cases.

In the absence of specific rules for the treatment of substance dependence, the general ethical rules for good medical practice apply. The four major principles are as follows: do no harm, improve the well-being, respect the autonomy, and apply justice. It is obvious that even these few principles cannot be followed without creating conflict [43].

Involuntary intervention to prevent harm is in conflict with the autonomy of an unwilling patient. Treating all patients as being equal (principle of justice) is impossible where the resources are limited. Also confidentiality and data protection often are in conflict with administrative and law enforcement interests in case of illicit drug use. All such conflicts must be carefully examined, in the best interest of all concerned. When the patient's interests collide with those of relatives or other third parties, a common solution must be found to the extent possible. It is advisable to recur to an ethical consilium if major consequences are expected from the decision. The principle of respecting the autonomy of the patient must never be overruled in the name of some abstract societal value without the presence of concrete harm implications for others.

56.2.2.3 Ethical Justification of Interventions

Human rights as well as medical ethics mention the interests of society, which may be in conflict with the interests of the individual. In fact, the ethical justification to interfere with a person's substance use or dependence resides in negative societal consequences. In the case of substance dependence, treatment is justified in order to avoid such negative consequences. Among the appropriate measures are all treatments which help to bring a majority of people with addictive behavior or dependence into treatment, without disregarding their autonomy, and to optimize accessibility of treatment services. In the case of hazardous and harmful use, treatment by early and short interventions (e.g., motivational interviewing) can have positive effects.

As in other medical fields, therapeutic interventions are justifiable if efficient and effective. This principle is part of what is named "consequential ethics," in contrast to dogmatic ethics which call for complying with a given norm whatever the consequences may be. A good example of consequential ethics is the acceptance of harm reduction measures for persons using drugs. On the one hand, a growing number of research findings on positive effects of harm reduction measures justify their integration into the range of interventions for substance users and substance dependence. On the other hand, a dogmatic position is exemplified with the refusal of all interventions except detoxification and abstinence-oriented treatment.

Substance use is a factor in many social and cultural events, as a facilitator of social contact and a source of emotional well-being but also of destructive or aggressive behavior. The acceptable limits of intoxication and behavior, of substances used, and of opportunities for consumption, are

culture specific and are to be respected when dealing with substance dependence [11]. For instance, a major difference between Western and Asian cultures is the place of the individual within the family system; while the individual's interests and autonomy are a core concept of most Western psychotherapies, the integrity and the interests of the family are the higher value in many Asian societies.

In a paternalistic attitude, substance-dependent persons must be protected against wasting their personal resources and potential achievements. However, such an attitude collides with the present position that interference is only justified on the basis of negative consequences of a person's behavior for others. Also, many people have lived or live a productive life in spite of their substance dependence, and to interfere with their lifestyle would cause more ethical concerns than to respect their autonomy.

Developing one's own resources and shaping one's own life is to be facilitated by education and by societal organization, but it is ultimately in the responsibility of the person itself. Conditional are the freedom of choice and the freedom of the will. Is addiction leaving any room for choices, is it a negation of free will and therefore the basis for involuntary intervention? This has been debated extensively. At present and on the basis of research evidence, we have a more differentiated view. The decision of many to change their lifestyle and go to treatment [5, 12] or to stop the dependence without professional support (the so-called self-healers) [31] demonstrates the ability of many persons with substance dependence or addictive behavior to make a choice and stick to it.

This notion is reinforced by observations of regaining consumption control by former addicts [30], and that not the substance alone but also the personality and the social environment had a role in the development of dependence, and that many users keep their consumption under control or regain control under more favorable conditions [42, 71].

A basic ambivalence – substance dependence as a medical condition or a moral weakness – is reflected in the opposition of medical and moral treatment. Moral treatment is understood to be educational and admonishing. The medical approach is to help the addict in getting motivated for change by appropriate empathy and information, while confrontation and reproaches risk reinforcing the resistance against any change. It is important to give the patient the feeling that they are taking the decisions and doing the necessary steps forward themselves. Special methods have been developed for enhancing the motivation for change, and they have become an important element in today's treatment of alcohol and other drug problems [25, 39].

In summary, treatment of substance dependence is expected to help the individual to make his own choices and to regain self-responsibility, rather than to make the decisions for him.

56.2.2.4 The Goals of Treatment: A Hierarchy of Objectives

The goals to be reached through treatments of substance dependence (and which therefore are the criteria for measuring outcome in treatment evaluation research) have changed over the last decades. While the goal of abstinence was traditionally on top of the list, the present situation can be summarized as follows: the primary goal is the patient's survival, moving to health improvements (or at least prevention of deterioration), to improvements in social integration, to reductions in substance use (moving away from addictive behavior), to improvements in quality of life (as defined subjectively by the patient), and ultimately resulting in a responsible and satisfactory lifestyle. Abstinence is not always needed for reaching these objectives, nor does abstinence guarantee to reach them.

A national example of listing the objectives is given in the report on Models of Care by the UK Department of Health [8]:

- Reduction of psychological, social, and other problems directly related to drug use
- Reduction of psychological, social, or other problems not directly attributable to drug use
- Reduction of harmful or risky behaviors associated with the use of drugs (e.g., sharing injecting equipment)

- Attainment of controlled, nondependent, or non-problematic drug use
- Abstinence from main problem drugs
- Abstinence from all drugs

This document fully endorses the principle of consequential ethics in prioritizing the reduction of the various forms of drug-related harm, including social, medical, legal, and financial problems, until the drug-dependent patient is ready and able to come off drugs.

56.2.2.5 Cure or Care?

Treatment is often identified with cure (in the sense of healing an illness), while care means serving a chronic patient without chances for healing. As such, care is an equivalent to harm reduction, meaning all interventions designed to improve the health and social status of a chronic addict who continues a dependent behavior (harm reduction is more than HIV prevention). The present debate on treatment and harm reduction is often a debate on opposing principles of action which cannot be reconciled. In this debate, harm reduction has been disqualified as an approach to prolong dependence, to make substance use acceptable for young people, and to undermine the readiness of addicts for treatment. A recent movement to promote recovery as a complete resocialization without drugs disqualifies agonist maintenance treatment, which is only accepted as "maintenance to abstinence."

Today, in the light of the updated treatment objectives, harm reduction is considered an ally rather than an opponent of treatment. Accordingly, the treatment system must be an integrated system that enables abstinence and harm reduction services to work together, in order to provide a continuum of care, including:

- Easily accessible low threshold services that meet the immediate needs of continuing drug users
- Clear processes for motivating users to move away from drug-dependent lifestyles
- Clear processes for referring users into structured treatment programs that promote stabilization or abstinence (quoted from Ref. [46], p. 6)

56.2.2.6 Tailoring Treatment to Individual Needs

Bearing in mind the diversity of etiology, symptoms, and stages of substance dependence, it becomes obvious that treatment cannot be uniform for all dependent persons. In addition, treatment needs in different age groups and other target groups (gender, ethnicity, comorbidity, etc.) may differ considerably as well. Treatment must respond to the specific needs of an individual patient, on the basis of a comprehensive needs assessment and a treatment planning process where patient and therapist work together on a shared understanding of what is needed and what should be done.

This concept of a needs-based treatment has been intensively researched. I mention two large studies from USA: the National Treatment Improvement Evaluation Study (NTIES) documented the results of needs-based treatment planning and found a significant correlation between 1-year outcomes (measured as drug-free urines) and the number of needs included in the treatment plan [24]. A comparison of basic, average, and enhanced services for heroin dependence evidenced better retention and outcomes in services, where psychiatric and social care was available to patients [35]. In both studies, covering the needs for psychiatric care and living conditions (housing, jobs) was found to be especially important. This again has consequences for the hierarchy of objectives: a reduction of substance use is facilitated by improved living conditions and not necessarily their precondition. "Matching treatment settings, interventions, and services to an individual's particular problems and needs is critical to his or her ultimate success in returning to productive functioning in the family, workplace, and society" is therefore one of the principles of addiction treatment [40].

56.2.2.7 Public Health Interventions Versus Individual Care

Coverage of Treatment Needs Reaching the majority of drug injectors became a primary objective in order to slow down the HIV epidemic. The public health priority is to offer treatment to all persons in need of treatment.

Individual care is optimized by high-quality treatment, but public health cannot accept high-quality standards for a few as long as the many are not reached adequately. This principle includes monitoring of the treatment needs in a given population and, accordingly, careful planning of the treatment system as a whole. The responsibilities – ethically and professionally – are well distributed: medical practitioners are responsible for good individual care, service directors are responsible for good practice in their services, and health authorities are responsible for good coverage of treatment needs.

Cost Effectiveness of Interventions When caring for the treatment system as a whole, the next step is to take the responsibility for making best use of the available human and financial resources for treatment. This means to look at how much effective treatment is provided at what costs. It does not suffice to give a priority to treatments with good evidence for effectiveness but to treatments which provide effectiveness at the lowest costs in terms of staff and budget. A recent approach was efforts which intend to make best use of resources through models of stepped care, matching patients to specific treatments, on the basis of their characteristics and needs (see Chap. 82 "Stepped Care Models in Addiction" in this section).

Harm Reduction An efficient protection of public health goes beyond providing treatment for substance-dependent persons. It includes all measures which are effective in protecting the health and social status of active users, in the interest of users as well as of the population at large.

Accessibility and Affordability of Treatment Neglect of patients in need of treatment can take many forms. For instance, an analysis of national guidelines for substitution treatments of opiate dependence showed a range of restrictive access criteria, such as minimal age, minimal duration of dependence, polydrug use, and lack of confidentiality, and likewise restrictive criteria for a continuation of treatment, such as persistent illicit substance use or bureaucratic limitation of treatment duration [53]. Other examples are the denial of social support and/or medical care to active alcohol or drug users or smokers. Examples are the denial of liver transplants to persons with alcohol problems, in spite of research evidence that survival rates in those who continue to drink are not lower than in other patients [19], and the denial of Hepatitis C treatment with Interferon to active drug injectors on the basis of wrongly presumed lack of compliance [10]. Excluding addiction treatment from health insurance and reserving treatment to those who can pay for it are other examples.

In summary, the ethical implications are obvious: without appropriate accessibility and affordability of treatment, there is no way to reach the "health for all" goal of good coverage and of treating all patients as equal.

Quasi-Compulsory and Compulsory Treatment Is it advisable to force individuals with addictive behavior or dependence into treatment, when they are not motivated to engage in it by themselves, in view of an objective of optimal coverage? It is a common understanding that those individuals do not opt for treatment unless there is some external or internal force behind such a decision. The forces are quite different, ranging from health concerns to social pressure by family or employer to legal pressure in order to avoid losing the driver's license or going to prison. This is called the "continuum of coercion" [61]. The scientific evidence on the effectiveness of such "coercion" is contradictory [23, 70]. A recent multi-country study on quasi-compulsory treatment (QCT, treatment on court order as an alternative to imprisonment, with the consent of the patient) documented that perceived pressure does not translate into higher motivation; no significant differences in outcome were found between QCT patients and control groups of voluntary patients [46].

Coercion through mutually agreed consequences of substance use during treatment (contingency management) is recognized to be

helpful, but more so when using positive reinforcers than sanctions [38, 44]. From an ethical standpoint, it is reluctantly accepted under the term of "Ulysses coercion" (Odysseus wanted to be bound to the mast of his ship in order to resist the temptations of the sirens, [48]).

In summary, the findings indicate that coercion may have a role in supporting patient motivation for change, on the basis of informed consent, but it cannot replace motivation by compulsory measures without consent.

56.2.2.8 The Case of Agonist Maintenance Treatment

Rationale and Origins At first view, prescribing agonists with dependence liability to persons suffering from substance dependence seems to be paradox. One of the main arguments against agonist prescribing refers to a prolongation of dependence, which is considered to be unethical. How can we understand the rise and successes of this therapeutic approach (also known under the terms substitution or replacement treatment)? The main objective is to replace uncontrolled use of an addictive substance, by the controlled provision of a medication acting on the same receptors, as the original substance. The secondary objectives to be reached are reduction of the uncontrolled substance use, reduction of adverse health and social effects of uncontrolled use (including a reduction in drug-related delinquency), and normalization of lifestyle (including drug-free social contacts, improved housing, and employment conditions). These objectives are in line with the hierarchy outlined above. The primary objective is reached by prescribing and controlled intake of an agonist, the secondary objectives by eliminating the need to purchase the original substance of dependence and by ancillary care.

The introduction of agonist maintenance treatment is closely linked to the experience of unsuccessful detoxification and abstinence-based treatment. Maintenance without substitution of the problem drug was practiced in Roman times (the emperor Marc Aurel was maintained on opium by Galenus, the eminent physician), and daily dosages of opium were provided to dependent persons in Southeast Asia in the nineteenth century [62]; ironically, after the ban of opium, these persons switched to heroin [63]. First attempts at substitution were to replace opium by alcohol in the sixteenth century [13], morphine by heroin [32], and morphine by cocaine [20] in the nineteenth century. These attempts were far from being successful. A first well-designed and scientifically based model was developed by Dole and Nyswander: the methadone maintenance scheme [9]. They used oral methadone, a full opiate agonist with a longer half-life than injected heroin (controlled intake of one dose per day can block the heroin craving effectively). The model included ancillary care for medical and social conditions of enrolled patients.

Apart from opiate replacement, only nicotine replacement has been introduced into present medical practice, while former alcohol maintenance for alcoholics is discontinued.

Result Methadone maintenance is one of the most frequently and best researched therapeutic approaches. Extensive reviews of the pharmacological aspects, of service delivery, and of therapeutic outcomes, have been published [3, 18, 27, 49, 60]. In addition to methadone, buprenorphine and retarded morphine have been introduced and researched as replacement medicines in the treatment of opioid dependence, with similar outcomes. For chronic opiate individuals who failed to profit from those agonist maintenance treatments, pharmaceutical heroin was tested and introduced as a "last resort" therapeutic approach with equally good results [47]. The positive findings in terms of health and social improvements, including a massive reduction of delinquency, were complemented by the fact that agonist maintenance treatment has the greatest potential to bring heroin-dependent persons into contact with therapy and care. It therefore became one of the most welcome instruments for limiting the spread of blood-borne diseases – HIV/Aids and hepatitis – among drug injectors. The reduction of risky injecting behavior and of seroconversion rates in methadone patients became evidenced for community-based programs [36] and for prison-based

programs [45]. Economic evaluation documented the cost-effectiveness of methadone and buprenorphine maintenance treatment [6].

Based on the evidence, methadone and buprenorphine have been scheduled by the World Health Organization as essential medicines [64, 65]. Also, international evidence-based scientific guidelines for agonist maintenance treatments have been published [66].

Concerns A major concern was a weakening of the motivation to change and therefore a prolongation of addictive behavior through agonist maintenance treatment. There is no evidence for this claim. A multisite major cohort study showed a relapse rate of methadone maintenance patients to daily opiate use of only 27% at 12-year follow-up [34]. The Drug Abuse Treatment Outcome Study (DATOS) study from USA and the National Treatment Outcome Research Study (NTORS) study of the UK, both multisite prospective cohort studies, found comparable outcomes at 5-year follow-up in patients who were enrolled in residential drug-free and in methadone maintenance treatment [26, 28].

In summary, the ethical justification of agonist maintenance treatment in the modern form was to provide otherwise treatment-resistant heroin addicts with an effective approach to improve their health and social situation without asking for total abstinence from narcotic substances.

56.2.2.9 Conflicts in Ethical and Legal Orientation

In numerous concrete situations, human rights and medical ethics are difficult or impossible to respect as well as national or local legal conditions. A number of such situations has have been indicated throughout this text. Sometimes, an appropriate conflict management may help, especially if the application of an opportunity principle is permitted. In other situations, there is no such solution. The way out is indicated by the ethical code of AMA: to engage in an effort to change laws which prove to be incompatible with responsible care for the addicts [1].

56.3 Conclusion

The essential ethical message is well summarized in the WHO international guidelines for the psychosocially assisted pharmacological treatment of opioid dependence [66]:

Clinical Relevance

When making clinical decisions for the treatment of people with opioid dependence, ethical principles should be considered, together with evidence from clinical trials; the human rights of opioid dependent individuals should always be respected. Treatment decisions should be based on standard principles of medical care ethics – providing equitable access to treatment and psychosocial support that best meets the needs of the individual patient. Treatment should respect and validate the autonomy of the individual, with patients being fully informed about the risks and benefits of treatment choices. Furthermore, programs should create supportive environments and relationships to facilitate treatment, provide coordinated treatment of comorbid mental and physical disorders, and address relevant psychosocial factors.

There is not much to be added. The statement applies fully as the main recommendation for all treatments of substance dependence. It is a perpetual agenda for future generations. The task is to update the key elements of this chapter: the legal framework for the treatment of addictive behavior and dependence, at international, national, and local levels; to reflect the ethical positions, their consequences, and limitations in the best interest of patients and all other concerned population segments; the changing societal norms as well as the changing background and needs of the individual patients.

Key Points

Clinicians engaged in the treatment and care of addicted persons find, in this chapter, the necessary information needed to keep their interventions within legal and ethical guidelines and to shape institutional care concepts accordingly, in the interest of acceptability and adequacy to societal and patient expectations.

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Monitoring and Evaluation of Addiction Treatment

57

Ambros Uchtenhagen

Contents

Abstract

Monitoring and evaluation (M & E) are research activities dedicated to document and analyze the processes and outcomes of addiction treatment. Before starting M & E, some conceptual issues apply, such as considering the objectives of a given treatment or treatment system, the outcome indicators to be used, the characteristics of the target population, and the basic understanding of the nature of addiction.

A range of different goals can be envisaged in M & E projects, from measuring treatment implementation and the use of the available resources to measuring efficacy and effectiveness. The overall goal, in general, is the improvement of services and treatment systems. The main steps in developing M & E projects are determining the research questions, the appropriate type and design of evaluation, and the resources and partners needed. Also, it is helpful to identify expected problems and obstacles.

Lists of evidence-based guidelines and instruments for evaluation are attached, as well as lists of high-quality publications reviewing the outcomes of evaluation studies.

Keywords

Monitoring · Evaluation · Tretament Workbooks · Outcome

A. Uchtenhagen (✉)
Swiss Research Foundation for Public Health and Addiction, Zurich University, Zurich, Switzerland
e-mail: ambros.uchtenhagen@isgf.uzh.ch

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57.1 Introduction

Monitoring and evaluation (M & E) are essential instruments for an optimal drug demand reduction through treatment and prevention. They serve the commitment to effective interventions, which are based on scientific evidence. Only a good knowledge on the effects of interventions can provide the evidence base for an adequate substance abuse policy.

The main objective of M & E is to assess the available intervention system at country, regional, or local level, to determine its adequacy for covering the treatment needs in the respective population, and to measure its intermediate, short-term, and long-term outcomes. This is instrumental for a targeted improvement of available intervention systems, as well as for an adaptation to new challenges from changes in substance-using populations, and the health and social consequences of use. Monitoring trends in substance-using populations out of treatment is helpful in order to observe such changes, for example, the arrival of new drugs.

M & E also covers structural and procedural properties of services and systems, as major instrumental elements for outcomes.

M & E can also serve other purposes, such as providing arguments for legitimizing the treatment or prevention approach against repressive approaches.

57.2 Main Aspects of Monitoring and Evaluation

57.2.1 Definitions and Rationale

There are no universally accepted definitions. Monitoring and evaluation are performed in many fields of activities, such as health and education, and the aims and definitions are adjusted to the respective field. For this chapter, the following definitions and rationale apply.

57.2.1.1 Monitoring Treatment

Monitoring is an activity to continuously document defined indicators of treatment implementation and outcomes.

Rationale: To determine the level of service performance and treatment results, as a starting point for improvements and for measuring change as a result of improvements.

57.2.1.2 Process Evaluation of Treatment

Process evaluation is a one-time or repetitive activity to document how therapeutic interventions are implemented, in terms of coping with predetermined rules and criteria.

Rationale: To determine the level of service responsiveness to needs and compliance with expected performance, in order to facilitate the expected results.

57.2.1.3 Outcome Evaluation of Treatment

Outcome evaluation is a one-time or repetitive activity to document the consequences of therapeutic interventions for the target population and/or any other sector of the population, in terms of predetermined goals and indicators.

Rationale: To measure the intended and unintended effects of therapeutic interventions, in order to determine the value of a given intervention, a service, or treatment system to serve the expected treatment objectives.

57.2.1.4 Economic Evaluation of Treatment

Economic evaluations are a specific type of outcome evaluation. They measure the proportions of costs and benefits of an intervention, a service, or a treatment system. Costs and benefits are measured at the individual or at society level. In cost-effectiveness evaluation, effectiveness is expressed in terms of costs per unit of outcome. Cost-utility evaluation determines the gains in years and quality of life in relation to costs.

Rationale: To explore satisfaction with the results of investments made.

57.2.1.5 Meta-Evaluation

The growing number of evaluation studies and their unequal quality invited an effort to review evaluation studies, on the basis of rigorous method-

ological analysis, resulting in reliable information about "what works" and "what works for whom."

57.2.1.6 Comparable Terms

Other terms for process and outcome evaluation, especially in the educational field, are formative and summative evaluations. Formative evaluation is typically conducted during the development or improvement of a program or course. Summative evaluation involves making judgments about the efficacy of a program or course at its conclusion.

For other and partly overlapping definitions of terms, see the referenced evaluation guidelines of the World Health Organization [5] and the European Monitoring Centre for Drugs and Drug Addiction [7, 9].

57.2.2 Preparing for Monitoring and Evaluation

A detailed M & E project is the key to the feasibility of data collection, to the validity of data, and to the usefulness of results. The following issues and steps must be considered before starting a project. It is recommendable to set up an M & E project in collaboration with an expert.

57.2.2.1 Conceptual Issues

Treatment Objectives

The specific objectives of a given therapeutic method or of a given program determine the type of outcome data to be collected, in order to know how far outcome responds to the objectives. Objectives may be reduction of main substance use or any substance use, abstinence from main substance use or any substance use, health improvements, reduction or abstinence of illegal activities, social integration such as gainful employment or participating in a social network, or complete recovery [8].

Outcome Criteria

If no specific treatment objectives are in place, any M & E project has to determine which type of outcomes are to be measured. This may be those mentioned earlier, but also others such as the quality of life of patients/clients or the reduction of negative consequences of addiction at population level in terms of substance-related crime and nuisance or blood-borne infectious disease. The following is a catalog of the most frequently used outcome indicators (adapted from [9], Table 2) (Table 57.1):

Table 57.1 Outcome indicators

Retention rate	Measuring time in treatment
Status at discharge	Regular versus irregular discharge (drop-out, exclusion)
Addictive behavior	Consumption patterns of legal and illegal addictive substances
Risk-taking behavior	Injecting drugs, needle sharing, and unsafe sex
Health status	Changes in somatic and psychological health
Social reintegration	Changes in living arrangements, employment, social networking, and criminal activities
Quality of life	Subjective Well-being

The choice of outcome criteria should meet the interests of all stakeholders, including the mandating and/or funding bodies for the project.

Characteristics of the Target Population

Intermediate, short-term, and long-term outcomes of therapeutic interventions are diverse for different target populations. Age, gender, level of education, level of social integration and social support, religious affiliation, health factors such as comorbidity, etc. have a potential to influence how well a person responds to a therapeutic intervention or program. Data collection therefore must be tailored to the specificities of the target groups an intervention or service is meant to serve.

Understanding Addiction

Also, the kind of data to be collected for M & E depends on how addictive behavior is interpreted. Various paradigms apply here: the use of psychotropic substances can be understood as self-medication for symptom relief [18], as a special variation of self-manipulation, tailoring use to a desired state of mind, or as instrumental for self-enhancement, optimizing function and output [15]. Or else, substance use is understood as a lifestyle phenomenon, in the sense of "consumerism" or of an expression of subcultural identity.

On the other side, addiction is understood as a brain disease, following repetitive substance use, resulting in structural changes [20] or on a vulnerability-stress model focusing on the impact of genetic and environmental factors on the brain changes [34]. For each of these paradigms, specific contextual data and patient/client characteristics are of interest in order to explain the value of intervention outcomes.

Also, understanding addiction as a chronic relapsing disorder has consequences for the design and methodology of evaluation studies [22]. Or else, addiction is conceived in a synthetic theory as a pathology of the motivational system, resulting in a deficit of other satisfactory/pleasurable experience, restricting such experience to repetitive substance use [36].

57.2.2.2 Goals of Monitoring and Evaluation Projects

M & E projects are made for a variety of purposes (see also Ref. [9], Chap. 1). The purpose is relevant for the research questions to be answered by the project; the research questions are relevant for the design and methodology to be used as well as for the data which are necessary for answering the questions.

Measuring Program Implementation

A comparison is made between the intended standards of a therapeutic program or protocol and the de facto characteristics of its implementation. It includes structural and procedural aspects. Among the many issues of interest are the indication criteria, staff composition and qualifications, infrastructure and location of service, links with other services, etc. It may also include an estimation of how well the treatment needs in the regional/local population are covered.

Such projects are mainly of the process evaluation type. A recent example is part of the WHO collaborative study on substitution therapy of opioid dependence and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) [19]. Continuous monitoring of the process has the advantage to document changes made over time in terms of program implementation.

Measuring Use of Resources

In an overall purpose to make best use of available human and financial resources, M & E projects can measure the overall utilization of the treatment capacity or the utilization by the intended target population. They can compare outcomes between services receiving similar investments and serving similar populations. More difficult and demanding are economic evaluations as mentioned earlier.

Measuring Efficacy and Effectiveness

Efficacy of therapeutic interventions is, as a rule, determined by clinical trials, using a randomized controlled design. These trials provide us with data showing the relative efficacy of a given intervention or medication in comparison to another intervention or medication, if the treatment is allocated at random and the sample characteristics are comparable.

In contrast, the effectiveness of an intervention or a treatment service is defined by how well an intervention or a service works in practice and produces the desired results. It is usually measured by cohort studies, including outcome evaluation with or without elements of process evaluation.

Efficacy and effectiveness studies contribute to a better knowledge on what treatment is best suitable, have the best chances for which patients/clients under which conditions, and thereby improve the indication criteria for patient/client placement.

Legitimation of Treatment

A frequent purpose of evaluation projects is demonstrating the value of a given intervention or service, in terms of desired outcomes, patient/client satisfaction, and positive economic balance of input and outcome. This can be done through a single-service follow-up study or a nonrandomized comparative study. The main issues why it is important to assure the legitimacy must be considered in the research questions and the study design.

Improvement of Services and Treatment Systems

M & E studies can provide data which allow to identify weaknesses, to initiate changes, and—in

a repetitive effort—to document the intended and unintended effects of such changes. Process evaluation and qualitative data are most helpful for improvement purposes [27].

57.2.2.3 Determining the Research Questions

The questions to be answered by an M & E project depend on the aims and must be made explicit, for an agreement between all stakeholders. The questions determine what kind of samples is needed, which data must be collected, and which study design is most appropriate.

Additional research questions may be included in order to address special interests by staff, funding agency, or other stakeholders. The inclusion of such questions has a potential to enhance cooperation and compliance with the main study.

The following types of research questions can be considered (see also WHO 2000, workbook 1 step 5, and [9], Chap. 3):

- *Descriptive questions* for precise information about observations made.
- *Normative questions* aiming at a comparison between observations and expectations (e.g., standards).
- *Impact questions* exploring the role of interventions or elements thereof for the observed outcomes.

57.2.2.4 Typology of Treatment Evaluation

There is no universally accepted typology. The following is mainly based on the types presented in the EMCDDA Guidelines [9] and in the WHO/United Nations Office on Drugs and Crime. (UNODC)/EMCDDA Evaluation workbooks [39].

Needs Assessment Evaluation

Needs assessment studies are used to determine and improve the coverage of treatment needs in a given population, in order to tailor treatment capacity, mix of services, and networking among services accordingly (WHO evaluation workbook 3).

Structure Evaluation

Evaluation of the appropriateness of infrastructure and other structural elements to facilitate the desired outcomes of treatment. This includes location, safety provisions, financial resources, staff composition and qualification, governance, and organization.

Process Evaluation

Process evaluation documents and analyzes how treatment is delivered. Assessment procedures, indication criteria, treatment planning, programming, qualification and attitudes of staff, continued training of staff, house rules, sanctions, etc. are some of the elements to be considered (WHO workbook 4, extensive list of available instruments for process evaluation on the EMCDDA instrument bank EIB).

Outcome Evaluation

The focus is on the consequences of treatment for patients/clients, their families, and the community. It provides information on which treatment modality has which consequences for which target groups under which conditions. It may consider the impact on other treatment approaches. It may become relevant for treatment motivation in the target population.

Outcome is measured against predefined behavior norms (normative evaluation), baseline pretreatment status (evaluation of change during treatment), or predefined treatment goals (goal-attainment evaluation). Outcome evaluation mainly uses quantitative methods (by randomized controlled trials (RCTs) or cohort studies), eventually a combination of quantitative and qualitative methods (WHO workbook 7, instruments on EIB of EMCDDA).

Patient/Client Satisfaction Evaluation

Patient/client satisfaction studies measure to what extent treatment provision and treatment results meet the expectations of patients/clients. They are a major source for service improvement, together with retention rates and drop-out rates (WHO workbook 6, instruments on EIB of EMCDDA).

Economic Evaluations

Various designs are used to describe and analyze economic factors in addiction treatment. Cost analysis measures the cost factors and overall

costs of treatment (e.g., per patient day, per treatment episode, per treatment modality, etc.). Cost-benefit evaluation determines the relation between costs and financial benefits (e.g., in terms of reduced health and social costs in a defined posttreatment period as compared to pretreatment values). Cost-effectiveness evaluation measures costs in relation to a specific unit of outcome (e.g., significant health improvement or significant reduction in addictive behavior). Cost-utility evaluation measures the utility of treatment for patients/clients, for example, in terms of disability-adjusted life years—DALYs [2] or as quality-adjusted life years—QALYs [25, 37]. For cost evaluations, see also WHO workbook 5; for economic evaluations, WHO workbook 8; and for instruments, see EIB of EMCDDA.

Formal Evaluation
This is an assessment of service compliance with professional, ethical, and legal standards.

Meta-Evaluation
Meta-evaluation is made on the basis of recognized procedures to combine quantitative results from several studies about the same or similar interventions, in order to establish composite outcome scores. This allows assessing the effectiveness of a given intervention with greater confidence than on the basis of a single study.

57.2.2.5 Evaluation by Whom?

External Evaluation
Outcome or/and process evaluation of treatment services or interventions by research professionals who are independent from the evaluated agency. This is the preferred modality because eventual bias in collecting client data is avoided, and the credibility of the study is enhanced. Disadvantages in comparison to internal evaluation may be the higher costs and resistance or noncompliance of treatment staff.

Internal Evaluation (Self-Evaluation)
This can be used as an internal learning process about the treatment program or in case of restricted funds for evaluation studies. However, internal evaluation is not recommended for outcome studies because credibility is lower in comparison to external evaluation. Collaboration with an external evaluation specialist is an advantage.

57.2.2.6 Evaluation Level and Timing

Evaluation Level
The target of M & E projects can be a specific type of intervention or therapeutic method. It can also be a specific service or setting for delivering treatment. In contrast to single intervention and service follow-up studies, a comparative evaluation focuses on the functioning and outcomes of a local, regional, or national treatment network of services or of the overall treatment system. Choosing the target implies the choice of an adequate type and design of the project.

One-Time and Repetitive Evaluation
One-time evaluation studies are frequently made for all purposes. More relevant are repeated studies or a continuous monitoring system, allowing for a documentation of specific changes in implementation and outcomes over time. However, such an approach has important cost implications. A possible compromise is the combination of a relatively simple monitoring of routine data with a more extensive evaluation study if indicated by changes in the monitoring data or after important program changes.

57.2.2.7 Resources

Estimations must be made on the amount of funds and type of manpower in order to conduct the planned M & E project, and the availability of these resources must be checked in advance, in order to avoid delays or restrictions during implementation. Also, the infrastructure for data storage and analysis must be made available.

In view of the difference in available resources between high-income and low−/middle-income countries, priority-oriented monitoring and evaluation research, as well as transnational collaboration, is recommendable.

Financial Resources
If an M & E study is mandated by an external agency (governmental or nongovernmental), the

budget available for the study must be identified, in order to design the study accordingly. Or else, the research group planning the study has to present a budget proposal and apply to a funding agency (Research council, Foundation, Health Authority, etc.).

If there are doubts about the feasibility of the study (e.g., access to services and patients/clients), a stepwise procedure may be preferred. In this case, a separate budget for the feasibility study is needed, and the results will determine the budget of the ensuing evaluation study.

Human Resources
Which staff is needed for carrying out a planned project? Various functions must be considered: expert support for setting up the research questions and protocol, for determining the appropriate methods and instruments, for training of interviewers, etc. Staff responsible for data collection, interviewers, staff for data control and entering into a master file, statistician for data analysis, etc. are needed. It is helpful to identify staff in advance, in order to avoid delays in implementation and in order to establish a realistic budget.

Infrastructure
Access to the necessary equipment for staff and for safe storage of data is to be ensured, as well as the disposition of the appropriate software for data handling and analysis.

57.2.2.8 Partners

Most M & E projects are a collaborative effort between various partners, especially in case of external evaluation of services and networks. Clear agreements on functions, responsibilities, temporal availability, and costs are recommended, eventually with written contracts.

Funding Partners
Agreements on the overall budget, bookkeeping, financial controls, timing of payments, and financial reports help to prevent misunderstandings and litigations. Such agreements should be made to protect the interests of all parties.

Therapeutic Partners
All projects on external evaluation are based on collaboration between researchers and treatment providers. Agreements are needed on the access to patient/client data and service data, access to patients/clients for external interviewers, responsible person in a given service for organizing and facilitating the research process, ownership of data, and arrangements for publishing the study results. Procedures in case of upcoming problems during project implementation should also be agreed upon in advance.

A special situation is created in case of a systematic evaluation at the system level, involving all or selected treatment providers.

Research Partners
In case multiple researchers or research groups are involved, a clear working arrangement should identify the functions, tasks, and responsibilities of the individual persons. If a service provider hires a researcher or research group for an internal or external evaluation, or monitoring system, there is also a need to identify the various functions, tasks, and responsibilities.

57.2.2.9 Expected Obstacles

Most problems occurring during project implementation are due to missing or incomplete preparation. However, even a carefully prepared project may meet some obstacles. Some of the frequent ones are mentioned here.

Compliance with Protocol
Staff involved in project implementation may disregard details of the research protocol and thereby weaken data reliability, even if well instructed. This may also happen in case of changes of staff. Tutoring staff activities over the entire duration of the project helps to avoid such failures. Also, efforts to make a strong evaluation culture at the system level acceptable will contribute essentially to overcome this type of obstacle.

Resistance from Patients/Clients
One of the most common problems is the refusal to participate in a randomized study, resulting in

an unacceptable degree of sample selectivity. This is especially to be expected if a control group with placebos or other forms of low therapeutic value are used or patients/clients are not confident that their data will be well protected against external parties, for example, in studies involving illicit substance use and/or drug-related criminal activities. Informed consent should cover not only aims and design of the study but also measures taken to guarantee data protection.

External Interference

It may so happen that family members of patients/client or other third parties raise opposition against an M & E project, on the basis of ethical concerns. It is advisable to have an explicit permission from an ethical committee, if not already prescribed by law.

57.2.3 Implementation of Monitoring and Evaluation

57.2.3.1 Available Guidelines and Instruments for Treatment Evaluation

International Guidelines for Treatment Evaluation

From the number of evaluation guidelines, a few are mentioned here, on the basis of their wide international applicability. It is highly recommendable to consult one or more guidelines before starting an M & E project.

WHO/UNODC/EMCDDA Evaluation of Psychoactive Substance Use Disorder Treatment Workbook Series (WHO 2000)

This publication consists of a series of workbooks intended to educate program planners, managers, staff, and other decision-makers about the evaluation of services and systems for the treatment of psychoactive substance use disorders. The objective of this series is to enhance their capacity for carrying out evaluation activities. The broader goal of the workbooks is to enhance treatment efficacy and cost-effectiveness, using the information that comes from these evaluation activities.

EMCDDA Guidelines for the Evaluation of Treatment in the Field of Problem Drug Use. A Manual for Researchers and Professionals [29, 9]

This publication provides basic information on the options, elements, and procedures of drug-related treatment evaluation. It also contains an overview of European and international evaluation and research networks.

Instruments for Treatment Evaluation

The EMCDDA evaluation instrument bank (EIB) covers a range of available instruments ready for data collection, including information on the target group specificity, the available languages (mostly English), copyrights, and eventual restrictions for use. Instruments are available for needs assessment and planning, for mediating and risk factors, for process and outcome evaluation, for patient/client satisfaction, and for staff knowledge and satisfaction.

The WHO/UNODC/EMCDDA evaluation workbooks present many instruments in the context of the various steps and approaches of treatment evaluation (WHO 2000).

A recent instrument for assessing and improving addiction treatment at the system level is the WHO Substance Abuse Instrument for Mapping Services (SAIMS) in high-income and middle–/low-income countries and disadvantaged regions [40].

57.2.3.2 Adaptation of Guidelines to Special Situations Recommendations

The recommendations made in guidelines do not always respond to the specificity of a given project. However, major deviations from recommendations should be highlighted and reasons should be given. Special situation may arise from restricted resources or ethical restrictions. While there is some research on how to adapt treatment guidelines to clinical practice [13], no such systematic effort is known for evaluation guidelines.

An innovative attempt is to be expected from the WHO SAIMS project [40].

57.2.3.3 Meta-Analysis and Reviews of Evaluation Studies

Two organizations have been established in order to review and analyze evaluation studies selected for their rigorous methodology: the Cochrane Collaboration and the Campbell Collaboration.

The Cochrane Collaboration (www.cochrane.org) has its focus on evaluation of medical treatments, while the Campbell collaboration (www.campbellcollaboration.org) has its focus on social interventions.

Both organizations make their reviews available in their respective online libraries (www.thecochranelibrary.com, www.campbellcollaboration.org/library.php). A growing number of reviews cover pharmacological and psychosocial treatments in addiction and their outcomes.

57.2.3.4 Study Designs and Protocols

The choice of the appropriate study design depends on the research questions and on the available resources. The most frequently used designs are presented in Table 57.2 (see also Ref. [9], Chap. 3, Table 1).

Cross-Sectional Studies

Cross-sectional studies are one-time studies to compare treatment services, treatment populations, and treatment outcomes at a given moment in time (e.g., intermediate outcomes during treatment or after terminating treatment). Cross-sectional studies cannot describe processes of change over time.

Table 57.2 Main types of study designs

Cross-sectional studies	Comparing interventions/services at a given point in time
Cohort studies	Comparing measurements of single interventions/services or several interventions/services at multiple points in time (baseline data, intermediate outcomes, outcomes at follow-up). Cohort studies are made prospectively or retrospectively (on the basis of past data files)
Randomized controlled studies RCT	
Quasi-experimental studies	
Comparing outcomes if interventions are assigned to patients/clients at random, not as in clinical practice (observational studies)	
RCT with special randomization procedures	

Cohort Studies

Cohort studies describe the course and outcomes of treatment populations, which receive their treatment as usual in practice, not allocated by randomization (observational or "naturalistic" studies). Cohort studies use retrospective or prospective data.

Longitudinal Retrospective Studies

Anamnestic data on pretreatment characteristics and outcomes of treatment populations are used to describe the therapeutic results of a given intervention/service alone or in comparison with other interventions/services. This type of study is more economic in comparison to prospective studies, which need multiple, at least two, measurement points in time; its usefulness, however, depends on the availability and quality of anamnestic data.

Longitudinal Prospective Studies

Collecting pretreatment, during-treatment, and posttreatment data at different time points allows a focused and detailed description of the treatment process and results. It avoids biased or missing baseline data and therefore provides for more reliable results of effectiveness. Prominent national studies comparing cohorts from different treatment settings are the DATOS study in the USA [28] and the National Treatment Outcome Research Study (NTORS) study in the UK [11].

Randomized Controlled Studies

Randomized controlled studies (RCT) are the "gold standard" for evaluating specific therapeutic modalities and medications in clinical research. Patients are allocated "at random" to an experimental group or to a control group, thereby minimizing selection factors between the two groups. As not all patients are willing to accept randomization, especially if not allocated to their preferred intervention, this design may suffer from refusal to participate or from elevated dropout rates. Randomized studies allow to identify the effectiveness of a modality or medication but

do not provide results of effectiveness due to their selectivity. An updated collection of RCTs on addiction treatment can be found in the Cochrane library.

Double-Blind Randomized

If assignment to the experimental or the control group is not revealed to patients and therapists, their preferences are better (although not completely) ruled out, and the study gets more reliable results about comparative treatment efficacy. This design is mainly used for a comparison of medications; psychosocial interventions cannot be "blinded."

Quasi-Experimental Designs

Instead of comparing two or more modalities, the effects of an experimental modality can be compared to the course while waiting to be accepted for that modality. In this case, the control group receives treatment as usual or no treatment while waiting.

In the Zelen design, informed consent is only asked after randomization and only from patients assigned to the experimental group, while those who are randomized to treatment as usual need not consent to participation in the study [31]. This design makes it easier for patients to participate because they do not have to consent to be randomized. Of course, blinding is not possible in this design.

Another design uses different sequences of treatment modalities, for example, A-B-A compared with B-A-B or B-B-A.

Role of Methodology for the Quality of Results

Grading of Evidence

Treatment evaluation searches for scientific evidence that can be used as a basis for therapeutic recommendations. However, there are grades of evidence, depending on the type of study design (see also Ref. [12]). The following is an adapted version (Table 57.3).

Standards for Consensus Building

Where evidence from quantitative studies is not available or feasible, recommendations for good practice are mainly based on expert opinion. In order to optimize the consensus-building process, rigorous rules have been established [1].

Table 57.3 Grading of evidence grade definition

A	Highest degree of evidence: Review from multiple randomized controlled studies (RCT) with convergent results
B	High degree of evidence; results from single RCT and controlled clinical studies
C	Moderate degree of evidence: Prospective comparative longitudinal studies (observational studies without control design)
D	Low degree of evidence: Single intervention/ service follow-up studies, case studies E very low degree of evidence: Nonsystematic observations
Z	Not known

57.2.3.5 Quantitative and Qualitative Methods

Quantitative Methods

Quantitative methods are used for outcome evaluation. They consist in collecting empirical data via standardized instruments (surveys, questionnaires, pre- and post-tests) for statistical analysis and mathematical modeling and in producing numerical results (statistics, percentages), which answer specific research questions. Data may come from existing databases (secondary data) or are collected directly from treatment samples (face to face, per telephone, or electronic media). Questionnaires may be self-administered or administered by trained interviewers. Sample size and homogeneity, reliability and validity of data, and appropriate statistical methods and models are essential for representative results.

Not all patients/clients who participate in a randomized evaluation study are compliant with the study protocol and available for follow-up data collection. Two concepts are therefore used for statistical analysis: the intention-to-treat (ITT) concept includes all participants who have been randomized, ignoring noncompliance and withdrawal, while the per-protocol concept includes only participants without any major protocol violations [14].

Qualitative Methods

Qualitative methods are mainly used for process evaluation. When indicating problem areas in the provision of treatments, they can also be useful for improvements and for generating new research questions. They provide information for the construction of questionnaires in process and outcome evaluation, and they can be used for the interpretation of quantitative findings [23].

The main methods are participant observation, semi-structured interviews, focus groups, and narrative research (see Ref. [9]). A standardized method for the selection of interview and focus group partners is the theoretical sampling model, allowing for the broadest possible spectrum of views and perspectives [10, 30].

57.2.3.6 Use of Results

It is advisable to determine at an early stage of an M & E project how the results will be communicated, by whom and how. This includes issues like data ownership and authorship in publications. In order to avoid later litigations, all agreements should be documented in written.

A first start to communicate evaluation results are intermediate and comprehensive final reports; for recommended components see [39] (workbook 2, step 4) and the EMCDDA Guidelines for treatment evaluation ([9], Chap. 6). Reports must at least be accessible to all stakeholders of an evaluation project. On the basis of the final results, a publication plan can help to make the best use of those. The scientific community is best reached by publications in peer-reviewed journals, and a wider audience eventually by open access journals, books, good practice documents (e.g., Ref. [33]), pamphlets, mass media articles, etc.

Once the results are known, what they mean and to whom they might be communicated should also be discussed in order to optimize their potential impact on treatments, on service planning and improvement, on treatment policy, etc.

57.2.3.7 Checklists for Assuring the Evaluation Process

All those involved in planning and implementation of a given project can profit from checklists which help to keep all elements of the project under control. The EMCDDA Guidelines for treatment evaluation present useful checklists for the preparation and implementation, as well as for the evaluation process ([9], Chap. 5).

57.2.4 Treatment Outcomes: Selected Evidence-Based Guidelines and Systematic Reviews

- Effectiveness of Therapeutic Communities: a systematic review [21].
- Principles of Drug Dependence Treatment. A Research Based Guide (NIDA [24]).
- Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence [38].
- Contemporary Drug Abuse Treatment. A Review of the Evidence Base (UNODC [32]).
- Reviews for specific interventions:
- Calabria et al. [4]
- Humphreys and McLellan [17]
- Malivert et al. [21]
- Hertzler et al. [16]
- O'Donnell et al. [26]
- Werb et al. [35]
- Bomparis [3]

57.2.4.1 Cochrane Library (Selected Reviews)

- Psychological therapies for pathological and problem gambling (2011)
- Methadone for non-cancer pain in adults (2012)
- Psychosocial interventions to reduce alcohol consumption in concurrent problem alcohol and illicit drug users (2012)

- Nicotine replacement therapy for smoking cessation (2012)
- Mobile phone–based interventions for smoking cessation (2012)
- Combined pharmacotherapy and behavioral interventions for smoking cessation (2012)
- Psychosocial interventions for benzodiazepine harmful use, abuse, and dependence (2012)
- Effects of psychostimulant drugs on cocaine dependence (2010)
- Acamprosate for alcohol dependence (2010)
- Opioid antagonists for alcohol dependence (2010)
- Psychosocial interventions for reducing injection and sexual risk behavior for preventing HIV in drug users (2010)
- Psychosocial interventions for people with both mental illness and substance abuse (2010)
- Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (2008)
- Psychosocial interventions for cocaine and psychostimulant amphetamines related disorders (2007)
- Alcoholics Anonymous and other 12-step programs for alcohol dependence (2006)
- Methadone maintenance at different dosages for opioid dependence (2003)

57.2.4.2 Campbell Library (Selected Reviews)

- Effects of early, brief, computerized interventions on Risky Alcohol and Cannabis Use Among Young People: A Systematic Review (2013)
- The Effectiveness of Incarceration-Based Drug Treatment on Criminal Behavior: A Systematic Review (2012)
- Brief Strategic Family Therapy for Young People in Treatment for Non-Opioid Drug Use (2012)
- Effects of drug substitution programs on offending among drug addicts (2009)
- Case management for persons with substance use disorders (2009)
- Motivational interviewing for substance abuse (2009)

Key Points

This chapter focuses on how treatment services and networks can be analyzed in regard to their functioning and usefulness, in a systematic long-term process, or in time-limited research projects. Essential elements are conceptual preparation of what should be learned (type of evidence), which patients and professional partners should be involved, what resources are needed and available, advantages and limitations of methods to be applied, and use of results in the interest of patients and all concerned.

Clinical Relevance

Treatment is about improving the symptoms of medical conditions, to learn about which interventions are effective for whom in the short and long term, and how to improve the patient's quality of life in caring for incurable conditions. This chapter helps clinicians to assess the patient situation beyond a formal diagnosis in all relevant aspects to develop and follow up an individual treatment plan and to learn about the effectiveness and side effects of their interventions.

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58 Pathways to the Specialty Recognition of Addiction Medicine

Cornelis A. J. De Jong, David Crockford, Gabrielle Welle-Strand, Shelly Iskandar, Siddharth Sarkar, Paul S. Haber, and Michael Miller

Contents

C. A. J. De Jong (✉)
Radboud University, Nijmegen, The Netherlands

D. Crockford
Department of Psychiatry, University of Calgary, Calgary, AB, Canada
e-mail: david.crockford@albertahealthservices.ca

G. Welle-Strand
Norwegian Center of Addiction Research/Oslo University Hospital, Oslo, Norway
e-mail: gabwel@online.no

S. Iskandar
Psychiatric Department, Hasan Sadikin Hospital, Padjajaran University, Bandung, Indonesia

S. Sarkar
Department of Psychiatry and National Drug Dependence Treatment Center, All India Institute of Medical Sciences, New Delhi, India

P. S. Haber
Drug Health Services, Sydney Local Health District, The University of Sydney Central Clinical School, Sydney, NSW, Australia
e-mail: paul.haber@sydney.edu.au

M. Miller
Department of Psychiatry, University of Wisconsin, Madison, WI, USA
e-mail: michael.miller@uwmf.wisc.edu

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Abstract

In the first edition of the International Society of Addicted Medicine (ISAM) textbook, specialized ways of training from The Netherlands, Canada, Norway and Indonesia were presented. In this chapter, an update of the training in these countries is presented. Contributions from India, Australia and the United States are new.

Although there are, of course, differences based on local settings and prevalence of substance-related disorders, there is a more or less consensus on the content of the educational courses. All contributions illustrate that it is not that difficult to reach consensus on a national level. What makes them all different is the adaptation to local educational and licensing requirements that govern the national practice of medicine.

A preliminary conclusion is that the process towards an Addiction Medicine (AM) specialty is universally incremental and currently in transition, creating unique challenges in implementation but also opportunities for international group support and collaboration.

Keywords

Addiction Medicine (AM) · Addiction Psychiatry · Educational courses · SWOT analysis · Medical speciality development International survey · Undergraduate curricula in AM · Postgraduate addiction-oriented courses

58.1 Introduction

Substance use disorders (SUD) affect every medical practice. It is a recent development that medical doctors specialize in the field of Addiction Medicine (AM). In the section on Education and Training in the first edition of the ISAM textbook, specialized ways of training in The Netherlands [6], Canada [5], Norway [19] and Indonesia [4] were presented. At the end of the introduction of the section, it was concluded that the initiatives described were uniformly recent ones and are at various stages of development [8]. It was hoped for that the section could promote more international collaboration and support. Concerning the training in different countries, it was also concluded that there is no 'one size model fitting all'.

A review paper summarized scientific publications that outlined the content of Addiction Medicine curricula and evaluated the evidence for efficacy for training in Addiction Medicine. One of the conclusions was that Addiction Medicine should get the same priority as other chronic diseases do and that it must be integrated into the core of medical curricula of under- and postgraduate training of medical doctors.

An international consultation on training in Addiction Medicine led to a global core set of knowledge, skills and attitudes and recommendations for the under- and postgraduate training of medical doctors. The need to tailor a curriculum to national settings and different specialities was recognized [2]. The journey towards specialty recognition must also adapt to local educational and licensing requirements that govern the national practice of medicine.

In this chapter, we will present an update of the training in Norway, The Netherlands, Canada and Indonesia. Initiatives from India, Australia and the United States are new in the chapter.

Some countries have adopted a focus on primary care; others have a focus on specialties, including psychiatry, internal medicine and community health, and most are adopting a multiple approach. In most paragraphs, the strengths, weaknesses, opportunities and threats are described, sometimes as a special subparagraph. A preliminary conclusion is that the process towards an AM specialty is universally incremental and currently in transition, creating unique challenges in implementation but also opportunities for international group support and collaboration.

58.2 The Netherlands

Between 2000 and 2005, it became clear for the medical directors in the Addiction Treatment facilities in the Netherlands that the quality of Addiction Medicine (AM) was problematic. This was due to shortage of medical doctors interested in AM, medical doctors in the field without

proper training, low perspective for career and being faced with the fact that the best doctors leave to specialize as psychiatrists, internists, neurologists or general physicians (GPs). In just two years, we managed to start a full-time, two-year professional training in AM in the Netherlands. In 2012, AM was approved as a medical subspecialty by the Royal Dutch Society of Medicine. The development of the Dutch Master in Addiction Medicine (MiAM) was described in detail in 2013(7).

The aim of this section is to describe the present status of the Dutch MiAM, to present an evaluation of the seven groups of medical doctors that graduated and to describe the process of re-registration of the doctors who were enrolled in the register from the start. First, some words will be spent on addiction psychiatry.

Addiction is not a special area of attention in the training for psychiatrists, and addiction psychiatry is not yet a super-specialty in the Netherlands. There are two structured ways to learn more on addiction as a graduated psychiatrist. The Radboud Center of Social Sciences of the Radboud University offers a 10-day course on addiction psychiatry for psychiatrists, focusing on the increase of knowledge and skills in individual psychiatrists. Multidisciplinary In-Company courses in addiction psychiatry for psychiatrists, psychologists and nursing specialists, focusing on increasing the quality of the integral care of the mental health institute for psychiatric patients with a co-occurring substance-related disorder, are developed and implemented by the first author (CDJ).

In the competency-based MiAM, theoretical courses are integrated with learning in clinical practice under guidance of an experienced clinical teacher: a dual education paradigm. The theoretical courses consist of evidence-based medicine, communication and basic psychotherapeutic skills, neurobiology of addiction, Addiction Medicine, addiction and psychiatry, clinical leadership and public health. The seven main competencies are concretized in 31 Entrustable Professional Activities (EPAs). EPAs are the units of a professional practice that constitute what clinicians do as daily work (8). They are integrated in a personal education plan (PEP) and are evaluated by different ways of examining and with a focus on stimulating self-reflection.

From the start of the MiAM in 2007 till 2019, a total of 139 medical doctors in 7 batches started the course, 65 women (47%) and 74 men (53%) with a mean age of 41.7 (SD 8.8) in a range of 26–59. Not all were native Dutch medical doctors, 39 (28%) came to the Netherlands and integrated as medical professionals after graduating as doctors again in the Netherlands. Many of them were refugees. Overall, 104 did graduate (75%) and 35 terminated the course prematurely (25%). The reasons for ending the course prematurely vary: severe physical illnesses, psychiatric or personality disorders, burnout, conflicts with management or a supervisor, inappropriate learning attitude or a combination of these.

In recent years, addiction doctors have gained a place within the medical community. Since the start of MiAM, the addiction doctor has become more professional and can therefore be designated as a treatment coordinator within the institutions for mental healthcare and addiction care. The programme is highly condensed, and 2 years is not enough to fully cover all aspects of AM. Although most graduates continue working in the addiction treatment centres, some of them wanted more and started psychiatry training to combine their clinical work as a PhD candidate.

Until the start of the MiAM in 2007, most doctors only worked in the specialized field of care for patients with SUD. In 2019, they also worked in general psychiatry, and there are opportunities for primary care, emergency care, liaison psychiatry, pain clinics and so on.

One of the challenges is to reassess the competences listed with the updated Canadian Medical Education Directives for Specialists (CanMEDS) competencies (9) and, above all, to integrate the educational milestones into clinical practice to illustrate how the competence of an addiction doctor progresses during his career—the journey from beginner to master.

In 2019, almost 200 medical doctors were included in the register of the Dutch Medical Society. In 2016–2017, there were almost 100 job offers. With an output of graduated doctors of 20 per 2 years from the MiAM, these job offers will never be fulfilled. The situation for the future is

even worse because it is expected that almost 40% of the registered will end their career within 10 years.

Postgraduates are registered as addiction specialists and have to re-register every 5 years. In order to keep the registration, one needs to meet certain criteria, for instance, for at least 16 h a week for the duration of 5 years, they need to have worked in patient care, attended training workshops and symposia, and participated in peer training meetings. The Dutch Society of Addiction Medicine developed the content and process of the individual evaluation programme that starts in 2020. Every Addiction Medicine Specialist will have to present a personal education plan, which will be evaluated every 5 years by a review committee. For former students of the MiAM, this will merely be a continuation of personalized learning. The older and mostly the self-taught group of experienced doctors face a new approach of lifelong learning.

58.3 Canada

Canadian medical practice, particularly in acute care settings, has needed to rapidly evolve to the opioid crisis, growing stimulant problems and the legalization of cannabis nationally. Substance use problems are cited as the third most important in order of competence for newly practising primary care physicians, ahead of ischaemic heart disease and diabetes [13]. Relatively small numbers of clinicians skilled in AM have been previously tied to a lack of available training in Canada, but that appears to be changing [13]. A number of initiatives nationally are underway to promote best practices and validate the special knowledge, skills and practices required for the practice of AM.

Initially, Canadian physicians sought specialty recognition through Certification and Board Diplomas of the American and International Societies of Addiction Medicine, which would be subsequently recognized by the Canadian Society of Addiction Medicine [7]. The strength of this was that it was accessible through a practice-eligible route, requiring less investment by practising physicians. But, while certification could ensure a certain knowledge base in AM, it may not ensure competence to practice AM or meaningfully structure training.

As medical training in Canada has shifted to being competency-based training [9], AM training initiatives have followed suit. The two primary licensing Colleges in Canada, the College of Family Physicians of Canada (CFPC) for primary care physicians and the Royal College of Physicians and Surgeons of Canada (RCPSC) for specialists, each approved added competencies for AM in 2016. The CFPC awards a Certificate of Added Competence (CAC), and the RCPSC awards a diploma in an Area of Focused Competence (AFC). They have slightly different but complementary approaches.

The CAC in AM approved by the CFPC in 2018 aims to determine competence at the advanced skills level for primary care providers. The CFPC has developed 13 priority topics specific to AM with key features to each. The priority topics were developed by a nominal group using an individual survey, followed by group discussion and consensus, as well as from a larger national survey of family practitioners. The priority topics include: (1) clinical boundaries; (2) AM screening, assessment and triage; (3) treatment planning and continuing care; (4) management of intoxication and withdrawal; (5) harm reduction within the continuum of care; (6) pharmacology; (7) psychotherapeutic techniques; (8) concurrent mental health disorders; (9) medical comorbidities; (10) pain and addiction; (11) special populations; (12) advocacy; and (13) provider health resilience. Each priority topic has key features to further specify and define them. Competence is indicated by consistent demonstration of most of the key features across a good sample of priority topics. Initial CACs will be awarded to family physicians who have previously acquired competence deemed worthy of recognition through practice experience, successful completion of a residency training programme and/or continuing professional development, and demonstrated leadership in the domain of the CAC. Thereafter, CACs are to be awarded based on the credentials and docu-

mented evidence as judged by a peer review committee process. It has led to the development of 1-year fellowships for primary care physicians in AM across Canada at multiple training sites. The strength of the CAC process is in its flexibility and accessibility to current primary care practitioners, as well as new graduates, so it is expected that there will be significant uptake of CACs and extend the specialty recognition of AM for those in primary care.

The AFC in AM approved by the RCPSC in 2019 applies to all medical specialties, so the development of the training requirements has been more complicated than that for the CAC. For residency training programmes to have an AFC programme in AM, they have to be accredited by the RSPSC, which can take 1–2 years to meet their requirements. To receive an AFC diploma in AM, trainees must be certified in their entry route discipline, in order to be eligible to submit a Royal College competency portfolio in AM to the AFC Program Committee at the accredited programme. Competencies are described in the CanMEDS roles [10] where diplomats are expected to function as a competent specialist in AM capable of enhanced practice within the scope of their discipline. The competency portfolio addresses eight goals, each having multiple milestones with standards of assessment and specific supporting documents that are required to be signed off upon by their supervisor. The eight goals include the responsibility for: (1) evaluation of patients for substance use or addiction(s) in urgent and elective settings; (2) acute stabilization and management of patients with addiction; (3) comprehensive ongoing management for patients with addiction; (4) health promotion practices for patients with addiction; (5) engaging and supporting individuals within a patient's social network; (6) acting as a resource for other health providers; (7) advocacy for patients with addiction, for addiction treatment or for addiction prevention and (8) advancement of the discipline of AM through teaching and scholarly activity. The AFC requirements are quite stringent, so it may be challenging for specialty residency training programmes beyond those in very large urban centres to be able to establish AFC accredited programmes and attract residents or fellows who are willing to commit further training time beyond the 5 years they already require for their specialty. Those who do the training, however, will be highly skilled and potentially greater advocates for the future of AM. By the standards being applicable to all specialties, it may also facilitate greater cross-pollenization in AM across specialties.

Specialty recognition of AM in Canada continues to expand through practice-eligible routes and formal residency training programmes, with there now being CACs and AFC diplomas for primary care and specialists, respectively. If the AFC diplomas are embraced by medical specialists, this may set the stage for the development of formal sub-specialties in AM in the future.

58.4 Norway

The development of the specialty in Norway was described in detail in 2015 [19]. The specialty and interim regulations were approved by the Ministry of Health in 2014, and the first AM Specialist was approved in 2015.

58.4.1 The Specialty Regulations and Other Requirements to Become a Specialist in Addiction Medicine

The specialty regulations are as follows: 5 years of internship in accredited institutions is required of which 42 months of internship in AM, including 12 months in a detoxification department, 6 months in inpatient/residential treatment, 12 months in outpatient treatment and, for the last 12 months, a range of services can be chosen. Twelve months of internship should be in psychiatry and a minimum of 6 months of these in an acute ward. The last 6 months of internship can be in other relevant areas of medicine, including somatic wards, pharmacology, psychiatry or general practice.

In addition, the candidate must have 270 h of national coursework during the 5 years and at

least 70 h of hospital coursework a year. The candidate must receive individual clinical supervision of at least 1 h per week throughout the clinical training and also group-based supervision. Further, the candidate must receive at least 30 h of specialized supervision in a specific therapeutic method.

58.4.2 The Status in June 2019

Overall, 129 doctors have been accredited full specialists in AM after interim regulations. Additionally, more than 100 medical doctors are in training across the country to become full specialists in AM. It is expected that approximately 20 of these candidates will be accredited full specialists in AM after the Specialty regulations in 2019.

Teaching hospitals have been established in all regions and at all larger hospitals in Norway. A total of 20 hospitals/institutions have been accredited as teaching hospitals.

A national coursework has been established. All candidates entering the structured education in AM will take part in a 4-week compulsory coursework over 2 years, covering a wide range of essential knowledge needed to be a specialist in AM. The third group of candidates in this compulsory coursework will finish the 4 weeks in the autumn of 2019, and a fourth group will be started the same autumn. Other coursework that have been established are courses of cognitive therapy, psychodynamic therapy and group therapy; pharmacology; treatment of attention deficit hyperactivity disorder (ADHD) for substance-dependent patients; as well as clinical toxicology. The candidate is also expected to use an online self-study portal and can, in this way, achieve competence in specific teaching goals.

58.4.3 National Conference in Addiction Medicine

Each year, a national conference for AM specialists, candidates and other medical doctors with interest in AM is arranged by the Norwegian Association of Addiction Medicine in order to further develop the new specialty and focus on new development and research in the addiction field. This conference is also an important meeting place for the new specialty.

58.4.4 Strengths, Weaknesses, Opportunities and Threats Analysis

The strengths of the full specialty in AM in Norway are several. We have successfully established the full specialty with accredited specialists and teaching hospitals in all regions of the country. The new specialty means that patients with substance use problems will receive specialist evaluation and treatment from well-qualified doctors in AM. The requirements for AM specialists are the same as for any other specialty in medicine, giving AM specialists a similar status as other medical specialists. The recruitment to the new specialty is very good because the medical doctors now have a possibility to make a career in AM. This means that the medical doctors will stay in the addiction field to a far greater extent than previously.

A weakness regarding the AM specialty is that not all the hospitals have enough specialists yet. However, as long as the recruitment into the specialty is very good, this is a situation which will improve with more medical doctors being accredited as specialists. Another possible weakness is that there is too little emphasis on somatic diseases in the specialist requirements.

Addiction research in Norway has developed a lot during the last 10–15 years and many PhD diplomas have been acquired both by medical doctors, psychologists and other professionals. Doctors in AM have good possibilities to finish a PhD as part of their specialist education or in addition to their specialty. Another opportunity is that having an AM specialty makes it easier to cooperate with regard to both treatment and research with somatic and psychiatric specialists, regarding acknowledging the many patients with co-occurring substance use problems and somatic and psychiatric diseases.

The establishment of the AM specialty has been viewed as a threat by some of the other professionals in the addiction field. The treatment of substance use disorders in Norway is a multiprofessional area, where social workers, psychologist, nurses, medical doctors and other professions work. It will be up to the AM specialists to prove that better educated medical doctors will be an asset, not only for the patients but also for the other professionals in the addiction field.

58.4.5 Conclusion

The full medical specialty in AM is well established in Norway. So far, 129 specialists in AM have been accredited. More than 100 specialist candidates are in structured training all over Norway to become full specialists in AM. There are enough medical doctors who want to start the structured training in AM. More than 20 teaching hospitals/institutions in AM across the country have been accredited. The national coursework for the candidates has been established and is well functioning. A yearly conference for AM has been established as an important meeting place for the thriving and developing specialty. A lot of work over a long time by many pioneering medical doctors in the addiction field has led to the successful establishment of a full specialty in AM in Norway. The Norwegian Medical Association views the establishment of the AM specialty as a success, in terms of how fast the specialty has developed and how well the AM specialists and training of the new candidates is spread around the hospitals in Norway during such a limited time period.

58.5 Indonesia

The development of a National Training Program on AM in Indonesia was described earlier [4]. Here, we describe the progress for the under- and postgraduate training. First, we like to globally describe the undergraduate AM Training (AMT). In 2019, the Atma Jaya Catholic University is the only medical school that provides AMT in a 5-week elective block for fourth-year medical students at the final semester of the pre-clinical level. After following the block, the participant is expected to have (1) increased knowledge and understanding of the basics of substance use and addiction (epidemiology, neurobiology, psychology, clinical, socio-cultural and medicolegal aspects) skills; (2) developed clinical skills (screening, diagnosis, early treatment), addiction counselling and public education; and (3) expressed positive attitudes towards patients with substance use and addiction.

The academic staff (Astri Parawita Ayu, Isadora Gracia and Kevin Kristian) that contributes to the AM block is mainly from the department of psychiatry. Atma Jaya has been organizing the AM block since 2009, and several evaluations have been performed. The AMT block improved students' attitude towards patients with addiction and changed their perceptions of addiction. Further development is threatened by the fact that human resources in the school of medicine are scarce. In 2019, the dean had requested the AMT team to propose topics that can be embedded in the medical curriculum and distributed throughout the pre-clinical and clinical training. Such a request is an opportunity to develop AMT in Atma Jaya further. To answer the dean, the academic staff and five students are running a training need assessment [15] among medical doctors who work in all primary healthcare facilities in Jakarta. Hopefully, other universities can collaborate, and replication of such an assessment by other universities will make the results eligible at the national level.

The Indonesian Standard Competency for Medical Doctors states that a general practitioner (GP) has to be competent in making a clinical diagnosis for a substance use disorder and providing initial treatment and referring a patient. However, there is no national curriculum for medical doctors in Indonesia yet. Each university has to develop its own excellency in one to three topics. Atma Jaya University is one of the universities that has a focus on addiction in the form of an elective block.

In Universitas Padjadjaran (UNPAD), another academic university, the focus is more on

postgraduate programmes [4], and the Indonesian Short Course on Addiction Medicine (ISCAN) was developed in 2010 [14]. After 2012, two batches of this 6-month course were conducted on the weekends for postgraduate medical doctors from all over Indonesia.

The first batch consists of 25 participants, most of them were recommended by municipal health departments in West Java as the requirements to be funded by UNPAD. The second batch were 30 participants, all of them were recommended and supported by national narcotics boards. We had evaluation on satisfaction to the topics and lecturers (Likert scale from 1–10). The average was an 8 for topics and lecturers in the first and second batch. We also have pre- and post-test for every module. It showed good improvement on knowledge. In general, the participants stated that the programme has been done well. They enjoyed the programme, although they had to spend their weekend to attend. The training would improve if behavioural addictions could also be tackled during the course, and if more workshops were integrated to improve their skills.

In 2017, the Department of Psychiatry of Medical Faculty-Universitas Indonesia/Cipto Mangunkusumo Hospital had started a training programme of subspecialty in addiction psychiatry in collaboration with the Kurihama Medical and Addiction Center, Japan, and Flinders University, Australia. Psychiatrists who want to become a consultant in addiction can enrol in this 2-year programme. By the end of the training, participants are expected to achieve academic and professional competence related to addiction psychiatry. In 2019, four addiction psychiatrists have graduated from such training. The training programme consists of a range of topics concerning drugs and behavioural addictions and characteristic psychiatric comorbidities. Participants are obliged to follow clinical rotation at hospitals, community services, prisons and the national rehabilitation centre. The academic activities include webinar lectures, case presentations, and, by the end of the training, participants should submit a research report.

A standard curriculum is needed for medical doctors, nurses, psychologists and pharmacists to develop interprofessional education modules. Specific training programmes for each professional to gain knowledge and develop special skills in providing addiction services from a positive attitude towards patients with substance-related disorders. For residents in psychiatry, a 3-month stage in the addiction division is obligatory. The continuity and development of those programmes face a lot of obstacles due to the willingness and leadership of the stakeholders, including lecturers, resources and budget.

The problem with the development of addiction curriculum in Indonesia is because there is no strong intention from stakeholders to provide standard services [3]. Several focus group discussions with stakeholders showed that addiction problems are increasing, and it was regarded as very important to provide standard competence for healthcare providers' work in the addiction field. However, there are no collaborating efforts to make AM curricula in Indonesia a priority yet.

Small and separate programmes have been developed in collaboration with the International Consortium of Universities for Drug Demand Reduction (ICUDDR), the Colombo Plan and the U.S. Bureau of International Narcotics and Law Enforcement Affairs (INL). Indonesian universities can use the whole or a part of the curriculum developed by ICUDDR.

Universities also work together with the national and provincial narcotic board and local governments to provide a 2-day addiction training for primary healthcare doctors. The problem is that they only offer little knowledge, and the training does not really improve the doctors' skills. Furthermore, there is no continuation of the training, and the rapid changes in the role of the primary health doctor limit the effects of the training. In this respect, national addiction curricula and standard competencies are needed.

The development of AMT in Indonesia has several strengths. The foundation of AM has been made, starting from a previous project Integrated Management of Prevention and Control & Treatment of hiv/aids (IMPACT). There are some psychiatrists and lecturers who are interested in AM, and collaboration with addiction experts in Indonesia and abroad has been established. However, there is not yet a strong leader to bring together all AMT programmes, there is lack of

support and budget from stakeholders such as faculty and government, and there is too limited time allocated for the development of an addiction curriculum due to overburden of the academic staff.

Although it is quite hard to develop AMT properly, there are opportunities for the future that are hopeful. Professional organizations acknowledge the need to improve skills of healthcare providers working in the addition field. There are new leaders and governmental regulations supporting addiction treatment, including training of professionals working in AM. Several non-governmental organizations are funding the development of AM curricula.

In our opinion, strong leadership and willingness to collaborate nationally and internationally are the keys to develop sustainable national addiction curricula.

58.6 India

In India, training in addiction has been ingrained in the 3-year postgraduate psychiatry course. Selection for the course is held generally through nationally competitive entrance examinations for medical graduates. The means and mechanisms for implementation of addiction training vary from institution to institution. Typically, case-based teaching is carried out as a part of the general psychiatric evaluations and mentoring from faculty members. Some of the institutions have dedicated clinics or centres where the postgraduate trainees are posted during their rotations, which last from weeks to up to 6 months. Seminars, case conferences and didactic lectures are the methods through which theoretical aspects of addiction psychiatry are discussed during the postgraduate general psychiatry training. The emphases on the addiction-related topics vary, but they form a part of the overall teaching curricula for the psychiatric trainees. Assessment is generally case-based and through written summative assessments, wherein addiction psychiatry may be an overall part of the psychiatric syllabus. There is heterogeneity and substantial variation in the manner in which teaching-learning of addiction psychiatry is carried out in different centres.

Overseeing the training programmes, a need has been felt for development of super-specialty courses in addiction psychiatry, on similar lines as super-specialty training in cardiology and neurosurgery after broad-based postgraduate training in medicine or surgery, respectively. Thus, the Doctorate in Medicine Addiction Psychiatry course has been launched, the first of such courses being instituted about 5 years back. Currently, at least four centres in India are running this course: All India Institute of Medical Sciences, New Delhi; Postgraduate Institute of Medical Education and Research, Chandigarh; National Institute of Mental Health and Neurosciences, Bengaluru; and All India Institute of Medical Sciences, Rishikesh. This 3-year super-specialty course is open to medical graduates who have completed a 3-year postgraduate degree in psychiatry, and selection is done through nationally open competitive examinations. The aim is to develop addiction psychiatry specialists who have wide clinical and research experience, deep theoretical knowledge and who are attuned to national realities in healthcare. They would be expected to provide better care for patients suffering from addictions and provide input for policy matters when required, apart from advancing the science related to AM.

Currently, the curricula vary across the centres offering the super-specialty course. The institutes have their own curricular structure, posting schedules, teaching-learning methods and assessment strategies. The variability enables utilization of the strengths and resources of each of the centre (e.g. research focus, clinical focus or public health engagement). The trainees have to engage in research or complete a dissertation under the guidance of a faculty member. Graduates from the super-specialty course in addiction psychiatry have been recruited in different teaching and clinical institutions.

The All India Institute of Medical Sciences, New Delhi, started the course in 2016 January. There are about five positions per year (highest in the country till date). Trainees have exposure to inpatient and outpatient clinical care, including outreach methadone and buprenorphine dispensing and engagement in community services. They are trained in laboratory services and psychother-

apy for patients with addictions. Consultation liaison addiction psychiatry services help them see referrals from other departments and the interface of addiction and multiple medical illnesses. The institute has a system of structured formative assessments as well, through written examination and case discussion. The trainees partake in teaching of other postgraduate students and indulge in peer-teaching as well. Many of them have undertaken additional research pursuits and have volunteered their time for organizing Continuing Medical Education (CME) and conferences in addiction psychiatry.

The strengths of a super-specialty in addiction psychiatry include deep focus on the various aspects of addiction, the availability of dedicated and experienced professionals and presence of a comparable accreditation framework as other super-specialty disciplines. The weaknesses include lack of wider and specific demand from patients and prospective employers, variations in the conduct and emphasis of the course across centres and the lack of an association dedicated specifically towards addiction psychiatry. The opportunities presented are the cross-institution dialogue for exchange of curricula and students, regularization into annual meeting and conferences, utilization of the super-specialty trainees to impart supervision and teaching to medical students and interns, changes in summative and formative assessment methods to reduce subjectivity, and greater exposure from humanistic and legal perspectives of addiction. The threats include failure to develop proper referral mechanisms so that the patients are able to reach the super-specialists, and inability to expand the number of centres offering the course due to dynamically changing healthcare priorities.

The number of positions for such super-specialty doctors have been limited (less than 20 psychiatry specialists who have completed the course), which is paltry compared to the large population of India (over a billion and counting). The overall number of medical health professionals and psychiatrists are limited in the country, and such super-specialty courses are nascent and niche. Yet, the keen interest shown by trainees has been encouraging. We hope that with time, the graduates of this super-specialty course would be able to provide leadership in the field of addiction psychiatry, by expanding clinical care, training other medical graduates, conducting relevant and ethical research, providing policy directions and advocating for the cause of those who have been suffering from addictive disorders.

58.7 Australia

The training in AM in Australia was described in detail in 2011 [11] and 2013 [12]. The Australian Medical and Professional Society on Alcohol and other Drugs (AMPSAD) began in 1981 and developed a short training course, but this was undertaken by very few medical practitioners.

The Chapter of AM (AChAM) formed in December 2001 within the Royal Australasian College of Physicians (RACP) [16], and the Australian government recognized AM as a medical specialty in November 2009. RACP is the largest specialist college in Australasia mainly comprising specialists in the various branches of internal medicine. AChAM has adopted a well-established and widely accepted training scheme. Specialist reimbursement item numbers commenced operating in November 2010 and were upgraded to match those of other RACP specialists in 2016. The number of trainees has been slowly growing, but there is still a significant shortage of AM specialists.

The Royal Australian and New Zealand College of Psychiatry (RANZCP) [17] established the Section of Addiction Psychiatry, initially, as a special interest group without formal training. Addiction psychiatry is now a recognized subspecialty of psychiatry with about 150 members and requires 2 years of clinical training (RANZCP). It leads to the Certificate of Advanced Training in Addiction Psychiatry and includes a formal education programme, case history and clinical skills development described as Entrustable Professional Activities (EPAs). This training is well structured and requires assessment of written assignments but without examination. There is healthy interest in this programme from trainees and a growing clinical workforce.

There is a special-interest network for general practitioners (GPs) interested in drugs and alcohol. This is one of the 29 of networks with a specific interest. As a part of GP training, candidates can do extended skills posts for 6–12 months, and AM is one of the options. There are no specific training requirements beyond this. A number of GPs have proceeded to AM specialist training as described in the next section.

58.7.1 Addiction Medicine Training Programme

Advanced training in AM follows a modification of the general Postgraduate Physician Training, which comprises 3 years of basic training in internal medicine post internship, followed by 3 years of advanced training in the chosen field. There is a written examination early during the third year of training, and successful candidates proceed to a difficult clinical examination in general internal medicine later that year. Once the clinical examination is passed, trainees may enter advanced training in AM or another field. Assessment is by assignments and supervisor reports on clinical work, but there is no examination. A key difference for AM is that the RACP clinical examination is not required for AM training. However, the title Fellow of RACP (FRACP) is not awarded unless the clinical examination is passed. Specialist physicians with FRACP have broader internal medicine training and clinical privileges compared to AM specialists (FAChAM). Remuneration is now the same.

Basic physician training is one pathway for entry, but it is only adopted by a minority of current AM trainees. Entry via other clinical training is accepted and provides flexibility (RACP).

Advanced training extends for 3 years of supervised clinical postings and structured learning activities (RACP). Core training requires at least 18 months in a clinical AM position. Of the total, at least 12 months must be spent in an ambulatory (community) assessment and/or detoxification service, in opioid agonist prescribing. Six months is required in a consultation-liaison term in a general hospital, in an in-patient unit and in a pain clinic. These attachments may be part-time and undertaken concurrently. Experience in Psychiatry is also required as part of AM rotation and/or as a separate rotation.

The curriculum for AM covers the broad themes of clinical assessment and management of alcohol and other substance use disorders in a broad range of settings, including consultation liaison in hospitals and other health services; public health and prevention of alcohol and other drug use–related harms; regulatory issues; and medicolegal and forensic aspects of the practice. The curriculum is supported by a number of online training modules accessible to accredited trainees via the RACP website. There is a weekly national training symposium that can be accessed face to face or by webinar.

Trainees work in accredited clinical sites for clinical training. Site accreditation for the AM training programme is the responsibility of Chapter Education Committee (ChEC) to ensure:

- An appropriate level of supervision by Fellows of the Chapter with Supervisor training.
- Exposure to a wide range of clinical presentations.
- Opportunities and support for continuing education and research.
- Suitable infrastructure for training–equipment, clinical and educational resources, quarantined training time.

Trainees are encouraged to nominate a mentor separate from their supervisor.

58.7.2 Outcomes to Date

Informal feedback has highlighted several strengths of the programme. Trainees appreciate rotation through different treatment services with exposure to diverse models of care and supervisors. In particular, the breadth of AM practice incorporating behavioural medicine, physical health and mental health is appealing to trainees. The focus on self-directed adult learning has been welcomed. The online training modules are popular, with standardized teaching that is accessible at any time. The public health work-

book and the research project were considered valuable learning activities.

The number of trainees has been slowly growing and while there were 30 trainees active in 2019, the number remains insufficient to meet workforce demands. In particular, most trainees are in the most populous state (New South Wales) with very few in other states.

58.8 United States

Health professions' academicians, under the leadership of David Lewis, MD, now the Donald G. Millar Emeritus Professor of Alcohol and Addiction Studies at Brown University, created the Association for Medical Education and Research in Substance Abuse (AMERSA) in 1976, an interdisciplinary professional society of faculty members in professional schools of medicine, nursing, psychology, social work and other disciplines. AMERSA (www.amersa.org) has been the most consistent driver of improvement in the curricula of professional schools so that all graduates are more knowledgeable about addiction, addiction treatment and the health impacts of unhealthy substance use. Sadly, the goals of AMERSA in this regard remain unfulfilled, as the incorporation of content about addiction and recovery into the curricula of professional schools remains spotty.

The American Society of AM (ASAM), the largest professional association of physicians (and, since 2013, other professionals) devoted to improving addiction treatment quality and access (www.asam.org), has long had a committee on medical education, but ASAM's most prominent success has been in offering continuing education courses to persons already in practice. The ASAM Annual Conference and State of the Art Conference attract attendees from dozens of nations worldwide. ASAM also had a fellowship committee in the 1990s, which collected information about AM fellowship programmes in existence at academic medical centres and located in treatment programmes; none of these were accredited at that time by the Accreditation Council on Graduate Medical Education (ACGME) [1].

In 1993, the field of psychiatry took the lead in developing ACGME accredited training for physicians [18]. These fellowship programmes in addiction psychiatry were open to psychiatrists who had completed general psychiatry training. There are currently 49 accredited fellowships in addiction psychiatry. Most of these programmes would admit a non-psychiatrist into training, but such graduates would not be eligible for certification in the field. Completion of a fellowship by a psychiatrist could lead to certification by the American Board of Medical Specialties (ABMS) and its member board, the American Board of Psychiatry and Neurology, in addiction psychiatry; physicians from internal medicine, family medicine or other disciplines completing an addiction psychiatry fellowship were not able to secure any certification recognized by the ABMS.

In 2007, ASAM decided that a necessary step in securing ABMS recognition of AM would be to have physician certification conferred not by a membership society such as ASAM, but by a free-standing certification board. Thus, ASAM assisted in the creation of the American Board of Addiction Medicine (ABAM), which began offering the national certification examination in 2010. ABAM created a sister organization named The ABAM Foundation renamed The Addiction Medicine Foundation, or TAMF, and on January 1, 2019, renamed the American College of Academic Addiction Medicine, ACAAM, www.acaam.org. The mission of ABAM was to certify individual physicians, via an examination, in the specialty of AM, while the mission of TAMF was to accredit fellowship training programmes in AM. The ABAM Foundation developed educational objectives for training programmes and accreditation guidelines for training programmes, and it did its best to have its processes mirror those of the ACGME in establishing educational objectives and a core curriculum for graduate medical education (GME) programmes. By 2018, ACAAM oversaw the development of 52 fellowship programmes which met the rigorous accreditation standards it had set. Around the time that the American Board of Preventive Medicine (ABPM), one of the 24 member boards of the ABMS, developed an application to the ABMS Board of Directors (with the assistance of ABAM

Directors and staff), TAMF approached the ACGME about taking over the accreditation of AM Fellowships. The ABMS approved the application of the ABPM in 2015, and a certification programme for physicians in the subspecialty of AM was established by ABPM under the auspices of the ABMS. The first examination offered by the ABPM was in 2017. The first training programmes accredited by the ACGME in 2018 were sponsored by various primary residency programmes and 1 year in duration. The ACGME will have accredited 54 AM Fellowships by June 2019 (ACGME). These are sponsored largely by academic departments in academic medical centres: 13 in Department of Internal Medicine, 25 in Department of Family Medicine, 27 in Department of Psychiatry, 1 in Department of Paediatrics and none in Department of Obstetrics and Gynaecology. Thus, graduate medical education at the fellowship level in the subspecialty of AM is now on a par with fellowship training in other medical disciplines. Of the total 74 ACGME and ACAAM accredited fellowships, 2 are in Puerto Rico and 3 are in Canada.

Undergraduate Medical Education (medical school training) in addiction continues to be far less robust than the scope of the public health problem of addiction and unhealthy substance use. The existence of ACGME accredited training programmes has gotten the attention of Deans of Schools of Medicine, and there is growing advocacy to expand and improve the education of all physicians in this area. ASAM continues to be interested in improvement in medical school curricula in addiction. A separate group, the Coalition on Physician Education (COPE) in Substance Use Disorders (https://www.copenow.org/), was created in the wake of a Leadership Conference on Medical Education in Substance Abuse co-sponsored by the ABAM Foundation and the White House Office on National Drug Control Policy in 2008. COPE continues to advocate for curriculum development in medical schools in addiction.

Parallel to medical education in allopathic medicine leading to a Doctor of Medicine (MD) degree is the education of physicians in osteopathic medicine. The American Osteopathic Association (AOA) accredits osteopathic medical schools akin to the way the American Association of Medical Colleges accredits allopathic medical schools, and the AOA also accredits osteopathic residency programmes akin to the way the ACGME accredits residencies. The AOA also offers certification programmes for individuals holding a Doctor of Osteopathy (DO) degree, and there is a subspecialty society for osteopathic physicians, the American Academy of Osteopathic Addiction Medicine (AAOAM). The AOA does not accredit any fellowships in Addiction Medicine, but physicians with DO degrees may enrol in ACGME accredited fellowship programmes in AM.

58.9 Conclusion

In this chapter, examples of the development of Addiction Medicine as a (sub)specialty are described. If we compare the situation in the countries that were described in 2015 with the current state of affairs, it appears that considerable progress has been made. Furthermore, we have the impression that the content of the training courses is not very different between the seven countries. All over the world, professionals in AM seem to share the same ideas about addiction and patients with substance-related disorders. Of course, the training courses are adapted, for instance, to prevalence of the use of certain psychoactive substances and their related disorders. To teach AM, they all adopted a framework of competencies similar to CanMEDS, but we are aware of different educational methods.

In general, it is encouraging that in a few countries, there is an AM specialty. In others, individual professionals or professional communities in the field are working on the establishment of AM as a specialty. In some countries, the focus is more on increasing the quality and quantity of training programmes in Addiction Psychiatry. We can confirm the statement that there is not ‘one size that fits all’ [8].

If we look in more detail to the line of development in the seven countries described, we notice, however, significant differences. Concerning the development and implementation of Addiction Medicine, the strengths, weak-

Table 58.1 Strengths, weaknesses, opportunities and threats during the development and implementation of Addiction Medicine as a specialty in seven countries

	Strengths	Weaknesses	Opportunities	Threats
The Netherlands	Recognized as specialty by the medical community. Dual educational system. Gained a place in medical community	Short (2 years) educational course and therefore different from other specialties. Still a small group of specialists.	Re-registration process guarantees quality. Emphasizes the existence of a specific group of specialists Destigmatization of patients with SUD	A lot of job offers and 40% leaving AM within 10 years Discussions and conflicts with other medical specialists on whose territory patients should be treated
Canada	The initiatives to improve the quality of Addiction Medicine are widely supported by the medical community	AM still part of other specialties	Growing interest in AM in several other specialties and acknowledgement of the importance by licensing authorities	Few AM specialists outside of major urban centres
Norway	Better educated doctors mean better treatment for patients. Recognized as specialty by the medical community. The requirements for AM specialists are the same as for any other specialty in medicine	Too little emphasis on somatic diseases in the specialist requirements	Chances for scientific research in the field of AM	It is up to the AM specialists to prove that better educated medical doctors will be an asset to the addiction field
Indonesia	In universities, there is a growing interest in and implementation of undergraduate education in AM and postgraduate Addiction Psychiatry. Well-appreciated short training in AM	No progress in establishing AM as a specialty	Professional organizations acknowledge the need to improve skills of healthcare providers working in the addition field International collaboration on AM	No strong leadership yet to convince the government of the importance of AM for public health. Limited resources and budget
India	Training in addiction has been ingrained in the three-year postgraduate psychiatry course.	No initiatives for an AM specialty, heterogeneity and substantial variation in teaching–learning of addiction psychiatry.	Development of super-specialty courses in addiction psychiatry	Failure to develop proper referral mechanisms for patients to reach the super-specialists, and inability to expand the number of centres offering the course
Australia	Addiction psychiatry is a recognized subspecialty of psychiatry, including a formal education programme. Dual-education system for advanced training in AM	There is still a significant shortage of AM specialists	Well-evaluated advanced training in AM and healthy interest in the Addiction Psychiatry programme from trainees	Too few specialists in less populated areas
United States	Accredited fellowships in Addiction Psychiatry. Fellowship level in the subspecialty of AM is now on a par with fellowship training in other medical disciplines	Addiction and recovery into the curricula of professional schools remains spotty	Formal agreement on AM as subspecialty by the medical communities	Undergraduate Medical Education in addiction continues to be far less robust than the scope of the public health problem of addiction

nesses, opportunities and threats are summarized in Table 58.1.

Working on the development of AM and setting up an AM specialty can certainly lead to AM being recognized as a successful specialty, as is clear in the Netherlands and Norway. However, the journey is not always that simple or successful. In the United States, it took a long time to get approval to establish AM as a specialty, and in Australia, it is quite difficult to attract enough trainees to meet the need for sufficient AM specialists. However, there is a stimulating message for the AM field: it is possible to set up an AM specialty. Even if it is not possible, the endeavour will still help the medical community to realize and to recognize that addiction is a chronic disease and thereby contributes to the destigmatization of patients.

Nevertheless, there is still a lot of work to do. The connection between the undergraduate curricula in AM and the postgraduate development or addiction-oriented courses in the training of other specialists is still lacunar in most countries. This also means that young doctors are usually unaware that it can be very interesting and beneficial to work with this group of patients. In case of a well-established AM speciality, the duration of the training is sometimes too short, and the content is not always properly attuned to, for example, the comorbidity of patients with a substance-related disorder. In large countries such as Canada, Indonesia, India and Australia, in particular, it is difficult to establish sufficient AM specialists outside of major urban centres or to create good training places there.

Although professional organizations acknowledge the need to improve knowledge and skills of healthcare providers working in the addiction field, inspiring leadership from the AM community is needed to make efforts in the development of training and teaching that matter. We have the impression that in our era social media stimulates international group support and that this should be encouraged in every possible way.

The increased interest in addiction and training in Addiction Medicine also stimulates scientific research in that field. After the recognition of AM as a specialty, it forces professional organizations to develop standards for the re-registration of AM specialists.

Finally, the recent progress in the development in AM should be stimulating for professionals in countries that are working in the field of AM and are struggling to take further steps; there is hope!

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Kristiana Siste,
Department of Psychiatry, Medical Faculty, Universitas Indonesia/CiptoMangunkusumo Hospital
Astri P. Ayu,
Addiction Medicine Study Group | Department of Psychiatry and Behavioural Sciences | School of Medicine and Health Sciences Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia
India
Anju Dhawan,
Department of Psychiatry and National Drug Dependence Treatment Center, All India Institute of Medical Sciences, New Delhi, India
Australia
Dan Lubman,
Eastern Health Clinical School, Monash Addiction Research Centre, Monash University, Richmond Victoria, Australia
United States
Randall Brown,
Department of Family Medicine & Community Health, University of Wisconsin, United States

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59 International Society of Addiction Medicine's International Certification of Addiction Medicine: The First 15 Years

Nady el-Guebaly and Claudio Violato

Contents

Abstract

This chapter reviews 15 years of effort by the International Society of Addiction Medicine to develop a multiple-choice test of knowledge and clinical judgment in the field. The process of establishing a pool of questions as well as criteria for eligibility to challenge such an examination is described.

Lessons derived from the repeated administration of the exam are reviewed. An international examination is possible, involving questions with good psychometric properties. The challenges of striving for an "a-cultural examination" as well as the necessities of cost accessibility, security, and sensitivity are reported.

Keywords

Certification · Multiple choice · Performance levels · Core competencies

59.1 Introduction

In 1999, the International Society of Addiction Medicine (ISAM) came into being. Its mission was to promote an international agenda, including advancing the knowledge about addiction seen as a treatable disease, advocating for the major role physicians play in its management as well as enhancing the credibility of their role, and, last, developing educational kits accessible to an international audience.

N. el-Guebaly (✉)
Division of Addiction, Department of Psychiatry, University of Calgary, Calgary, AB, Canada
e-mail: nady.el-Guebaly@ahs.ca

C. Violato
University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: cviolato@umn.edu

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The need for improved medical education in the field is well recognized in both developed and developing countries and is detailed in other chapters of this textbook's section. The call for educating all physicians in playing their respective roles in the care of patients affected with the disorders of addiction has been made repeatedly [2, 3, 13]. An increasing number of generalists and specialist physicians are dedicating a major portion, if not all of their practice, to this significant public health issue. Enhancing their credibility and validating their practice through a formal process of certification became a goal of ISAM.

There is a growing international consensus about the core competencies required of every physician in treating abusing or addicted patients. They are screening, brief intervention, including motivational interviewing, and awareness of referral for treatment options, including mutual help. In the USA, these competencies are known by their acronym Screening, Brief Intervention, Referral to Treatment (SBIRT) [8]. By comparison, the boundaries of individual specialty competencies are understandably less defined. Based on core concepts from the basic sciences, evidence-based practices include, but are not limited to, prevention strategies; diagnosis, assessment, and early interventions; detoxification and craving; relapse prevention; psychotherapy, Cognitive Behavioral Therapy (CBT), 12-step, motivational enhancement, contingency management, and cue exposure; psychopharmacology, general and specific, including maintenance and medication interaction; physical and psychiatric concurrent disorders, primary or secondary disorders; ethical and legal issues around the workplace, including a physician's own impairment; chronic pain; forensic issues; cultural factors; age and gender issues; and behavioral addictions.

In the USA, the first medical association's certification examination in the field was held in 1983 by the California Society of Addiction Medicine, followed by the first national examination in 1986 under the auspices of the American Society of Addiction Medicine (ASAM). The American Academy of Addiction Psychiatry established the first subspecialty examination under the auspices of the American Boards in 1993. In 2009, the American Society of Addiction Medicine created an independent American Board of Addiction Medicine (ABAM), followed, in 2016, by admission to the American Boards as part of the American Board of Preventive Medicine (ABPN). Currently, those board certifications or diplomas are valid for 10 years. A commitment to maintenance of certification through documented lifelong learning and assessment of practice-based performance is also required. The criteria of eligibility for challenging these examinations limit the access to candidates mostly from within North America. Examples of other national efforts to validate the training of Addiction Medicine specialists are described in Chap. 59, Education: International Pathways.

59.2 The Certification Process

59.2.1 Chronological Development of an International Certification

Based on the US experience, in September 2003, in Amsterdam, the Board of the International Society of Addiction Medicine (ISAM) accepted to set up a valid and affordable international certification. An Editorial Board was formed composed of 10 senior clinician members of ISAM from 7 countries. An expert in medical education research, including examination psychometrics (C.V.), joined that Board.

ISAM initially recognized three English language multiauthored textbooks as a repository of current knowledge in the field through their successive editions [6, 11, 12]. The most current editions are Galanter, Kleber, and Brady 2015 [7] and Miller et al. 2018 [9]. These texts are backed by some 150 peer-reviewed journals in the field, ranging from basic science to clinical practice. An increasing number of research institutes are disseminating information across the world, including leading institutions such as, in the USA, the National Institute of Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism.

To meet the criterion of affordability as well as reducing the differential access to the literature in different parts of the world, the knowledge basis of the examination was originally based on a primary reliance on the Principles of Addiction Medicine [11]. Since then, further changes have occurred: the nomenclatures of Diagnostic and Statistical Manual of Mental Disorders (fifth ed.; DSM-5; [1]) and International Statistical Classification of Diseases and Related Health Problems, 11th Revision (ICD 11) [16]. Since 2015, the main reference for the ISAM Certification has become the Textbook of Addiction Treatment: International Perspectives [4].

From the onset as part of the drafting of multiple-choice questions, a concerted effort was made to select as many "culture-neutral" questions as possible. Half of the Editorial Board were holders of ASAM certificates and aware of the preponderance of research data based on US populations in the textbooks that would be of lesser significance in other continents. This meant that the epidemiological database had to shift to the data collected by international bodies such as the World Health Organization (WHO) and the United Nations Office on Drugs and Crime (UNODC). Another implication was the exclusion of questions about national legislation replaced by questions about the International Conventions. At the end, from an initial pool of 450 questions, 200 multiple choice questions (MCQs) were selected at a 2-day meeting in September 2004 in Calgary. It was recommended that four options for each MCQ were sufficient (25% chance per option instead of five with 20% chance). From the very onset, it was clearly stated that the certification would be a test of knowledge with some vignettes assessing clinical judgment. The number of questions allocated to each content area was debated at length. It was eventually agreed that the proportion of content questions would reflect the extent of coverage of the topic in the selected textbooks. A subsequent update of the exam questions in 2015, using the Textbook of Addiction Treatment: International Perspectives, similarly reflects the major content areas (see Table 59.1).

Table 59.1 List of certification examination content areas and questions (2016)

Content area	Number of questions
I. Basic sciences and clinical foundations	20
II. Screening and early interventions	30
III. Drugs of abuse and pharmacotherapies for substance use disorders	35
IV. Behavioral approaches	20
V. Social therapies, treatment settings and systems approach to addiction treatment	20
VI. Behavioral addictions and management applications	20
VII. Medical disorders, complications of alcohol and drugs, pain and addiction	28
VIII. Psychiatric comorbidity complications of alcohol and other drugs	27
IX. Children, adolescents, young adults, and special populations	25
Total	225

59.2.2 The Minimum Performance Level Method

To fulfill their mandate of protecting the public, licensure and certification boards in the health professions need to determine which candidates are qualified to attain certification (pass the examinations) or not (fail). Many of these organizations use criterion-referenced testing with predetermined cutoff scores for pass/fail on licensing or certification examinations. There are many ways to set such cutoff scores, but most rely on expert judgment, employing empirical approaches such as the Nedelsky [10] procedure, based on the principle of minimum performance levels (MPLs). Accordingly, we employed a modified Nedelsky procedure for setting cutoff scores using MPLs.

In this criterion-referenced testing procedure, the total test score MPL is the sum of each item MPL [15]. The item writer, therefore, sets an MPL for each item. The MPL is the value ranging between 0.25 and 1.0, which reflects the probability that even a minimally competent candidate can answer this item correctly. An MPL of

0.25 indicates a very difficult item with an MPL of 1.0 reflecting an easy one.

59.2.2.1 Example Item from an ISAM Examination

An added formulation of buprenorphine designed to discourage intravenous use contains? (stem)

(a) Gabapentin (distracter)
(b) Nalmefene (distracter)
(c) Acetylcysteine (distracter)
(d) *Naloxone (keyed response)

A = 1.0 b = 0.75 c = 0.75 d*
MPL = 1/(4 – sum of p) = 1/(4–2:50) = 0:67

Each question having undergone a thorough and rigorous editing process receives an MPL. The construction and psychometric analysis of the exam is under the auspices of faculty from the Cumming School of Medicine at the University of Calgary as well as the University of Minnesota Medical School.

To renew the pool from September 2006, 25 "dummy" or experimental questions were added for psychometric testing and formed the basis of new yearly questions. This is a common practice in the testing industry to identify questions performing well enough to be retained for future test takers. More recently, feedback from the examination applicants also inform the need to upgrade specific questions for the next exam sitting.

The current exam is in two parts with an allowed duration of 2 h and 15 min each.

59.2.3 Psychometric Analysis

59.2.3.1 Item Analysis

A complete analysis of the test requires an item analysis. There are three essential features that constitute an item analysis: (1) difficulty of the item, (2) item discrimination, and (3) distracter effectiveness [5].

The difficulty of the item is the percentage or proportion of people who got the item correct. Item discrimination has to do with the extent to which an item distinguishes or "discriminates" between high test scorers and low test scorers. Distracter effectiveness refers to the ability of distracters in attracting responses. A distracter that attracts no response is not effective; it begins to become effective when it attracts some responses.

59.2.3.2 Reliability and Validity

The reliability of scores is assessed using the coefficient α. Coefficient α estimates the amount of variability in applicants' scores that is due to the difference in ability rather than random influences such as guessing. In the initial series of applicants, the reliabilities of all subtests ranged from adequate to good. In an 8-year study (2011–2018) of the overall test and subtests, alpha has ranged from 0.68 to 0.87, adequate to good. Validity of a test has to do with extent to which it measures whatever it is supposed to measure. As very careful attention is given to the development of the appropriate sampling of the subject matter and content (i.e., addiction medicine) of the ISAM test, it has adequate content validity. Empirical evidence of validity is sought by evaluating the correlations between the subscales of the test. Over the 8-year study period, subscale correlations have ranged from 0.25 to 0.78, providing evidence of both discriminant and convergent validity [14].

59.2.4 Criteria of Eligibility and Applicants' Countries of Practice

To enhance access to the examination by an international audience, the following eligibility criteria were recommended:

- Graduation from a medical school recognized by the WHO
- Valid license to practice medicine from a licensing jurisdiction (national, regional)
- Good standing in medical community, evidenced by at least three letters of recommendation, from physicians knowing the applicant for at least 2 years, including, if possible, one current ISAM member

- Completion of a formal university-based 1-year fellowship or equivalent in the addiction field
- Documented substantial portion of medical practice including evidence of continuing education (conferences, workshops, courses, etc.) over a 3-year period in the addiction field

The above criteria seem to be within the reach of all applicants, and no noticeable impediment to access of the required information has been recorded.

Fee

An international money order payable to the International Society of Addiction Medicine for US$800 (non-ISAM members), US$700 (ISAM members), and US$725 US (Affiliate Societies' members) is forwarded, along with the application.

From 2005 to 2018 inclusive, the examination has been held 23 times. Practitioners from Canada, Egypt, and Saudi Arabia have formed the bulk of the applicants so far. Candidates from Antigua, Hong Kong, Iceland, India, Iran, Jordan, Kuwait, Oman, Sudan, Turkey, UAE, the UK, Ukraine, the USA, and Vietnam have also challenged the examination. The overall pass rate has been a steady 78% so far.

59.2.5 Lessons Learned

In North America, the Canadian Society of Addiction Medicine recognizes both ASAM and ISAM certificates as equivalent. These qualifications are readily recognized to designate experts in courts and with independent medical examinations (IMEs) for a host of insurance and other agencies.

In Egypt, the ISAM certification is recognized by the Ministry of Health as a professional qualifier. The universities have agreed to use the examination as an end of training knowledge qualifier followed by a clinical skills examination.

A dialogue is ongoing, in several countries in Europe, to use the certification as adjunct to local diplomas. Setting a valid and reliable examination is a time- and resource-intensive exercise, and from our experience, the process of testing core knowledge does not need to be duplicated in every country. Potential addition of questions of national interest to the core questions is a possibility.

As the ISAM certification enters its 15th year, a review of the experience leads to the following conclusions:

1. An international certification examination is possible! While the experience so far focuses on Canada and the Middle East, the process is slowly gaining credibility, judging from the inquiries from other regions. The examination is also available to international fellows training in North America's leading institutions. Local leadership support to disseminate information and promote the value of a clinical knowledge qualifier is critical.
2. The questions show good discriminatory performance. Following the first exam set of 200, 9 questions were dropped and new ones added from the pool, and 36 others had their MPL readjusted, "raising the bar." To renew the pool, 25 "dummy" questions were added to be tested in each examination. The first major editorial update was conducted in 2010, resulting in the replacement of one-third of the questions by new ones and another third being modified. Only the references of the remaining third were updated. A second update occurred in 2015–2016, with the inclusion of the new reference source, The Textbook of Addiction Treatment: International Perspectives. The third cycle of editorial update will begin in 2020, coinciding with the publication of the second edition of the Textbook of Addiction Treatment: International Perspectives.
3. The careful development of the ISAM test has resulted in evidence for both validity (content, empirical) and reliability (internal consistency), and items that are carefully reviewed and evaluated for difficulty, discrimination, and distracter effectiveness.
4. The recommended curriculum should inform examination and vice versa. Topics where

the candidates are the weakest included pain and addiction; behavioral addictions; and diagnosis, assessment, and early intervention. In several countries, the field of addiction is limited to the management of substance misuse. Addition of "local" questions to the core examination has been proposed to accommodate the local legislative and possible cultural needs.

5. An "a-cultural" examination may be only a goal to strive for. Biological or laboratory tests may be largely culture-free, although epigenetic findings are showing a number of ethnic differences. Epidemiological data, psychological treatments, mutual help resources, and workplace guidelines are more influenced by the local culture. Many countries forbid the use of methadone maintenance, for example. Can a core examination be fair globally when the medical practices are subject to different cultural and economic constraints? Candidates appreciate the need to be aware of evidence-based treatment options available in other parts of the world and may promote their culturally sensitive adaptation in their own country.
6. The cost, integrity, and sensitivity of the examination are critical in all areas of the world but particularly in developing countries. Requests have been made to create a network of examination centers where the certification could be disseminated electronically. While this remains under consideration, there remains concerns about test security as well as a sustainable critical mass of applicants.
7. We have moved from a reliance on national textbooks to an internationally collaborated textbook, which is available in electronic version.
8. Each successful candidate receives a numbered certificate to avoid forgery. Displays of association membership certificates in practitioners' offices as evidence of competence have been reported. This increases the need for a recognized certificate, testing clinical knowledge through MCQs, and clinical vignettes.
9. The repeated experience of the examination in developing countries is that the pool of often university-based candidates readily achieves pass and higher scores. This pool is however finite. This observation calls for enhanced national efforts to increase the pool of justified candidates practicing evidence-based medicine across the nation.
10. Presenting standardized review courses and complementing the test of clinical knowledge with a standardized objective structural clinical exam (OSCE), administered locally, is the next frontier.

There is no doubt that language proficiency can be a barrier. Discussions have been underway to translate the examination into Spanish and Italian. Settings where a computerized version of the examination can be administered are being contemplated. The security of this process may be improving. The cost remains significant. The search for funding support is ongoing. Several examination sets are being administered by different academic institutions worldwide; must we reinvent the wheel time and time again?

Key Points

- An international examination is possible, involving questions with good psychometric properties.
- The eligibility criteria appear to be within reach of many countries with some English proficiency.
- The examination sections address a broad-based addiction medicine practice.
- The certification is a test of knowledge with some vignettes addressing clinical judgment.
- The ISAM Certification can be a useful adjunct to local diplomas.
- Cultural adaptation can be facilitated through evidence-based treatment options in the examination.

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National Institute on Drug Abuse International Fellowships: Research Training for Addiction Specialists

60

Steven W. Gust

Contents

Abstract

Despite the widespread prevalence and increasing risk of disability or death associated with drug use disorders, access to evidence-based treatment is rare. The United Nations estimates that only one in six people who need drug treatment receive it, and cites the lack of research and training as barriers to expanding evidence-based treatment. Professional associations in the United States and the United Kingdom call for mentored research training to help health care professionals learn how to conduct research and understand and implement research findings in practice. Recent evaluations of research training programs found that physicians, service planners, and policymakers benefitted from mentored research training. Effective mentoring programs helped trainees conduct research, analyze data, publish findings, present at scientific meetings, collaborate with senior researchers, meet government officials, and continue networking after the conclusion of the fellowship. These components of effective research training programs are available through fellowships offered by the National Institute on Drug Abuse (NIDA) International Program. The NIDA fellowships for postdoctoral, mid-career, and senior addiction specialists are reviewed, including credential and citizenship requirements for applicants, and professional advantages are described. Former fellows head academic research centers and

S. W. Gust (✉)
International Program, National Institute on Drug Abuse, National Institutes of Health, US Department of Health and Human Services, Washington, DC, USA
e-mail: ipdirector@nida.nih.gov

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nongovernmental organizations, provide addiction treatment, serve as government officials, and play key roles in international drug policy. NIDA fellows collaborate with international partners, receive grants from NIDA and other funders, publish articles, and present at conferences. They form a global network of drug abuse scientists working collaboratively to develop, validate, and implement evidence-based treatment and prevention programs around the world.

Keywords

NIDA International · Addiction Research · Drug Abuse Fellowships

60.1 Introduction

Training an international cohort of health care professionals to research and treat drug use disorders is an increasingly urgent priority. The United Nations Office on Drugs and Crime (UNODC) estimated that 275 million people aged 16–64 used drugs in 2016 [1]. Of those individuals, 31 million were diagnosed with a substance use disorder. In 2015, drug use was associated with 450,000 deaths, an increase of 60% since 2000 [1]. The Global Burden of Disease research team reported that 31.8 million disability-adjusted life years (DALYs) in 2016 were attributable to drug use as a risk factor [2]. In 2017, drug use disorders were ranked 21 among the top sources of DALYs for men, an increase of 26.6% since 2007 [3]. Foreman and colleagues predict that by 2040, drug use disorders will be among the top 10 causes of years of life lost in Australasia, Eastern Europe, and high-income North America [4].

Despite the widespread prevalence and growing risk of disability or death associated with drug use disorders, access to evidence-based treatment remains limited. UNODC reports that only one in six individuals who need drug treatment have access to treatment services [1]. Barriers to evidence-based drug treatment include a lack of research, particularly in real-world health care settings, and a shortage of health care professionals trained in public health and medical models of drug treatment [5].

In the United States, the American Board of Medical Specialties formally recognized Addiction Medicine as a subspecialty in March 2016. Decades earlier, National Consensus Standards on postgraduate medical fellowship training in alcoholism and drug abuse called for a "meaningful, supervised research experience" ([6], p., 6). The Consensus Standard priorities included learning about research methods and how to design and interpret research studies. Conducting an independent research project was "desirable" ([6], p., 10). In 2018, the Association for Multidisciplinary Education and Research in Substance Use and Addiction (AMERSA) revised its standards for health care professional training. AMERSA recommends that physicians, nurses, pharmacists, social workers, and physician assistants who assess and treat patients who use alcohol and drugs should learn how to understand and implement research findings in treatment and participate in interdisciplinary activities, including research [7]. The United Kingdom General Medical Council essential capabilities for postgraduate medical curricula include "Research and Scholarship" among nine domains. The 2017 document describes requirements that doctors-in-training understand research methods and principles, learn to interpret public health epidemiology findings, and know how to translate research into practice [8].

Medical students who participate in mentored research programs develop positive opinions about both clinical care and academic research in substance abuse [9, 10]. Recent evaluations of research training programs conducted in both low- and high-income countries found that mentored research programs influenced fellows' research careers and success. This was especially true of programs that helped trainees develop and publish their own research and provided long-term networking after the conclusion of the fellowship [11–17]. For fellowships that focused on trainees from low-income countries, mentored research that prepared individuals for independent careers was enhanced by international col-

laboration with senior researchers, participation in workshops and scientific meetings, guidance in data analysis and scientific writing, and visits to the US National Institutes of Health (NIH) [18–20]. Treatment providers, service planners, and policymakers from low- and middle-income countries also benefitted from research training programs [14, 21].

60.2 Fellowships Supported by the National Institute on Drug Abuse International Program

Since 1990, the NIDA International Program has developed drug abuse research fellowships to facilitate an international network of scientists trained to investigate the causes, prevention, treatment, and consequences of drug use and addiction. NIDA's global network now includes scientists and drug abuse professionals from more than 110 countries who have completed more than 500 fellowships. Fellows work with NIDA grantees at US institutions and have conducted research in every aspect of the NIDA portfolio, including preclinical research and studies in epidemiology, prevention, treatment, and clinical trials.

NIDA currently supports four postdoctoral fellowship programs, a fellowship for mid-career drug abuse professionals from eligible low- and middle-income countries, and two professional development programs for senior scientists. NIDA International fellowship programs train substance use researchers from other countries in US research methods, help fellows enhance their understanding of the scientific basis of drug use and addiction, and promote research collaboration by introducing NIDA grantees to talented drug use researchers from other countries. The seven fellowship and scientific exchange programs expand the Institute's ability to build networks, mentor junior investigators, conduct needs assessments, and transfer knowledge. Table 60.1 summarizes the fellowship career levels, activities, eligibility requirements, and application deadlines. Additional details are available on the NIDA International Program website: https://www.drugabuse.gov/international/fellowships-landing.

The four INVEST fellowships combine postdoctoral research training in the United States with professional development activities such as preparing publications, poster or oral presentations at scientific meetings, and grant-writing guidance. The program is designed to enhance the ability of junior drug use scientists from other countries to conduct independent research upon return to their home country. Three fellowships are open to applicants from any other country—the INVEST Drug Abuse Research Fellowships, INVEST/Clinical Trials Network (CTN) Drug Abuse Research Fellowships, and the INVEST Drug Abuse Prevention Research Fellowship. The INVEST NIDA–Inserm Postdoctoral Drug Abuse Research Fellowship is restricted to US and French scientists, with US researchers working at Inserm laboratories in France and French researchers working with NIDA grantees in the United States. All fellows are invited to present their research at an appropriate scientific meeting, such as the NIDA International Forum satellite to the College on Problems of Drug Dependence, and meetings sponsored by the Society for Prevention Research or the Society for Neuroscience.

The NIDA Hubert H. Humphrey Drug Abuse Research Fellowships bring fellows from eligible low- and middle-income countries to study and work with colleagues in the United States. NIDA Humphrey Fellowships are part of a larger program coordinated by the US Department of State that provides mid-career experts with advanced leadership training that includes academic, practical, and cultural activities in the United States. NIDA Humphrey Fellows also receive training in addiction science and public health through specialized coursework, professional affiliations with US substance abuse experts, visits to NIH, and participation in the NIDA International Forum. The fellowships are particularly appropriate for treatment providers and policymakers who need to understand the science of addiction in order to adopt evidence-based treatment practice guidelines and government policies.

Table 60.1 NIDA International Program training opportunities for US and international scientists

Career level	Program name	Eligible audience	What fellowship includes	Application deadline
Postdoctoral training	INVEST Drug Abuse Research Fellowship	Non-US citizens, any topic	12-month training and professional development with a NIDA grantee at a US institution. May apply to renew once.	October 1
	INVEST/Clinical Trials Network (CTN) Drug Abuse Research Fellowship	Non-US citizens, topic of interest to CTN	12-month training and professional development with a NIDA grantee affiliated with a CTN Node at a US institution. May apply to renew once.	October 1
	INVEST Prevention Drug Abuse Research Fellowship	Non-US citizens or permanent residents conducting prevention research	12-month training and professional development with a NIDA-supported prevention researcher at a US institution. May apply to renew once.	October 1
	INVEST NIDA–Inserm Postdoctoral Drug Abuse Research Fellowship	French citizens work with a NIDA grantee at a US institution US citizens work at an Inserm lab in France	6- to 12-month training and professional development. May apply to renew once.	Applications may be submitted at any time
Mid-career training	NIDA Hubert H. Humphrey Drug Abuse Research Fellowship	US State Department identifies eligible countries and reviews applications	10-month academic study and professional development activities	Deadlines vary Apply through US Embassy or Fulbright Commission in eligible countries
Senior researcher exchanges	Distinguished International Scientist Collaboration Award (DISCA) and USDISCA	DISCA: Non-US citizens visit NIDA grantees in US USDISCA: US citizens and permanent residents visit research partners in other countries	Research exchange visits of at least 1 month to finalize a specific task that could not be completed without face-to-face consultation	December 1

The competitive Distinguished International Scientist Collaboration Awards (DISCA) and the companion Distinguished International Scientist Collaboration Awards for US Citizens and Permanent Residents (USDISCA) programs support brief research exchange visits between senior researchers from other countries and NIDA grantees. The research team must propose a specific task that could not be completed without face-to-face consultation.

60.3 Professional Advantages of the National Institute on Drug Abuse International Program Fellowships

Former NIDA International Program Fellows advance scientific knowledge on drug use and addiction through their research and professional careers. Former fellows head academic research centers and nongovernmental organizations,

provide addiction treatment, serve as government officials, and play key roles in international drug policy through international organizations such as the Colombo Plan Drug Advisory Programme, European Union, Inter-American Drug Abuse Control Commission (CICAD) at the Organization of American States, United Nations, and the World Health Organization (WHO). For example, former NIDA International Program fellows played key roles in developing WHO and UNODC guidelines for substance use treatment and prevention, pharmacological and psychosocial approaches to treating opioid dependence, community efforts to address opioid overdose, treating substance use disorders in pregnant women and people involved in the criminal justice system, and the effects of nonmedical cannabis use. Former NIDA Fellows also contributed to the joint European Monitoring Centre for Drugs and Drug Addiction/Organization of American States handbook on building a national drug observatory, and have led the Drug Advisory Programme at the Colombo Plan.

Fellows conduct and publish peer-reviewed research. An analysis of fellows' publications during 2016 and 2017 identified 561 unique articles published in peer-reviewed publications indexed by the NIH PubMed database. More than half (52.4%) of former NIDA International Program postdoctoral fellows and more than one-fourth (25.8%) of all former fellows published articles during that time frame [22].

An evaluation of the Virginia Commonwealth University host campus for the NIDA Humphrey Fellowship program found that former fellows reported collaborating with international partners, receiving grants, publishing articles, presenting at conferences, and obtaining new credentials since completing their fellowships. Of the 108 former fellows from 52 countries, 34.7% had collaborated with a US partner, 24.3% had collaborated with other former fellows, and 19% had received grant support. Nearly one-third (30%) had published a manuscript, 49% had presented at a conference, and 46% had conducted research. About one-fourth had received a license or certification (26%), and 21% had enrolled in an academic program since completing their fellowship [23].

The NIDA International Program helps fellows build on their research training through the annual NIDA International Forum. About 200 researchers participate, nearly half from the United States and other high-income countries. Former fellows and other participants make oral or poster presentations, network with former mentors and other fellows, and establish new research partnerships. Between 2012 and 2017, more than 30 NIDA grants were associated with the Forum; the foreign principal investigator on 23 of those grants was a former NIDA International Program fellow [22].

60.4 The Way Forward

Although the NIDA International Program fellowships are unique, a few other NIH research training programs are available for addiction specialists who are not US citizens or permanent residents. The Visiting Program supports NIDA Intramural Research Program (IRP) fellowships for non-US postdoctoral researchers and temporary full-time research positions for international scientists. NIDA IRP also offers limited predoctoral research opportunities for international students. The NIDA IRP training opportunities are online at https://irp.drugabuse.gov/training/. Information about other NIH Institutes that participate in the NIH Visiting Program is available at https://www.ors.od.nih.gov/pes/dis/VisitingScientists/Pages/default.aspx. The NIH Fogarty International Center (https://fic.nih.gov) supports a number of training programs for scientists and clinicians from low- and middle-income countries, and NIDA participates in the Fogarty D43 institutional training grant for Chronic, Non-Communicable Diseases and Disorders Across the Lifespan.

NIDA promotes international collaborative research through a dedicated funding opportunity (PA-18-773, International Collaborative Research on Drug Abuse and Addiction Research) that requires a partnership between a US scientist and their partners in another country. Many other NIH funding opportunities are open to participation by non-US researchers. Each funding opportunity announcement includes an eligibility

section that will specify what types of foreign participation are permitted for that announcement. Currently, about 8% of the NIDA research portfolio is allocated for international research, primarily through grants to US domestic organizations with foreign partners. All international research must meet special requirements, such as providing access to unusual talent, resources, populations, or environmental conditions not available domestically, demonstrating how the international research will significantly advance US health sciences, and documenting relevance to the NIDA mission.

NIDA works closely with international organizations devoted to improving drug addiction research and treatment, such as CICAD, Colombo Plan, European Monitoring Centre for Drugs and Drug Addiction, International Consortium of Universities for Drug Demand Reduction (ICUDDR), International Society of Substance Use Professionals, UNODC, and WHO. Most of these training programs are designed for the global health care workforce, but few offer mentored research training. ICUDDR members are developing undergraduate, graduate, and postdoctoral training programs within their own universities, and international research training opportunities will expand as these programs mature.

60.5 Conclusions

The need for evidence-based drug use and addiction treatment is increasing, along with the need for addiction specialists who understand the principles of research and know how to implement findings into practice. Organizations such as AMERSA and the UK General Medical Council call research training essential for qualified addiction specialists. Practitioners who participate in effective research training programs report improved job satisfaction and professional success in both clinical and research careers. Effective research training programs include components such as conducting research, analyzing data, publishing findings, presenting at scientific meetings, collaborating with senior researchers, meeting government officials, and networking after the conclusion of the fellowship. Since their creation in 1990, the NIDA International Program drug abuse research fellowships have provided effective mentoring and networking for addiction specialists from other countries. The NIDA fellows' successful clinical and research careers document the professional advantages mentored research training can offer.

NIDA will continue to support its international drug abuse research fellowships, adapting and expanding the program as funding permits to meet the growing demand for mentored addiction research opportunities. The current NIDA–Inserm fellowship provides a model for addiction research training partnerships with similar institutions in other countries: NIDA supports French researchers who train in the United States, and Inserm supports US researchers who train in France. We invite current and new partners interested in addiction research training to join NIDA in meeting this critical need.

Key Points

- Professional associations such as the American Board of Medical Specialties and credentialing bodies such as the UK General Medical Council recommend research training to help addiction specialists evaluate and implement research findings in practice.
- Since 1990, NIDA has supported more than 500 research training fellowships for postdoctoral researchers, mid-career professionals, and senior scientists from 110 countries.
- These NIDA International Fellowships include components proven to be effective, such as conducting research, analyzing data, publishing findings, presenting at scientific meetings, collaborating with senior researchers, meeting government officials, and networking after the conclusion of the fellowship.

- NIDA International Fellowships contribute to former Fellows' successful careers and advance scientific knowledge about drug abuse:
  - Former fellows head academic research centers and nongovernmental organizations, provide addiction treatment, serve as government officials, and play key roles in international drug policy through roles at international organizations.
  - Between 2012 and 2017, more than 30 NIDA grants were associated with the NIDA International Forum; the foreign principal investigator on 23 of those grants was a former NIDA International Program fellow.
  - In 2016–2017, former NIDA fellows published 521 unique research articles indexed by PubMed.

Clinical Relevance

Clinicians are better prepared to adopt evidence-based treatments if they have research experience and can integrate published research findings into practice.

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Undergraduate Medical Training in Substance Misuse

61

Ilana B. Crome and Christine M. Goodair

Contents

Abstract

Whilst addiction psychiatry is a recognised subspecialty in the UK, research into UK medical schools during the 1990s showed very low levels of exposure of future doctors to teaching on drug and alcohol misuse issues. Substance misuse is prevalent in almost all branches of medicine. As a result, there are extensive opportunities to teach and learn about it. However, this also leads to the risk that the topic may be fragmented, poorly coordinated and spread too thinly, so that it is often ultimately barely visible to students. In the UK, a 'Substance Misuse in the Undergraduate Medical Curriculum Project' was funded with the aim of improving the teaching of substance misuse to medical undergraduates so as to enhance medical education in addictions and improve treatment services in the future.

I. B. Crome
Keele University, Staffordshire, UK

St George's, University of London, London, UK

C. M. Goodair (✉)
Population Health Research Institute, St George's, University of London, London, UK
e-mail: cgoodair@sgul.ac.uk

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61.1 Introduction

This chapter focuses on the need for training and education on substance-related disorders for undergraduate medical students and describes initiatives undertaken in the UK. It provides a brief historical and contextual introduction, describes work undertaken and explores issues of sustainability within a constant changing health landscape.

61.2 Historical and Contextual

Substance misuse has been a national and international public health challenge for many years. The use and misuse of alcohol, drugs (licit and illicit), prescribed and over-the-counter medications, and tobacco impacts individual patients, their families and communities. Doctors and other health professionals across all medical specialities are highly likely to encounter individuals with substance-related health problems, given the extent of these problems. All health professionals have a key role in improving not only the health of their individual patients but also the nation's public health. This was recognised by both the World Health Organization [25] and the United Nations [18, 19] who have recommended to governments that substance misuse should be included in medical teaching.

UK statistics show that, in 2016, there were estimated to be 77,900 deaths attributable to smoking amongst adults aged 35 and over based on the original cause of death. Hospital admissions estimated to be attributable to

smoking indicates that 22% of all admissions were for respiratory diseases, 15% for circulatory diseases and 9% for cancers. Of the admissions for cancers, 47% were caused by smoking, with 40% of admissions for respiratory diseases that can be caused by smoking, were estimated to be attributable to smoking [20, 21]. The total cost to society (in England) is approximately £12.9 billion a year and includes the cost to the NHS of treating diseases caused by smoking and lost productivity due to premature deaths, smoking breaks and absenteeism [1].

In 2017–2018, there were 338,000 estimated admissions to hospitals that were attributable to alcohol, and, in England, in 2017, there were 5,843 alcohol-specific deaths with alcoholic liver disease accounting for 80% of the deaths, and 9% were from mental and behavioural disorders due to the use of alcohol [23]. Alcohol is estimated to cost the NHS around £3.5 billion per year [14].

About 3 million adults aged 16–59 in England and Wales in 2017–2018 had used illicit drugs, with Class A drug use (typically opioids and cocaine) increasing since 2011–2012. In 2017–2018, there were 7258 hospital admissions for drug-related mental and behavioural disorders, and 2503 deaths were related to poisoning by drug misuse. In the same period, 268,390 individuals were in contact with drug and alcohol services during 2017–2018 with those in treatment for opiate dependence making up the largest proportion of the total numbers in treatment (53% or 141,189) [20–22].

In 2014, the National Treatment Agency estimated that the overall annual cost of drug misuse was around £15.4 billion. A total of £13.9 billion was due to drug-related crime, while around £0.5 billion was NHS costs for treating drug misuse [2].

Research, including surveys into the undergraduate medical UK curricula between the late 1980s and 2004, found that substance misuse was generally very poorly represented in the training of future doctors, and the number of hours allocated to formal teaching about substance misuse was small. It was taught mainly within the disciplines of psychiatry and pharmacology, thus reinforcing the false notion that substance misuse is a niche specialty topic [3, 4, 7, 12]. Whilst it was found that there were numerous initiatives in North America, some establishing a core curriculum and others developing teaching and learning

innovations, very little innovation was taking place in the UK. The lessons were clear: substance misuse has to be integrated into the curriculum of medical students, and it has to be a topic introduced from the very beginning of the course—not least for students' own health and professional behaviour.

Previous initiatives undertaken by St George's, University of London, and the World Health Organization (WHO) on substance misuse education for doctors, pharmacists and nurses resulted in the WHO recommending to governments that substance misuse should be included in the medical curricula [6, 11, 25].

Proposals were submitted to the Department of Health to develop a consensus approach to the enhancement of substance misuse training in medical and nursing schools in the UK. Funding was awarded in 2005 to improve the education of doctors in substance misuse and to develop a consensus approach to substance misuse training in medical schools, and a national project, 'Substance Misuse in the Undergraduate Curriculum', was established and led by Professor Hamid Ghodse, Director of the then International Centre for Drug Policy at St George's Medical School.

61.3 Description of the Project

This project has comprised three phases. In Phase 1, during 2005–2007, a UK corporate guidance document was developed that set out core aims and learning outcomes for substance misuse teaching and learning in the undergraduate medical curricula. Phase 2, during 2008–2011, focused on implementing the guidance through the appointment of curriculum coordinators in English medical schools to identify what substance misuse teaching was being undertaken, and to recommend changes to ensure that substance misuse issues were fully covered. Phase 3, from 2012 onwards, concentrated on developing and extensively revising a set of factsheets, initially written in Phase 2, and which covered substance misuse relevant to a range of clinical conditions, groups of patients, specialities and settings.

61.3.1 Phase 1

Building on the research done in the late 1980s and 1990s, during Phase 1, the project further reviewed the ways in which substance misuse problems was being taught in all UK medical schools [3, 6, 7, 12, 13]. It sought to establish the reasons for ineffectiveness and to make proposals for improvement in medical schools throughout the country. The project aimed to understand the reasons why medical education was not preparing doctors appropriately in this respect; to identify initiatives that different medical schools could take to improve matters; and make recommendations for further action.

A survey was undertaken in 2005 which provided an overview of the state of substance misuse education in all UK medical schools. The aim of the survey was to gather information about substance misuse teaching and learning, including strategies medical schools used for embedding the topic in the curriculum, and to collect examples of good quality learning materials. Responses were obtained from each of the 32 UK medical schools.

The survey findings included the following:

- There was no commonality of approach in what was taught about substance misuse: learning outcomes differed hugely in style, level of detail and emphasis.
- Many schools covered a lot about alcohol, but relatively few covered teaching about drugs—with this aspect frequently being left to psychiatrists only.
- Only two schools planned and coordinated their substance misuse curriculum as a whole. Mostly, the teaching was concentrated in the specialty niches.
- Assessment of substance misuse within curricula was rarely planned. As 'blueprinting' against curriculum outcomes was being increasingly introduced, more formal planning in this area was expected.
- About half the schools had some provision of optional learning about substance misuse through 'student-selected components' (SSCs).

The main outcome of Phase 1 of the project was the production of a UK-wide consensus guidance document on substance misuse in the undergraduate medical curriculum and agreed by all medical schools. The document, 'Substance misuse in the undergraduate medical curriculum' set out core aims and learning outcomes for undergraduate curricula [15].

This guidance document, endorsed by the Chief Medical Officer (England) and the General Medical Council, was a milestone in medical education on substance misuse, setting out three core aims for undergraduate medical education in substance misuse that are still relevant today.

1. Students should be able to recognise, assess and understand the management of substance misuse and associated health and social problems, and contribute to the prevention of addiction.
2. Students should be aware of the effects of substance misuse on their own behaviour and health and on their professional practice and conduct.
3. Students' education and training should challenge the stigma and discrimination that are often experienced by people with addiction problems.

61.4 Substance Misuse Core Curriculum Aims and Learning Outcomes

It is acknowledged that one of the difficulties in mapping and tracking the teaching of substance misuse is that topics associated with substance misuse permeate the whole curriculum and are not simply confined to certain clinical specialties or basic science subject disciplines. In order to aid curriculum planning and integration of substance misuse topics into appropriate course areas, the outcomes have been grouped under six key areas:

1. Bio-psychosocial models of addiction
2. Professionalism and self-care
3. Clinical assessment of patients
4. Treatment interventions
5. Epidemiology, public health and society
6. Specific disease and specialty topics

The outcomes are presented as high-level outcomes, so as to make them as flexible as possible in comparing them with and applying them to the diversity of UK curricula. Each area is mapped on to the outcomes prescribed by the General Medical Council (GMC) in Tomorrow's Doctors 2003 (paragraphs 4–10), the relevant sections of which are summarised under each of the areas. Keywords are highlighted in italics within each of the learning outcomes so as to help curriculum mapping.

61.4.1 Core Topics and Learning Outcomes

1. Bio-psychosocial Models of Addiction

On graduation, students should be able to:

- Define *substance misuse*, mechanisms of dependence (both physical and psychological), tolerance, withdrawal and addictive behaviour
- Demonstrate awareness of the range of substances that can be misused; the different *types and classes of licit, illicit and over-the-counter (OTC) substances*; and other colloquial names and their effects
- Demonstrate awareness of the psychological, social and biological aspects of *dependence*; the interactions between such factors in the individual; and the different *models* used to describe addiction
- Describe the *mechanisms of tolerance, dependence and withdrawal* of different drugs and the involvement of different neurotransmitter systems

Meets GMC outcome:

– *4b – Know about, understand and be able to apply and integrate the clinical, basic, behavioural and social sciences on which medical practice is based*

2. Professionalism, Fitness to Practise and Students' Own Health

On graduation, students should be able to:

- Describe the *principles of rational prescribing* and the use of psychoactive medication
- Demonstrate *professional behaviour* towards individuals with problems of addiction, which incorporates a non-judgemental compassionate approach and respect for a patient's autonomy
- Describe the *ethical and legal issues* associated with dealing with cases of substance misuse
- Explain and outline the problems of *iatrogenic addiction*
- Describe the *risk factors* for substance misuse in medical students and in health professionals
- Describe how substance misuse problems may affect a *health professional's* judgement, performance and care of their patients
- Describe the need to balance due concern for the health of a colleague with responsibilities for the *safety and welfare of patients*
- Outline the role of the medical schools and the GMC in ensuring students and doctors' *fitness to practise*
- Describe the *sources of help* for students and doctors with drug and alcohol-related problems

Meets GMC outcomes:

– 4a (i) – *Know and understand our guidance on the principles of good medical practice and the standards of competence, care and conduct expected of doctors in the UK.*
– 4d – *Recognise personal and professional limits and be willing to ask for help where necessary and recognise the duty to protect patients and others by taking action if a colleague's health, performance or conduct is putting patients at risk.*
– 5c – *Be willing to respond constructively to the outcome of appraisal, performance review and assessment.*
– 10 – *Graduates must be aware of the health hazards of medical practice, the importance of their own health and the effect that their health has on their ability to practise safely and effectively as a doctor.*

3. Clinical Assessment of Patients

On graduation, students should be able to:

- Describe the major *clinical features* of alcohol abuse, drug dependence and tobacco use
- Describe the possible *outcomes of different treatment regimens for substance misuse* and discuss the prognosis and management
- Take a focused drug and alcohol *history*
- Elicit signs of misuse of alcohol, tobacco and illicit or over-the-counter (OTC) drugs through *physical and mental state examinations* and identify and prioritise medical and psychosocial problems associated with substance misuse
- Demonstrate appropriate skills for communicating sensitively with patients about substance misuse issues and know how to *deal with challenging, aggressive or intoxicated patients*, balancing

assessment need with their own safety and that of others
- Appropriately order and interpret *urine, blood and other appropriate tests* for drugs of addiction; use standardised *screening and assessment instruments* to detect alcohol and drug levels; and describe other special investigations and how to interpret results
- Carry out a *psychological assessment* of a patient's readiness to implement change

Meets GMC outcomes:

– 4a(iii) – *Know about and understand how errors can happen in practice and the principles of managing risks*
– 4c – *Be able to perform clinical and practical skills safely*
– 6b – *Be able to communicate effectively with individuals and groups*
– 6c – *Understand the principles of audit and the importance of using the results of audit to improve practice*

4. Treatment Interventions
On graduation, students should be able to:

- Describe the *common treatment regimens* for various types of addictions and withdrawal states
- Describe the basis of *commonly used therapies* for addiction
- Describe the variety of UK agencies to which patients with addiction problems can be referred, and how and where to make appropriate *referrals for treatment*
- Demonstrate awareness of risk related to *needle use and disposal* for healthcare workers and patients and risk prevention
- Advise a patient appropriately on *reducing or abstaining from drinking and smoking* and list appropriate agencies or individuals to which patients can be referred to create a treatment plan
- Advise women on the effect of substance use and the impact on *foetal and maternal health*
- Demonstrate awareness of the need to assess patients' *capacity to consent* to treatment
- Describe the impact of substance misuse on *drug interactions* and a patient's compliance with treatment

Meets GMC outcomes:

– *4b – Know about, understand and be able to apply and integrate the clinical, basic, behavioural and social sciences on which medical practice is based*
– *7a – Know about, understand and respect the roles and expertise of other health and social care professionals*

5. Epidemiology, Public Health and Society
On graduation, students should be able to:

- Outline *UK policies* on misuse of drugs, drug prescribing and dispensing, and on alcohol and smoking
- Outline *UK legislation* controlling drugs, alcohol and tobacco, including the legal alcohol limits for driving
- Explain *hazardous and harmful levels of alcohol consumption*, and the *recommended limits for alcohol consumption*
- Outline UK *strategies for the prevention and treatment of drug misuse*
- Outline *international policies and strategies* to limit drug supply and demand
- Describe the *epidemiology* of alcohol consumption, smoking, drug misuse in the general population, vulnerable groups and specifically in doctors and other health care professionals

- Describe the problems associated with *self-medication*
- Demonstrate awareness of the risks in different *work environments* and the need for employers to have *drug and alcohol policies*
- Describe the *effects of addiction* on individuals, their families, friends and colleagues in a range of age-groups; from children and adolescents to older people
- Describe the long-term *physical, psychological and social consequences* of various types of addiction and substance misuse, including the economic consequences and the links between crime and substance misuse
- Describe the risks to the children of addicted parents, including *child protection policies* and a doctor's duty to implement these

Meets GMC outcomes:

- *4a(ii) – Know about and understand the environment in which medicine is practised in the UK*
- *4a(iii) – Know about and understand how errors can happen in practice and the principles of managing risks*
- *4b – Know about, understand and be able to apply and integrate the clinical, basic, behavioural and social sciences on which medical practice is based*
- *6c – Understand the principles of audit and the importance of using the results of audit to improve practice*

6. Specific Disease and Speciality Topics
On graduation, students should be able to:

- Recognise *life-threatening complications* of substance misuse, including septicaemia, pulmonary emboli and overdose and be able to carry out appropriate interventions
- Describe and explain the links between substance misuse and:
  - Accidents and violence (including sexual assault and sexually transmitted diseases—STDs)
  - Lung disease, specifically tobacco, 'crack' cocaine and cannabis
  - Anxiety, depression, dementia, schizophrenia
  - Acute psychotic episodes
  - Self-harm and suicide
  - Heart disease, hypertension and myocardial infarct and cocaine use
  - Liver disease, pancreatitis and gastritis
  - Infectious diseases, including human immunodeficiency virus (HIV) and hepatitis B and C virus infections

From International Centre for Drug Policy [17] *Substance Misuse in the Undergraduate Curriculum Project Report, Appendix 1.*

61.4.2 Phase 2

The second phase (2008–2011) provided a time-limited period of intensive support for the development and implementation of the new curriculum guidance into the teaching and learning opportunities of the medical schools at a local level, and into their local curriculum planning processes; promoted a self-sustaining network of all English medical schools involved in changing their curricula; and developed and validated a toolkit [16] of guidance for the effective implementation/development of substance misuse training in the undergraduate medical curriculum. A series of fact sheets, written by clinicians with in-depth knowledge of substance misuse, were produced to provide concise, relevant and up-to-date information on specific areas of substance misuse teaching. They were found to be

very valuable resource since they provided a framework for developing current teaching material as well as being used as stand-alone teaching resources.

Each medical school was required to identify a local academic champion whose role was to motivate change and to supervise the work of the appointed local curriculum coordinator to implement the integration of substance misuse teaching and assessment in the undergraduate curriculum. Specifically, the role of the local curriculum development coordinators was to manage the implementation of the substance misuse Toolkit across the medical school for undergraduate education; to map and review the current curriculum compared to the guidance recommendations; and to make recommendations for implementation. These roles were supported by a national coordinator whose key task was to oversee the management of the implementation phase and work with the participating schools.

In the UK, medical education is regulated by the General Medical Council, with all school curricula being bound by the structures and demands of the key policy documents 'Tomorrow's Doctors' [8, 9]. Undergraduate medical training in the UK was comprehensively reformed, following the recommendations of 'Tomorrow's Doctors' [8, 9] and the subsequent Outcomes for Graduates [10]. Although curricula are structured differently across the participating medical schools, they all share the aims of providing high-quality medical education for students and of producing well trained and competent doctors [24].

Within the participating medical schools, a range of teaching and learning methods and corresponding range of assessment methods are used. Curricula set around a pre-clinical phase of learning (typically for 2 years), followed by a clinical phase, moving away from purely academic and theoretical studies towards more applied work. Intensive patient contact and clinical experience are used by some of the schools, whilst others use the approach of learning through a problem/case-based learning (PBL/CBL). This approach typically uses patient 'cases' or particular medical 'problems' to exemplify the learning required of students throughout the course. These cases are likely to link to a spiral curriculum, where layers of learning, for example, around physiology, anatomy or basic science, are revisited repeatedly in increasing detail. PBL or CBL course structures are more likely to include clinical placements right from the start of the course.

In each participating medical school, the current teaching and learning of substance misuse within the undergraduate medical curriculum was identified. Coordinators undertook a mapping exercise that enabled them to construct a comprehensive overview of substance misuse teaching within their respective school, and for their findings to be aligned to the substance misuse learning outcomes from the core curriculum guidance. This process identified what was covered, not covered and what could be added to within substance misuse teaching, including areas of commonality across the schools.

Broad areas that were identified as needing more development through this process included professionalism (e.g. attitudes, values, judgement, coping with substance misuse on placements); iatrogenic addiction; fitness to practise issues; self-care; child-related issues (e.g. parenting, potential neglect, foetal and maternal health); drug policies and work environment; strategies and policies on drug use; treatments for addicts (e.g. engagement, motivation, referrals, risk-reduction strategies); sources of help for students/doctors who misuse substances; specific clinical issues (e.g. needle use, outcomes of addiction, prescribing, neurological issues, complications, drug use/types); and communication issues (including capacity to consent). It was encouraging to note that such a key topic for future public health as 'advising a patient appropriately on reducing or abstaining from drinking and smoking and implementing a treatment plan with the patient' was one of the most widely covered topics. Concurrently, student views and experiences of substance misuse teaching were gathered through surveys and focus groups in some of the participating schools. The findings from each survey were compiled, and in summary, the views of students were that they perceived substance misuse to be an important

aspect of undergraduate medical education, with the teaching being comprehensive and sufficient. Overall, the bio-psychosocial aspects of addiction were covered well in teaching sessions, but more could be done regarding the clinical assessment of patients. Most of the teaching and learning was perceived to occur through independent study or via formal sessions, such as lectures or intercalation degrees.

Students perceived the teaching of alcohol, smoking and illicit drug use to be well covered; however, they felt that they could be taught more about over-the-counter drugs and prescription drug misuse. Students also recommended more teaching on how to manage addicts and about the effects of different substances when used on their own or combined. Students varied in their confidence of performing different skills with patients who misuse substances and did not feel particularly confident in taking an illicit drug history, discussing options for patients to cut down to stop alcohol or illicit drug use, and in recommending appropriate organisations which could help patients stop misusing substances.

The work during this phase enabled the changes to their curricula made by the coordinators to be delivered over a rapid timescale, and brought about important changes to the teaching and learning opportunities for future doctors. These changes addressed key recommendations that were made to improve substance misuse learning. In addition to modifying the learning outcomes, the coordinators, supported by the academic champions, introduced a range of initiatives, including new lectures and special study module components, and provided additional substance misuse resources for students to use, which supported the taught sessions. Initiatives were undertaken to raise awareness of substance misuse issues, including workshops, quizzes and working with external organisations. The toolkit and fast fact sheets that were developed across the two phases of the project were also important in providing useful materials for use in a wide variety of settings, disciplines and learning opportunities, and for integration across all years of training. These fact sheets have continued to be updated and the number of titles expanded to reflect changes such as the development of e-cigarettes, and emerging issues like gambling, and novel psychoactive substances. (https://www.addiction-ssa.org/hot-topic/factsheets/).

61.5 Opportunities and Threats

Major changes or re-structuring of curricula poses both opportunities and pitfalls for substance misuse teaching. New recommendations made during a re-structuring may build on developments to date, potentially with additional substance misuse learning opportunities, but positive changes can also fall by the wayside, especially if local enthusiasm and championing of the issue falter.

Taking new opportunities as they arise may enable sustainability. Making use of those areas of teaching which are currently ‘hot topics’ could be helpful, such as the question of professionalism, substance misuse by older people, teaching about emerging drugs such as novel psychoactive drugs, e-cigarettes and training in prescribing for medical cannabis. Similarly, a focus on issues of public concern, such as addiction to prescribed drugs, drug deaths, from both illicit and licit substances, might help maintain and highlight the need for substance misuse teaching to be clearly evident in the curriculum.

61.6 Evaluation

Although there was no formal evaluation of the project as it was not part of the funding, the National Steering Group for the Project decided to incorporate it within the timescale of the project as it was felt that this is an integral part of any training programme or initiative. In 2010, a small working group was established to evaluate the development, implementation and short-term outcome of the substance misuse undergraduate medical curriculum project. The views of both curriculum coordinators and academic champions were collected through interviews, questionnaires and a focus group.

The evaluation component of the project produced several recommendations concerning resources, training and sustainability:

- A core expert group/advisory panel should continue to meet on a biannual or annual basis for 2–3 years to ensure that substance misuse teaching objectives remain embedded within undergraduate curricula so that the following recommendations are actioned
- To develop a generic 1-day curriculum mapping/review training course that could be accessed online or rolled out as a package for others working on similar projects. This would be delivered on commencement of the curriculum development post
- To develop a database/resource of all SSCs and SSMs currently offered by medical schools in the area of substance misuse
- To develop a resource-sharing portal where all project resources can be collated and accessed for teaching purposes, including a core list of recommended addiction teaching and learning resources.
- To maintain and update the fact sheets
- To develop guidance on topics and questions for assessment and to provide questions for the Medical Schools Council Assessment Alliance (MSCAA) common assessment ban of questions
- To identify a 'link person' for substance misuse teaching should be identified in each participating school
- To develop specifically designed tools, such as Google desktop or Google box to assist the process of curriculum mapping. Such software might potentially be used to create a database with ability to rate content
- To ensure continuity of undergraduate substance misuse–related learning outcomes through to postgraduate education and with appropriate professional postgraduate medical education initiatives
- Relationships with Third Sector providers and other partners should be built to ensure that teaching via placements continues.
- In the light of ongoing changes to drug and alcohol service provision, medical schools should actively seek recognition of time and resources for teaching undergraduate medical students to be included within commissioning tender documents and service specifications [17].

We are well aware that the changes in the treatment policy landscape in the UK has also resulted in a reduction in addiction psychiatry services over the past decade. This has very serious implications for training since the number of specialist addiction psychiatrists, who often contribute to teaching medical students as described earlier and also provide clinical placements, has been halved [5].

A key question now, some years on from the conclusion of the major phases of the project, is how best to sustain the positive changes implemented in the teaching of substance misuse to future doctors, so that future graduating medical students continue to be better equipped to deal with substance misuse? This undoubtedly requires a group of passionate and compassionate addiction specialists who can act as lecturers, trainers, mentors, supervisors and advisors for medical students, as well as for generalist or specialist doctors and their teams. The range of medical specialties to which substance misusers present.

How will different models of learning be implemented and compared? How can substance misuse education be 'normalised' within curricula so this is not perceived as an optional extra, rather than an essential component? Who will ensure that the new emerging issues described earlier, for example, the training needed for prescription of medical cannabis, the recognition of substance use in older people, the rising numbers of alcohol- and drug-related admissions and deaths, are highlighted in the undergraduate and postgraduate medical curricula. How will post-qualification postgraduate training and continuing professional development be organised? And what about other professional groups who play a major role in the detection and treatment of addiction problems?

61.7 Conclusions

This model comprising national guidance on core curriculum content, a toolkit to aid the implementation process and which is supported with teaching resources, has the potential to be adapted and implemented in many different settings and professional disciplines such as nursing, pharmacy and psychology. It can be extended to provide in-depth specialist professional training as well as continuing professional development for general practitioners, psychiatrists and medical specialists such as physicians, obstetricians and surgeons, as well as dentists. It is eminently suitable for undergraduate, postgraduate and continuing professional training for those professional groups allied to the medical profession, including nurses, occupational therapists, social workers, psychologists and pharmacists. This model and the curriculum content provide a core learning resource for any organisation that is considering the development and implementation of a programme on substance misuse. While some components are universally applicable, some may need to be developed with the particular programme in mind. However, this gives the opportunity for some initiatives to take account of their own special circumstances and expand the resources in line with their needs.

It still seems paradoxical that given the nature and extent of addiction problems in almost every branch of medicine, it is not accepted, and therefore acceptable, that addiction training is considered a 'must have' like cancer, heart disease and diabetes rather than a possible optional extra for which a case still has to be made.

A national strategy which has direction and funding from government and coordinated support from diverse stakeholders is a valuable start. Educators with the range of clinical skills and up-to-date knowledge base are an essential element for the introduction and continuation of integration of substance misuse education into the undergraduate medical school curriculum, specialist programmes and continuing development.

61.7.1 Clinical Relevance

As substances are ubiquitous, substance problems resonate throughout virtually every medical speciality. Patients will be misusing combinations of tobacco, alcohol, prescribed and over-the-counter medications, as well as illicit drugs. Thus, they will present with overt and covert clinical symptoms and syndromes related to substance use, misuse and dependence. Without a detailed understanding of the complex interrelationships, patient care will be compromised. Hence, it is essential that medical students have a systematic knowledge of the effects, side effects, consequences and causes of substance misuse, in order that they can undertake a thorough assessment. Training in detailed history taking will lead to more accurate diagnosis, which can inform better targeted treatment. Since there are a range of effective psychological and pharmacological treatments available for the management of substance-related conditions, students need to have the opportunity to develop the skills to administer these interventions. Doctors also need to understand how the medical profession interacts with other colleagues, for example, nurses, psychologists, pharmacists, in the provision of comprehensive services for patients. Furthermore, exposure of students to collaborative working and integration of medical, social and psychological approaches within a multidisciplinary team structure can demonstrate how patients can be adequately supported to achieve the best possible outcomes. Finally, there are exciting new developments in neuroscience, and it is important that tomorrow's doctors gain a deeper appreciation of the biological basis of addiction, while not detracting from the contribution of psychosocial treatment and the role of a public health approach.

In conclusion, it is important to bring out some key points that should be taken into account:

- The use and misuse of alcohol, illicit drugs, tobacco, prescribed and over-the-counter medications are a major public health challenge facing society today. It impacts not only

patients but also their families and their communities in general.

- Those who suffer physical, psychological and social harms as a result of misuse of substances will almost certainly be seen by doctors and their teams at some stage. Therefore, the medical profession has a vital role to play in the recognition, assessment and management of problems associated with substance misuse.
- However, the changes in commissioning addiction treatment services to organisations which are not part of the National Health Service, as well as the significant reduction in funding for treatment facilities, have implications far beyond the implementation of interventions. It threatens the provision of appropriate high-quality teaching and training for future medical students and trainee doctors in the numerous specialties to which patients with substance problems present.
- If health professionals are to succeed in dealing with the problem of substance abuse, they require a systematic training so that they have better understanding of the nature and complexity of the problems associated with substance misuse as well as the interventions which are available.
- They need to be continually updated as new scientific developments emerge and debate some controversial issues, which have recently surfaced, such as the use of medical cannabis, vaping cigarettes and other substances, and the misuse of prescribed medication, for example, gabapentinoids.
- Thus, a sustainable strategy, which sees as its core aim for medical education that medical students have the skills and knowledge to effectively manage substance misuse when they meet it, needs to be outlined and realised.
- Ensuring financial assistance for qualified staff to support implementation of the new curriculum at a local level has contributed to improvements in the extent and quality of teaching on substance misuse issues. This depends on high-level support within medical schools and at governmental level so that the programme can be initiated, maintained and evaluated so it becomes a salient component of the undergraduate medical course.

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Part VI

Behavioural Addictions & Management Implications

Nady el-Guebaly and Henrietta Bowden-Jones

62 Behavioral Addictions and Management Applications: An Introduction

Nady el-Guebaly and Henrietta Bowden-Jones

This section is dedicated to the increasing recognition of the behavioral addictions as a significant component of our field of practice and windows into human nature without the effect of substances. The inclusion of gambling disorder under the DSM-5 diagnostic code of substance-related and addictive disorders as well as the recent recognition of Internet gaming disorder in the ICD11 are but examples of the awareness of an expanding empirical basis. At the same time, the increasing range of behaviors susceptible to develop from an excessive engagement to a habitual or compulsive pattern behooves us to seek for common as well as distinct features.

Two overview chapters investigate the empirical "state of the science." Drs. Yau, Leeman and Potenza review the "Biological Underpinnings of Behavioral Addictions" including frontostriatal brain imaging findings, the implication of neurotransmitters and genetic heritability, as well as their potential in management (Chap. 65). Drs. Kim and Hodgins present an overview of "Transdiagnostic Mechanisms" among behavioral and substance addictions as well as potential empirically supported interventions that target these similarly (Chap. 66).

The next seven chapters address common and distinct features of currently recognized clinically significant behaviors.

Drs. Echeburúa and Amor's chapter (Chap. 67), "Psychological Management of Gambling Disorder with or without Comorbidities" details the current psychological treatment options including inpatient and outpatient treatments, individual and group cognitive-behavioral therapies, motivational enhancement therapies, Gamblers Anonymous, and relapse prevention. Various pharmacotherapies may reinforce psychological therapy along with incremental benefits with comorbid disorders.

Further information is required about the specific features of gambling by women. Drs. Bowden-Jones, Zendle and Althaus chapter (Chap. 68), "Gambling and Gaming Addictions in Women," covers the gender specifications, similarities and differences in epidemiology, courses, comorbidities and treatment.

The next two chapters detail the intertwined investigations of the current highlighted interests in "Problematic Internet Use" (Chap. 69) and "Internet Gaming Disorder" (Chap. 70).

N. el-Guebaly (✉)
Division of Addiction, Department of Psychiatry, University of Calgary, Calgary, AB, Canada
e-mail: nady.el-guebaly@ahs.ca

H. Bowden-Jones
Honorary Professor, Division of Psychology and Language Science, University College London, London, UK

Honorary Senior Visiting Fellow, Cambridge University, London, UK

President of Psychiatry Section, Royal Society of Medicine, London, UK

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Drs. Kiraly and Demetrovics discuss the concept of Internet addiction and its criticisms, the development of diagnostic criteria as well as prevalence estimates and the main treatment approaches. Drs. Kaye, Kuss and Rumpf provide a related overview of the current conceptual and methodological challenges in gaming disorder from the ICD 11 as well as DSM-5 appendix perspectives.

The last three chapters are an intriguing exploration of three "required" behavioral needs, that is, shopping, sex, and food, and the determinants of their evaluation into disorders. Drs. Filomensky and Tavares review the epidemiological challenge, assessment scales, comorbidities, clinical manifestation and determinants of "Compulsive Buying Disorders" (Chap. 71). The existing pilot treatment trials are identified with the best evidence favoring cognitive behavioral models.

Drs. Hertzsprung and Amadala provide a sensitive review of the evolution of excessive and maladaptive sexual behaviors into the diagnostic syndrome of "Sex Addiction" (Chap. 72). Available screening and assessment instruments are described as well as a synopsis of etiological determinants and comorbidities. The prevailing psycho-social approaches and a laudable search to validate staff training are outlined as well as the current pharmacological trials.

Dr. Yarnell-MacGrory et al.'s concluding chapter is an insightful description of the common elements between "Binge Eating, Obesity, and Addiction" (Chap. 73). This interaction has come to prominence as a result of the public concern over the pandemic of obesity rising worldwide and the identification of addictive features in the development of binge eating. Intriguing common neurobiological and psychosocial features are identified as well as a brand-new field of investigation into the phenomenon of food addiction and its optimal management.

This section hopefully conveys the potential for insights of behavioral addictions as windows on human nature without the effect of substances. Each new behavior contributes its own perspectives, but we should beware of the public concern over pathologizing an ever-expanding list of behaviors. The section merely makes reference to exercise and work as other candidate behaviors; there are others. Recommendations for the addition of new behaviors tend to emphasize the presence of inclusive criteria. The identification of exclusion criteria will also be necessary for the credibility of the diagnostic process.

A comprehensive biopsychosociocultural conceptualization of these disorders is critical, and the relative significance of each of these components is yet to be determined. In sum, current or potential candidates for a behavioral addiction have to present solid evidence of the involvement of the brain reward circuitry as the basis for a shared psychopathology involving a decision-making bias and inhibitory control deficits.

Besides the recognition of gambling disorder as an addiction, the new nosologies also acknowledge the prominence of craving in the addiction process. As we approach a better model of addiction, we shall be able to depend less and less on a model based on negative consequences and avoid the perils of a circular logic, that is, it is an addiction because it is harmful and it is harmful because it is an addiction. Along with craving, the careful reader will notice that the two other implicit concepts crosscutting the chapters from this section are loss of control and compulsion (defined as repetitively performing a behavior as a strategy to deal with an emotional imbalance). Starting with this triad, we may get closer to an evidence-based phenomenological model of addiction, while distancing from a harm-based model, which may be unduly vulnerable to ever-changing cultural values and judgment calls (take, e.g., the recent evolution of the gambling perspective from frowned upon behavior to government-embraced leisure activity).

That is not to deny the obvious impact of sociocultural factors especially in the determination of new behavioral addictions such as Internet and video gaming. Even in the case of essential behaviors such as sex, eating, and shopping, never before in history have individuals and communities had a wider access to services, products, and credit. Our "information" society suffuses

people with news about novel and potentially gratifying behaviors, shortening the time to adequately ponder and decide.

Finally, besides perfecting and broadening the contours of the addiction model, behavioral addictions may challenge previous widely accepted treatment goals such as abstinence. Popular goal posts promoted by 12-step-based programs such as "avoid the first drink" or "avoid the first dose" become unrealistic when expanded to "avoid the first log-on," "avoid the first purchase" and "avoid intercourse," and in the case of compulsive eaters, "avoid the first bite" is an utterly impossible goal! Compulsive eaters anonymous meetings discuss "avoiding the first compulsive bite," which relates to eating when under the influence of an emotional turmoil in an unconscious attempt to deal with it, which will likely lead to loss of control. Clusters of components/symptoms must be identified for each of these behaviors in order to build tailored preventive and treatment strategies more effectively than current broader behavior-focused approaches.

63 Biological Underpinning of Behavioral Addictions and Management Implications

Yvonne H. C. Yau, Robert F. Leeman, and Marc N. Potenza

Contents

Y. H. C. Yau
Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada

R. F. Leeman
Department of Health Education and Behavior, University of Florida, Gainesville, FL, USA

Department of Psychiatry, Yale University, New Haven, CT, USA

M. N. Potenza (✉)
Department of Psychiatry, Yale University, New Haven, CT, USA

Departments of Child Study and Neurobiology, Yale University, New Haven, CT, USA
e-mail: marc.potenza@yale.edu

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Abstract

Neurobiological and clinical data indicate that maladaptive engagement in certain behaviors warrants consideration as "behavioral" or non-substance addictions. This chapter reviews existing neurobiological and genetic/family history evidence for behavioral addictions involving gambling, internet use, video-gaming, sex, eating, and shopping. At a neurochemical level, behavioral addictions may involve dysregulation of serotoninergic, dopaminergic, noradrenergic, and opioidergic systems. At a neurocircuitry level, findings suggest dysfunction in subcortical and frontal areas; disruption in these regions and related circuits could lead to disadvantageous decision making, impaired inhibition, and increased cue-induced craving. While a genetic understanding is at an early stage, genetics/family-history data support heritability for behavioral addictions and suggest genetic overlap with other psychopathologies. As this represents an emerging area of research, data remain sparse in multiple domains. An improved understanding of behavioral addictions will help in establishing appropriate nomenclature and enhance the ability to recognize, prevent, and treat these disorders more effectively.

Keywords

Behavioral Addictions · Neurobiology · Genetics/Family History

63.1 Introduction

While the term addiction has traditionally been associated with excessive alcohol and drug use, the Latin word (*addicere*) from which it is derived was not initially linked to substance use. Addiction professionals and the public are recognizing that certain behaviors bear resemblance to alcohol and drug dependence, and data have been forwarded that these behaviors warrant consideration as non-substance or "behavioral" addictions. Excessive engagement in such behaviors as gambling, internet use, video-game play, sex, eating, and shopping may represent addictions, with a minority of individuals displaying such habitual or compulsive engagement. Shaffer et al. [61] proposed that addiction should be considered as a syndrome with multiple opportunistic expressions (e.g., substance abuse, pathological gambling, food addictions). Aided by data from neurobiological studies, this view has gained momentum in the past decade and, importantly, has led to the category of "Substance Use and Addictive Disorders" to replace "Substance-related Disorders" in the *DSM-5* [2]. Although gambling disorder is presently the only condition included in this category, other conditions were considered. Notably, internet gaming disorder has been included in the DSM-5 as a condition requiring further study. Along similar lines, gambling disorder and gaming disorder have been included in the 11th edition of the *International Classification of Diseases* (ICD-

11) as "Disorders Due to Addictive Behaviours" [70]. Establishing nomenclature and criteria for behavioral addictions may enhance our capacity to recognize and define their presence.

Biochemical, functional neuroimaging, genetic, and pharmacological research in substance addiction has implicated several neurobiological processes. Multiple neurotransmitters (e.g., serotonergic, dopaminergic, noradrenergic, opioidergic) may contribute to the pathophysiologies of addictions [58]. For example, dysregulated dopamine systems, which are involved with learning, motivation, and salience of stimuli and rewards, and serotonin (5-HT) systems, implicated in behavioral control, may significantly contribute to addictive disorders. Prolonged engagement in an addictive behavior may lead to a reduction of sensitivity to biological rewards and decrease an individual's perceived control over seeking and eventual engagement in the behavior. At the neurocircuitry level, the mesolimbic dopaminergic pathway (linking the ventral tegmental area to the nucleus accumbens and frontal areas) may contribute to decision-making circuitry in risk-reward assessment. Preclinical and clinical work suggest that disruptions in these regions could lead to disadvantageous decision making (e.g., choosing immediate gains versus long-term consequences), impaired ability or willingness to inhibit response to drugs/addictive behaviors when exposed to them, and increased drug- and cue-induced craving [72].

Research also indicates genetic effects on the use and misuse of substances [39]. Several putative risk genes have been identified. Examples include the A1 allele of the Taq1A polymorphism of the dopamine D2-receptor (*DRD2*) gene, associated with measures of impulsivity and behavioral inhibition, and the low transcribing short-allele of the serotonin transport gene (*5HTTLPR*), implicated in moderating the impact of stressful life events on risk of psychiatric conditions such as depression and anxiety [72]. These genes have shown associations with addictions in some but not all studies.

Behavioral addictions frequently co-occur and appear to share important elements with substance-related addictions [72]. In terms of phenomenology, both behavioral and substance addictions may be thematically categorized along four domains: craving, compulsion, diminished control, and persistence of behaviors despite negative consequences [61]. Moreover, both have been characterized as disorders of motivation, reward and decision making [58, 72]. Growing evidence, particularly in pathological gambling, indicates that behavioral addictions share overlapping neurobiological mechanisms and genetic contributions with substance addictions. However, differences have also been observed, and the extent to which findings from substance addictions extend to individual behavioral addictions may differ.

This chapter reviews existing neurobiological and genetic/family history evidence pertaining to behavioral addictions in an attempt to shed light on these emerging mental health problems from a neuroscientific perspective. Specifically, the following sections discuss the neural systems, neurotransmitters, and genetics/family history findings relating to gambling disorder, internet addiction, internet gaming disorder, compulsive sexual behavior disorder, food addiction, and compulsive shopping or buying. As this is an emerging area of research, data are sparse in some domains. Similarities and differences with substance-addition findings are highlighted. Epidemiologies are addressed briefly, and more detailed descriptions of clinical features and treatment methods can be found in other chapters. An overview of the neural systems, neurochemistry, and genetic results can be found in Tables 63.1, 63.2, and 63.3, respectively.

Table 63.1 Overview of neural system results for selected behavioral addictions, with a focus on fronto-striatal findings

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
Gambling disorder	*Frontal areas:* *Cognitive tasks:* Most findings suggest reduced activity in multiple frontal regions in GD, but also findings suggest increased activity and negative findings *Cue-induction studies:* Suggest differences in activity, but the precise nature of differences warrants additional study	Between-group differences are observed in SUD and control comparison subjects with many tasks indicating reduced frontal activity, but precise nature of differences warrants additional study
	Striatal areas: *Cognitive tasks:* Reduced ventral striatal activity to monetary reward anticipation *Cue-induction studies:* Mixed with some studies showing reduced striatal activity in GD compared to controls *Others:* Ventral striatal activity inversely correlated with impulsivity measures and problem-gambling severity	Many findings suggest reduced ventral striatal activity during monetary reward anticipation in individuals with SUDs compared to controls
	White and gray matter: Poorer white matter integrity in multiple regions; some volumetric differences in gray matter and white matter differences between GD and controls, some of which overlap with SUDs; gray matter reduction observed in frontal regions, independent of SUDs comorbidity	Poorer white matter integrity and decreased gray matter volumes in SUDs
Internet addiction disorder	*Frontal areas:* *Cognitive tasks:* EEG studies indicate diminished efficiency of response inhibition; differential ACC activity to decision conflicts between IAD and controls *Resting state:* Differences in regional homogeneity in multiple frontal regions, but the precise nature of differences warrants additional study	Underactive feedback valence in individuals with SUDs Preliminary studies suggest reduced regional homogeneity in SUDs
	White and gray matter: Lower gray matter density in multiple regions including dlPFC, ACC, and insula; differences in white matter integrity between IAD and controls involving the internal capsule, but effects may be potentially widespread	Poorer white matter integrity and decreased gray matter volumes in SUDs
Internet gaming disorder	*Frontal areas:* *Cognitive tasks:* Diminished functional connectivity within executive networks linked to poorer cognitive control *Cue-induction studies:* Greater activation of multiple frontal areas including the OFC and dlPFC; findings linked to transitions and treatment outcomes	Between-group differences are observed in SUD and control comparison subjects, but precise nature of differences warrants additional study
	Striatal areas: *Cognitive tasks:* Diminished activation of ventral striatum during reward processing *Cue-induction studies:* Increased activity in the ventral striatum compared to control subjects *Resting state:* Reduced fronto-striatal connectivity linked to cognitive control deficits in IGD	Reduced ventral striatal activity typically reported; however, findings may differ per task
	Gray matter: Relatively reduced gray matter volumes in cortical regions including ACC and vmPFC	Decreased striatal and cortical gray matter volume (including ACC and vmPFC) in SUDs

Table 63.1 (continued)

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
Compulsive sexual behavior disorder	*Fronto-striatal areas:* *Cue-induction studies:* Activation of emotion and reward regions and networks, as well as thalamic activity	Cue reactivity to drug cues activates emotion and reward regions and networks among SUD subjects
	White matter: Higher integrity of lower superior frontal region	Poorer white matter integrity in SUDs
Food addiction	*Frontal areas:* Increased OFC activation in response to food cues but decreased activity upon ingestion of food among individuals with high food addiction scores	Between-group differences are observed in SUD and control comparison subjects, but precise nature of differences warrants additional study
	Other regions: Increased ACC and amygdala activation in response to food cues among individuals with high food addiction scores	Evidence for ACC activity in risky decision making in SUDs; amygdala activity associated with trait craving in SUDs
Compulsive shopping disorder	*Striatal areas:* Increased activity in ventral striatum upon product presentation	Reduced ventral striatal activity typically reported; however, findings may differ by task
	Other regions: Reduced activity in insula and ACC during price presentation	Insula activity in response to substance cues; evidence for ACC activity in risky decision making in SUDs

GD gambling disorder, *SUDs* substance use disorders, *IAD* internet addiction disorder, *IGD* internet gaming disorder, *EEG* electroencephalography, *dlPFC* dorsolateral prefrontal cortex, *ACC* anterior cingulate cortex, *OFC* orbitofrontal cortex, *vmPFC* ventromedial prefrontal cortex

Table 63.2 Overview of neurochemistry results for selected behavioral addictions

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
Gambling disorder	*Dopamine:* Mixed reports of dopamine involvement; negative between-group findings for between-group differences in D2-like receptor availability at rest; dopamine antagonist administration may promote gambling motivations in GD and medications not efficacious, although efficacy may be influenced by individual differences; dopamine release and function may contribute to impulsivity and decision making	Dopamine release has been related to substance use; reduced D2-like receptor availability in SUDs typically reported for stimulant and alcohol SUDs; mixed clinical findings with dopamine antagonists; individual differences in dopamine release and function may contribute to variability in impulsivity and risky decision making in SUDs
	Serotonin: Mixed results with SSRIs; possible individual differences in serotonin function	Evidence suggest between-group differences in serotonergic function; mixed clinical results with SSRIs suggest possible individual differences
	Opioids: Positive clinical findings with opioid antagonists, with some evidence of lasting effect, although findings mixed	Multiple positive clinical findings suggest role for opioid systems, particularly for opiate and alcohol dependence
	Other neurotransmitters: Noradrenergic levels elevated among GD; preliminary positive clinical findings with glutamate antagonist suggest glutamate may contribute to impulsive and compulsive behaviors	Findings suggest elevated noradrenergic levels in some SUDs; positive clinical findings suggest role for glutamatergic systems

(continued)

Table 63.2 (continued)

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
Internet addiction disorder	*Dopamine:* Decreased striatal dopamine transporter expression in preliminary IAD studies; limited findings suggest differential D2-like receptor availability in the striatum – however results may differ between subdivisions	Mixed findings regarding levels of dopamine expression in striatum; reduced D2-like receptor availability in some SUDs typically reported
Problematic video-game playing	*Dopamine:* Limited and preliminary findings suggest increased dopamine release in ventral striatum during video-game play; dopamine dysregulation in striatum may relate to duration of IGD	Dopamine release has been related to substance use and studies indicate between-group differences in dopaminergic activity in some SUDs
Compulsive sexual behavior disorder	*Serotonin:* Positive results from clinical trials with SSRIs, but may treat comorbid psychiatric disorders which in turn helps address CSBs	Mixed clinical results with SSRIs, with some positive and others negative
	Opioids: Initial positive findings for high doses of opioid receptor antagonist; however, positive results not long last	Multiple positive clinical findings suggest a role for opioid systems in SUDs
Food addiction	*Dopamine:* Dopamine release related to food and food cues; reduced D2-like receptor availability in very obese humans and mice; animal models of food addiction suggest consumption of hyperpalatable foods decreased dopamine release and receptor expression following withdrawal; pro-dopaminergic stimulant lisdexamfetamine approved for treatment of BED; the role of dopaminergic activity in food addiction has not been directly investigated in humans	Dopamine release has been related to SUDs and studies indicate between-group differences in dopaminergic activity in some SUDs; decreased dopamine release and receptor expression follow substance use withdrawal, particularly in striatal regions, for some SUDs
	Serotonin: Positive findings in open-label and double-blind studies with SSRIs for BED but not food addiction *per se*	Mixed clinical results with SSRIs, with some positive and others negative
	Opioids: Positive findings for high doses of opiate antagonist in rodents, but the precise nature is unclear; different nutrients may have different effects on the opioid system	Multiple positive clinical findings suggest a role for opioid systems in SUDs
Compulsive shopping disorder	*Serotonin:* Some positive results from clinical trials with SSRIs, while controlled results for others have been typically negative	Mixed clinical results with SSRIs, with some positive and others negative

GD gambling disorder, *SUDs* substance use disorders, *IAD* internet addiction disorder, *PVG* problematic video-game playing, *CSB* compulsive sexual behavior disorder, *SSRIs* selective serotonin reuptake inhibitors, *BED* binge-eating disorder

Table 63.3 Overview of selected genetic results for selected behavioral addictions

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
Gambling disorder	*Family history:* GD highly heritable; twin studies indicate genetic factors may share similar magnitudes with or contribute more than environmental factors to overall risk for developing GD	SUDs highly heritable; twin studies indicate genetic and environmental factors share similar magnitudes of influence on overall risk for developing a drug use disorder
	Molecular genetics: Preliminary findings suggest genetic polymorphisms related to dopamine (*DRD2*) and serotonin transmission (*5HTTLPR, MAO-A*); genome-wide association studies have not identified single nucleotide polymorphisms that significantly contribute to GD	Associations with polymorphisms related to dopamine and serotonin transmission; genome-wide associations indicate different contributions to individual SUDs

Table 63.3 (continued)

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
Internet addiction disorder	*Molecular genetics*: Preliminary findings suggest over-expression of ss *5HTTLPR* genotype in males with IAD	Associations with serotonin transporter gene polymorphisms
Problematic video-game playing	*Molecular genetics:* Preliminary findings suggest the presence of Taq1A polymorphism of *DRD2* receptor gene and low activity *COMT* alleles more likely in males with online PVG	Links between SUDs and Taq1A polymorphisms, but not universally replicated; low activity *COMT* variant linked to various SUDs (e.g., nicotine, methamphetamine, and alcohol)
Compulsive sexual behavior disorder	*Family history:* More likely to have parent with hypersexual disorder; more likely to have first-degree relative with SUDs	Individuals with SUDs more likely to have first-degree relative with various SUDs and psychopathology
Food addiction	*Family history:* Obesity ten-fold more likely in people with an obese first-degree relative	Individuals with SUDs more likely to have first-degree relative with various SUDs and psychopathology
	Molecular genetics: Obese individuals with BED, compared to non-BED, had lower frequencies of the *Taq1A1* polymorphism of *DRD2* receptor gene and higher frequencies of the G118 polymorphism of the mu-opioid receptor gene (*OPRM1*); over-expression of ss *5HTTLPR* genotype in overweight adolescent; *FTO* linked to BMI and enhanced neural response to food cues	Associations with polymorphisms related to dopamine and serotonin transmission; *OPRM1* polymorphisms may mediate reward effects of drugs of abuse (e.g., opiates, alcohol, heroin) – however results in clinical populations have been mixed; *FTO* gene linked to alcohol dependence
Compulsive shopping disorder	*Family history*: Relationship to parental history of compulsive shopping disorder and first-degree relative with SUDs	Individuals with SUDs more likely to have first-degree relative with various SUDs and psychopathology
	Molecular: Negative findings for *5HTTLPR* polymorphisms	Associations with serotonin transporter gene polymorphisms

GD gambling disorder, *SUDs* substance use disorders, *IAD* internet addiction disorder, *PVG* problematic video-game playing, *DRD2* D2 dopamine receptor gene, *5HTTLPR* serotonin transporter-linked polymorphic region, *MAO-A* monoamine oxidase A gene, *COMT* catechol-O-methyltransferase gene, *OPRM1* mu-1 opioid receptor gene, *BMI* body mass index

63.2 Gambling Disorder

In the last decade, pathological gambling or gambling disorder (GD) has developed a strong research base in the wake of worldwide legalized gambling and concerns over gambling's possible health and social impacts. In the *DSM-5,* pathological gambling was renamed as GD and recategorized to the newly expanded "Substance-Related and Addictive Disorders" category. With this move, GD became the first recognized non-substance behavioral addiction, implying many shared features between GD and substance use disorders (SUDs). GD can include preoccupations with gambling, gambling with greater amounts of money to receive the same level of desired experience (tolerance), repeated unsuccessful efforts to control or stop gambling (impaired control), restlessness/irritability when trying to stop gambling (withdrawal), and interferences in major areas of life functioning. High comorbidity rates for GD and substance addictions have been observed, with a meta-analysis suggesting a mean co-occurrence of 57.5% [48].

63.2.1 Neural Systems

The basis of GD is likely multifactorial. Changes in processing of gambling cues and gambling

decisions, including those relating risk/reward decision making, reward processing, and impulse control, are likely contributing factors [72]. Research on GD that coincided with the *DSM-5* reclassification included neuroimaging studies that have typically investigated frontal and striatal circuits, although several lines of evidence also suggest the involvement of other regions [58].

Neuropsychological findings in GD have indicated impaired decision making and deficits in executive functions compared to controls [72]. Functional magnetic resonance imaging (fMRI) studies during cognitive tasks have implicated frontal areas. In particular, multiple investigations have observed differences in ventromedial prefrontal cortex (vmPFC) function in GD. For example, GD (versus control) subjects have exhibited relatively diminished vmPFC activation during presentation of incongruent stimuli in the Stroop color-word interference task, during anticipation of gains and losses in the monetary incentive delay (MID) task, and during a simulated gambling task [58]. However, seemingly contradictory findings have also been reported. During high-risk gambling decisions in the IGT, fMRI findings demonstrated that GD individuals exhibited relatively greater frontal lobe and basal ganglia activation, particularly in the vmPFC, caudate, and amygdala [59]. Across individuals with and without GD, performance on the IGT correlated largely with ventral striatal activity during a prospect phase of reward and loss processing on the MID task [8]. Differences in findings across studies may relate to the specific tasks used [45], populations studied or other factors. Cue-induction studies have also reported both relatively decreased and increased vmPFC activity for problematic gambling/GD (versus control) in response to gambling stimuli [58]. Taken together, dysfunction in frontal areas responsible for decisional processes appears to contribute to GD, although the precise nature of the dysfunction is unclear.

Dysfunction in the striatum may also contribute to GD. A recent meta-analysis indicates striatal hypoactivation during reward anticipation in individuals with GD or SUDs compared to controls [49]. The GD and SUD groups diverged during reward outcome: while individuals with SUDs showed increased ventral striatum activation, individuals with GD showed decreased activation in the dorsal striatum. In gambling cue-exposure tasks, GD exhibited decreased activation in the ventral [56] and dorsal [15] striatum compared to control subjects. In both GD and alcohol dependence, ventral striatal activation during reward anticipation was inversely correlated with impulsivity measures [6].

Aside from frontal and striatal circuits, other brain regions have also been implicated. GD (versus controls) displayed significantly greater activity in regions involved in sensory encoding (e.g., parahippocampal gyrus and occipital cortex) to video presentation of gambling cues [58]. Among GD subjects, subjective intensities of gambling urges following viewing of gambling videos correlated positively with activation in brain regions implicated in the retrieval and processing of emotion including the bilateral temporal poles, medial temporal gyrus, and medial occipital gyrus and inversely with activation in the left dorsal medial frontal cortex, an area involved in performance monitoring. Control participants did not show gambling-urge-related correlations at the same threshold [7]. Relatively diminished insula activation in GD during reward processing has also been noted [6]. Insula involvement in craving responses have also been noted [58].

Neuroanatomical alterations may also exist in GD. Diffusion tensor imaging has been largely consistent in indicating disrupted white matter integrity, as indexed by fractional anisotropy values, although findings are diffuse [58]. Multiple regression analyses suggest that this reduction may be predicted by GD status, as well as age and past alcohol abuse/dependence [58]. Microstructural white matter differences may similarly impact GD and cocaine-use disorder [73]. Using voxel-based morphometry (VBM) to assess gray and white matter differences revealed a lack of structural differences in individuals with GD compared to control subjects [58]. In one large structural MRI study ($N = 205$), Zois et al. [81] found significant gray matter reduction in frontal regions in GD, independent of SUDs comorbidity, compared to healthy controls.

Another large study found altered sulcogyral patterns in the orbitofrontal cortex linked to GD [46].

63.2.2 Neurochemistry

Dopaminergic findings in GD present a complicated picture and questions have been raised regarding how central dopamine may be in GD, especially given the lack of replicability of findings [57]. Using positron emission tomography (PET) with the tracer [^{11}C]raclopride, one small study reported that GD individuals performed worse on the IGT than control subjects, and among GD subjects, dopamine release in the ventral striatum was positively associated with excitement levels [47]. Another tracer, [^{18}F]fluorodopa, for dopamine precursor indicated increased dopamine synthesis in GD [65], though negative findings have also been reported [50]. In another small study, D2/D3 receptor availability has also been shown to negatively correlate with mood-related impulsivity ("urgency") within the striatum [14] and positively correlate with problem-gambling severity within the dorsal striatum [12] among GD. While there were no differences in the magnitude of dopamine release between GD and control subjects during a slot machine gambling task, among GD, dopamine release correlated positively with problem-gambling severity [30]. However, unlike findings in substance addictions, especially to stimulants [66], no significant difference in D2/D3 receptor availability at resting state was observed between GD and control subjects [58]. These findings and others have led investigators to question the role for dopamine in addictions [55]. Dopamine agonists have been associated with impulse control disorders in Parkinson's disease [58]. Further, oral administration of a D2-like receptor antagonist, haloperidol, increased gambling motivations among GD subjects while no such effect was observed among control subjects [58], although individual differences may be important [58]. Individual differences or other factors (e.g., placebo responses) may explain with the lack of efficacy of D2-like antagonist drugs (e.g., olanzapine) in the treatment of GD [72]. Taken together, these data raise questions regarding a precise role for dopamine in GD.

Pharmacological studies also implicate serotonin in GD. Selective serotonin receptor inhibitors (SSRIs) have had mixed results for GD and substance addictions [58]. For example, some randomized control trials have found fluvoxamine and paroxetine to be superior to placebo in treatment of GD, while others have reported negative findings [72]. Heterogeneity in treatment response may result from individual differences, with some data suggesting that individuals with co-occurring anxiety disorders may respond well to SSRIs [58].

Other neurotransmitter systems may also contribute to GD. Dysregulated hypothalamic-pituitary-adrenal (HPA) axis and increased noradrenergic levels have been observed in GD [58]. Opioid antagonists (e.g., naltrexone and nalmefene) have demonstrated superiority over placebo in multiple randomized clinical trials [58]. Following a 6-month open-label naltrexone treatment, the majority of GD patients did not relapse during a 6-month medication-free follow-up [58]. Thus, opioid antagonist treatment may have lasting effects, although controlled trials with longer-term follow-up are needed to examine this possibility. Lithium and the glutamatergic nutraceutical n-acetyl cysteine have also shown promise in small controlled trials [58]. Topiramate in conjunction with behavioral therapy has also shown promise [58]. Memantine, an N-methyl-D-aspartate (NMDA) type glutamate receptor antagonist, reduced both the number of hours spent gambling per week and money spent gambling in GD after 10 weeks of medication; in addition, GD subjects reported improved cognitive flexibility post-treatment, suggesting that glutamate may contribute to impulsive and compulsive behaviors [58].

63.2.3 Genetics/Family History

Data from the Vietnam Era Twin Registry estimate the heritability of GD to be 50–60% [58]. This estimate is similar to those from substance addictions [39]. Twin studies suggest that genetic

factors may contribute more than environmental factors to the overall variance of risk for developing of GD [58]. Shared genetic contributions between GD and SUDs have been identified [58].

Genetic polymorphisms related to dopamine transmission (e.g., *DRD2* and Taq1A1) and serotonin transmission (e.g., *5HTTLPR* and *MAO-A*) have been associated with GD, albeit not in a consistent fashion, and may have additive effects [72]. Genetic studies are best considered preliminary given the small sample sizes and absence of stratification by demographics. Replication of candidate gene studies using alternate designs is needed. Towards this end, genome-wide association studies to date of GD have not identified single nucleotide polymorphisms (SNPs) reaching genome-wide significance [58].

63.2.4 Conclusion

GD has been the most frequently studied behavioral addiction. Although the neurobiology of GD is incompletely understood, recent neuroimaging, neurocognitive, neurochemical, and genetic work indicate similarities with SUDs.

63.3 Internet Addiction Disorder

The internet is integrated firmly into modern society and has substantially changed the way we conduct our daily lives. Its popularity, particularly among youth, has raised concern over its potential harms. While moderate internet use may enhance one's quality of life by widening social circles and enhancing psychological well-being [72], diminished control over internet use may impact negatively on daily function, family relationships, physical and mental health, and may lead to incarceration and legal troubles [72]. No formal diagnostic criteria for "internet addiction disorder" (IAD) or problematic internet use currently exist in the DSM-5 or ICD-11 as the groups considering internet use behaviors have seen the internet as a delivery system that permits certain behaviors like gaming or gambling, and gaming and gambling disorders have online and offline specifiers in ICD-11 [70]. Definitions of IAD are often based on *DSM-IV-TR* criteria for pathological gambling [75] with some, such as Young's Internet Addiction Scale, having demonstrated sufficient reliability [72]. In terms of comorbidity, IAD may frequently co-occur with not only SUDs, but also various psychiatric conditions including mood, impulse-control, and personality disorders [72].

63.3.1 Neural Systems

Electrophysiological studies indicate diminished efficiency of response inhibition in IAD. Electroencephalography recordings of the P3 amplitude, an event-related potential associated with response evaluation and inhibitory processing, was found to be higher and have longer peak latency among IAD versus control subjects during a Go/No Go task [72]. These findings suggest IAD individuals may need to engage more cognitive resources to inhibit behavior and are less efficient in information processing. Another study by the same research group found that for incongruent conditions during the Stroop task, IAD versus control subjects showed reduced medial frontal negativity, suggesting impaired cognitive control [72].

Anterior cingulate cortex (ACC), a region implicated in decision conflicts, has been associated with IAD. Compared to controls, IAD subjects demonstrated greater ACC activation for incongruent conditions during the Stroop task and more severe scores on Young's Internet Addiction scale [72]. In a guessing task with monetary gain and losses, increased activation of the orbitofrontal cortex to gain trials and decreased ACC in loss trials was observed in IAD compared to control subjects, suggesting sensitization to reward and desensitization to loss [72]. Resting-state differences in IAD subjects have also been detected with increased regional homogeneity observed in the right frontal region, left superior frontal gyrus, right cingulate gyrus, bilateral parahippocampus, and other regions [72]. Increased regional homogeneity may reflect enhancement of synchronization among these

regions which may consequently enhance sensitivity to rewards.

Evidence also indicates potential structural differences. Using MRI, lower gray matter density in regions tied to emotion regulation including the ACC, posterior cingulate cortex, insula, and lingual gyrus has been found [72]. Moreover, gray matter volumes of the right dorsolateral prefrontal cortex (dlPFC), left ACC, the right supplementary motor area, and white matter fractional anisotropy measures in the posterior limb of the internal capsule have been negatively correlated with the duration of IAD [76].

In the same study, Yuan et al. [76] also reported increased fractional anisotropy within the region of the left internal capsule accompanied by decreased fractional anisotropy within the right parahippocampal gyrus among IAD adolescents. Others have reported widespread reduction of fractional anisotropy beyond the parahippocampal gyrus in major white matter pathways and abnormal white matter structure in IAD adolescents [72].

63.3.2 Neurochemistry

Several small studies have explored dopaminergic functioning in IAD. A recent study using single-photon emission computed tomography (SPECT) scans reported decreased striatal dopamine transporter expression among male IAD subjects compared to age-matched controls [72]. In addition, the authors reported significantly decreased volume of the bilateral corpus striatum among IAD subjects. Another study using [^{11}C] raclopride (PET) scanning reported that adult males with IAD (versus male control subjects) had reduced dopamine D2-like receptor availability in subdivisions of the striatum including the bilateral dorsal caudate and left dorsal putamen compared to controls; moreover, receptor availability was negatively correlated with IAD severity [33]. Interestingly, dopamine receptor availability in the ventral striatum did not differ between the control and IAD groups [33], contrasting results from SUDs [72]. Further studies are needed regarding the role of dopamine in IAD, particularly given the small sample sizes in studies to date.

63.3.3 Genetics/Family History

Few studies have investigated the genetics underlying IAD. Homozygosity of the short allelic variant of the *5HTTLPR* (*SS-5HTTLPR)* gene may be more frequent among male IAD adolescents. IAD subjects expressing *SS-5HTTLPR* showed higher harm avoidance and scored higher on Young's Internet Addiction Scale than IAD individuals who expressed other variants of the gene [43, 72]. The nicotinic acetylcholine receptor subunit alpha 4 (CHRNA4) gene may also contribute to IAD. The T-variant (CC genotype) of the rs1044396 polymorphism on the CHRNA4 gene occurred more frequently among IAD (versus control) subjects; further analyses revealed that this finding was driven by females, suggesting sex-specific genetic effects [72].

63.3.4 Conclusion

IAD may be increasingly prevalent concurrent with increased internet availability, accessibility, and popularity. It is important to note that many studies have involved adolescent males and have been performed in Asia; therefore, results may not be generalizable to other populations.

63.4 Internet Gaming Disorder

There has been debate whether problematic video-game playing warranted consideration as a unique mental disorder. While the DSM-5 workgroup concluded that there was insufficient evidence to include "internet gaming disorder" (IGD) as a behavioral addiction in its main text, the World Health Organization included "gaming disorder" in ICD-11 [70]. Some have argued that IGD is a subtype of IAD and both should be considered under the umbrella term pathological technology use [72]. However, it is important to consider the two conditions individually, as each

may be associated with different clinical and health-related correlates [72]. IGD may be both similar to and distinct from other behavioral addictions such as GD and IAD in terms of availability and use of visual and auditory rewards, – and such differences may contribute to IGD's unique features [72]. Unfortunately, research on IGD often does not differentiate between online and off-line games, making it difficult to separate IGD from IAD findings.

63.4.1 Neural Systems

Electrophysiological data indicate reduced frontal-central error-related negativity amplitudes among IGD (versus controls) in response to incorrect trials relative to correct trials in the Go/NoGo task, suggesting compromised error processing among IGD subjects [72]. In addition, frontal-central error-related negativity amplitude was negatively correlated with weekly gaming hours [72], suggesting potential desensitization to negative consequences.

Changes in reward processing and reward sensitivity are considered crucially important for addiction. In one study, Kühn et al. [42] conducted MRI scans on 154 14-year-olds and found both functional and structural differences between frequent (≥9 hours/ week) and infrequent (<9 hours/week) video-game players. In the MID task, frequent players showed greater activation of the ventral striatum during loss feedback compared with no loss. Moreover, higher left striatal gray matter volume was observed among frequent compared to infrequent players, and this volumetric difference was found to negatively correlate with deliberation time on the Cambridge Gambling Task (CGT). Striatal differences have also been noted in cue-induction studies. Post-cue changes indicative of increased activity have been found in the right ventral striatum and caudate nucleus among male adults playing >30 hours/ week on the "World of Warcraft" game compared to "non-heavy" gamers playing <2 hours/week [34].

In addition to striatal findings, Ko et al. [34] also reported greater activation in the right orbitofrontal cortex, bilateral ACC, medial frontal cortex, and right dlPFC in heavy (versus non-heavy) players following cue presentation. Activation of these areas was positively correlated with self-reported gaming urge and recall of gaming experience provoked by "World of Warcraft" pictures [34]. Similar findings have been reported in subsequent studies examining individuals with current IGD [72] and those in remission from online IGD [72]. Moreover, reduced fronto-striatal in resting state functional connectivity was linked to cognitive control deficits in IGD [77]. Taken together, this suggests deficient modulation of reward-driven behavior may be associated with dysfunctions in the frontal cortex.

More recent studies have additionally implicated fronto-cortical mechanisms in IGD [64]. For example, resting state differences in executive control networks have been found, with weaker strength among IGD relative to non-IGD subjects in a manner that was linked to cognitive control [17]. Additionally, relative blunted ventral striatal activation has been observed during reward processing in IGD [16], as has been reported in GD and SUDs [49].

Findings have also linked brain mechanisms to transitions in IGD and its treatment. For example, cue-related activation of the lentiform nucleus has been linked to emergence of IGD, [20] and relatively decreased engagement of the dlPFC and increased engagement of the insula may be linked to persistence of IGD [18]. Treatment studies have implicated activation and connectivity patterns to outcome measures, implicating regions like the insula and precuneus [78] as well as orbitofrontal cortex, hippocampal, and supplementary motor regions [79]. These findings suggest that treatment may operate to change regional connectivity patterns underlying cue-responsivity and learned associations linked to gaming behaviors. Gender-related differences are also important to consider and may provide insight into why males may be more vulnerable to developing IGD [19, 21].

White matter and gray matter studies have been conducted with some evidence suggesting better white matter integrity in IGD [22]. A meta-analysis

has shown reduced gray matter volumes in IGD in regions including the vmPFC and ACC [71], as has been seen in substance addictions [74].

63.4.2 Neurochemistry

In an early neurobiological study of video-game playing using [^{11}C]raclopride (PET) scanning, increased release of dopamine to D2-like receptors in the ventral striatum was observed following 50 minute of video-game playing in eight healthy adult males [72]. A more recent study using SPECT similarly suggested increased dopamine release in the caudate during a motorbike racing computer game, compared to baseline measures among healthy adult males [72]. Video-game playing appears to induce dopamine release that may be comparable to the effects of psychoactive substances [72]. However, the relevance to IGD remains to be studied, although preliminary studies suggest that dysregulation of D2-like receptors in the striatum may be linked to duration of IGD [63].

Following a 6-week trial of bupropion (a drug with influences on dopaminergic and other neurotransmitter systems), individuals with IGD (>30 hour StarCraft/week) demonstrated decreased craving for video-game play, reduced total gameplay time, and less cue-induced brain activity in the dlPFC compared to pre-treatment [72].

63.4.3 Genetics/Family History

Genetic studies for IGD are limited. Han et al. [27] reported that the presence of the Taq1A1 allele of *DRD2* and the low-activity Val158Met variant of COMT genes was more prevalent among online PVG adolescent males than controls. Genome-wide association studies are needed.

63.4.4 Conclusion

With public attention, IGD is actively being studied. Preliminary studies suggest neurobiological similarities with substance addictions. The decision to include gaming disorder in the ICD-11 should further promote research efforts and attention of health professionals to this disorder.

63.5 Hypersexual Disorder or Compulsive Sexual Behavior Disorder

"Hypersexual disorder," "sexual addiction," or "compulsive sexual behavior disorder" may be defined as recurrent or repetitive sexual behavior that interferes in areas of life functioning. Hypersexual disorder, conceptualized as a nonparaphilic sexual desire disorder with impulsivity and/or compulsivity components [31], was considered for inclusion in DSM-5 but was excluded [2]. However, the ICD-11 has included criteria for compulsive sexual behavior disorder (CSBD) as an impulse control disorder [70], and as such we use this term in this chapter. However, as most research has not employed the recently developed diagnostic criteria, we will also refer to CSBs, as appropriate. Some individuals who suffer from CSBD may display clinical features that resemble addictive disorders including craving prior to behavioral engagement, impaired control over behavioral engagement and behavioral engagement despite adverse consequences [35].

63.5.1 Neural Systems

Early neuroimaging studies often focused on cue-induced reactivity. A recent meta-analysis of functional neuroimaging studies suggest overlapping as well as distinct neural substrates of cue reactivity to drug, gambling, food, and sex rewards [54]. Much like drug cues, cue reactivity to sexual stimuli may involve networks that process rewards, emotions, and habits (including cingulate gyrus, insula, head of the caudate, frontal gyrus, and cerebellum). However, sexual reward cues may induce unique activation of the pulvinar in thalamus. Structurally, gray matter volume of the right caudate has been found to be negatively associated with reported pornography

hours per week [41]. Taken together, these findings suggest that exposure to sexual stimuli may relate to fronto-striatal pathways.

Early neuroimaging studies of CSBs used varying approaches. Using diffusion tensor imaging, Miner et al. [52] found that although mean diffusivity in the inferior frontal region was negatively correlated with impulsivity, fractional anisotropy and mean diffusivity measures of this area did not differ between individuals with and without CSBs. These data suggest possible differences from GD and some other behavioral addictions in which associations with inferior frontal white matter disorganization have been reported (i.e., low fractional anisotropy and high mean diffusivity), albeit not always in inferior frontal regions [72].

Men with CSBs as compared to those without have shown greater activation of the ACC, ventral striatum, and amygdala in response to sexual cues, and functional connectivity of these regions was associated with sexual desire more strongly in men with CSBs [68]. Men with problematic pornography use as compared to those without have shown greater ventral striatal activation to cues predicting the possible receipt of viewing sexual/erotic images, with the degree of neural activation correlating with task response times and out-of-the-magnet measures of sexual addiction, pornography viewing, and masturbation [26]. These and other findings suggest links between CSBs and formally defined addictions [37, 62].

Animal research suggests that the medial prefrontal cortex (mPFC) contributes to sexual behaviors. Lesions of the mPFC in rats may block the acquisition of sex-aversion condition and impair the suppression of seeking of sexual rewards in the face of aversive consequences [72]. How the mPFC may contribute to CSBD requires further study.

63.5.2 Neurochemistry

Our current understanding of the neurochemistry of CSBD is predominantly derived from pharmacological studies. In a double-blind, placebo-controlled study of CSBD in homosexual and bisexual men, the selective serotonin reuptake inhibitor (SSRI) citalopram was found to reduce sexual desire without lessening sexual satisfaction [72]. Another SSRI, fluoxetine, was found to be effective in reducing symptoms in men with either paraphilia or paraphilia-related disorders [72]. In addition, better results were obtained when methylphenidate was used in conjunction with fluoxetine, suggesting an additive effect and implicating possible involvement of dopamine and norepinephrine [72]. A case series of men with problematic pornography use being treated with paroxetine suggested possible efficacy with respect to reducing anxiety and pornography use but was also associated with the emergence of other problematic sexual behaviors [25].

Naltrexone, an opioid receptor antagonist, appears effective in treating hypersexual disorder. Administration of high doses (100–200 mg/day) has been reported to successfully reduce hypersexual disorder symptoms, sexual urges, sexual fantasies, and masturbation in two case report studies [72]. These features, however, recurred following naltrexone discontinuation. Naltrexone has also been reported to reduce urges in problematic pornography use in a man receiving cognitive behavioral therapy [38].

Other investigators have suggested that medications (such as SSRIs and lithium) may not specifically manage sexually addictive behaviors but rather treat comorbid psychiatric disorders, which may, in turn, help patients address CSBs [72]. Controlled trials and systematic studies are needed to examine efficacy and tolerability of medications for CSBD.

63.5.3 Genetics/Family History

Individuals with CSBD appear more likely to have parents with a similar condition and were more likely to have a first-degree relative with SUDs [72]. Carnes [13] reported that 87% of CSBD patients come from families with addiction problems.

63.5.4 Conclusion

CSBD is a clinical condition that may have substantial negative impacts. Neurobiological research in CSBD is emerging, and the inclusion of defined criteria in the ICD-11 should help promote consistency across studies.

63.6 Food Addiction

Food addiction has been discussed in the popular media and has received considerable research attention. Addictive processes have been suggested to underlie obesity [72]. Emerging neurobiological research suggests both substance use and eating behaviors may engage similar neurocircuitry and have consequently led to the conceptualization of "foods as drugs." However, the concept of food addiction remains debated with some investigators arguing that existing research has yielded conflicting results [80] and others arguing that this construct may be particularly relevant to certain subgroups of obese individuals, such as those with binge-eating disorder (BED) [72]. Although not labeled as such, several core features of BED share similarities with those for substance dependence including strong food cravings and diminished control over eating [72]. Over a quarter of clinicians report often or always using addiction-based therapies for BED [72], further suggesting clinical and phenomenological similarities. It is important to note that for some individuals, overeating is a relatively passive event that takes the form of liberal snacking, eating large portions, and physical inactivity [3], and the extent to which these behaviors may constitute an addiction has been debated.

63.6.1 Neural Systems

With regard to cognitive control circuits, imaging studies in obese (versus lean) subjects have documented increased frontal activation of the vmPFC, dlPFC, and cingulate gyrus upon exposure to food-related stimuli and have been implicated in feeding motivations [72]. Obese versus lean individuals have also shown enhanced corticolimbic-striatal activation to favorite food cues and stress cues in a guided imagery fMRI task [29]. In the same study, measures of insulin resistance correlated positively with regional brain activations to favorite-food, stress, and neutral-relaxing cues in obese but not lean individuals and regional brain activations (particularly in the thalamus) mediated the relationships between insulin resistance and favorite-food-cue-induced craving in obese but not lean individuals. These data suggest that obese individuals may be hyper-responsive to food cues (particularly those of high-caloric value), and that metabolic measures may relate to these brain activations differently in obese and lean individuals.

Obesity is a heterogeneous construct and data suggest that certain subgroups, such as those with BED, may exhibit food-addiction features more so than others. Individuals with BED compared to body mass index (BMI)-matched non-BED obese and lean individuals showed relatively diminished activity in the vmPFC, inferior frontal gyrus, and insula during the Stroop task [9]. The same research group found that during a MID task, BED obese individuals showed relatively diminished ventral striatal activity during anticipatory phases relative to non-BED obese individuals, whereas non-BED obese individuals showed heightened ventral striatal and vmPFC responses compared to lean individuals [9]. Further, preliminary data link relatively diminished ventral striatal activation to poorer treatment outcome in BED [5]. Taken together, these results suggest that neural differences exist between obesity subgroups.

Neuroimaging studies have directly assessed food addiction. Gearhardt et al. [24] found that activation in the ACC, medial orbitofrontal cortex, and amygdala in response to anticipated receipt of food was positively correlated with food addiction scores among lean and obese young females. Furthermore, females with high food addiction scores, compared to those with low scores, showed decreased activation in the orbitofrontal cortex during food intake. No significant correlation was observed between food addiction score and BMI, suggesting that food

addiction and related neural functioning may occur among individuals with a range of body weights. In another study, Feldstein Ewing et al. [23] found greater response across the orbitofrontal cortex, ventral striatum, and additional frontoparietal and temporal regions among overweight/obese individuals in an fMRI gustatory cue exposure task when comparing task-related response after consumption of a high-calorie versus low-calorie drink. These neural responses were, however, not related to food addiction scores.

63.6.2 Neurochemistry

Dopamine release has been related to food and food cues [72]. Overconsumption of energy-rich foods may condition dopaminergic responses to food cues and concurrently down-regulate dopamine responses to other incentives [67]. Administration of dopamine antagonists may abolish responding for food in rats [72]. Development of addiction-like reward deficits and onset of compulsive-like food-seeking may be accelerated by lentivirus-mediated knockdown of striatal D2-like receptors in rats with extended access to palatable, high-fat food [72]. Studies using [^{11}C]raclopride (PET) scanning have demonstrated that D2-like receptor availability is reduced in obese individuals and mice [72]. Moreover, among obese individuals, D2-like receptor availability correlated negatively with BMI scores [72].

Data from animal models suggest ingestion of foods of different palatability and energy density may produce different effects in dopaminergic systems. Rats classified as prone to binge-eating consumed significantly more highly palatable and energy-dense (high-fat, high-sugar) food and tolerated higher levels of foot-shock for such foods than binge-eating-resistant rats [72]. Regular consumption of energy-dense food may have lasting consequences on the brain. Using a diet-induced model of obesity, rats fed a high-sugar diet compared to those on an unrestricted diet showed decreased dopamine release in the nucleus accumbens following 36 hours of food deprivation [72]. Similarly, Alsiö et al. [1] found that rats fed a high-fat (versus unrestricted) diet showed decreased expression of D1 and D2 receptors in the ventral tegmental area, nucleus accumbens and prefrontal cortex (PFC) following a 18-day withdrawal. Furthermore, obesity-prone rats showed increased craving and anxiety compared to obesity-resistant rats during the second withdrawal week following discontinuation of the energy-dense diet [72]. Future studies are needed to examine whether these dietary findings may extend to human subjects.

The only medication with a formal indication in the treatment of BED is lisdexamfetamine [51]. Lisdexamfetamine is a stimulant pro-drug whose product (dextroamphetamine) promotes dopaminergic and noradrenergic effects by blocking their reuptake and increasing their concentrations in the synaptic cleft, and as such models of BED consider roles for dopaminergic and noradrenergic systems [28, 32].

The serotonin and norepinephrine reuptake inhibitor sibutramine and SSRI fluoxetine have shown some efficacy in treating eating disorders and were approved by the Food and Drug Administration for treatment of obesity and bulimia nervosa, respectively, although the former has been recalled in the United States for cardiovascular safety concerns [51]. SSRIs in general may be effective in targeting binge-eating, psychiatric and weight symptoms [60], although the effectiveness and duration of these medications remain under debate. Open-label studies report initial SSRI (citalopram and fluoxetine) administration reduced binge-eating and weight loss in BED patients; at a 6-month follow-up, these beneficial effects were maintained with continuation of SSRI treatment [44] though there has been conflicting evidence on their long-lasting effects [72]. In a randomized, double-blind, 12-week study of escitalopram for the treatment of individuals with co-occurring BED and obesity, individuals receiving high-dose escitalopram treatment had significantly greater reductions in weight, BMI, frequency of binge episodes, and global severity of illness scores than those receiving placebo treatment [72].

Opioids are implicated in eating behaviors [72], although the precise nature of their influences are unclear. High doses of the opiate antagonist, naloxone, increased sugar consumption, and opiate-like withdrawal symptoms including elevated plus-maze anxiety, teeth chattering and head shakes in sugar-binging rats following a period of abstinence [72]. These findings may, however, be unique to sugar binging. Bocarsly et al. [11] reported that rats on high-fat diets did not show signs of opiate-like withdrawal when exposed to naloxone. Taken together, these findings suggest that the brain opioid system may be differently affected by the overeating of different nutrients.

63.6.3 Genetics/Family History

Obesity is ten-fold more likely in people with an obese first-degree relative [72]. When pregnant rats maintained a highly palatable and energy-dense (high fat, high sugar) diet, their offspring showed an increased preference for sugar and fat in comparison to those with mothers on a control diet [69]. Additionally, dopamine and opioid receptor expression was increased in reward-related brain regions including the ventral striatum, PFC and hypothalamus [69].

In humans, obese individuals with BED, in contrast to non-BED obese controls, had lower frequencies of the Taq1A1 allele of the *DRD2* gene and higher frequencies of the G118 allele of the mu-opioid receptor gene (*OPRM1*) [72]. Non-obese individuals with a variant of the fat mass and obesity-associated (*FTO*) gene – a gene linked to the regulation of the activity of dopaminergic midbrain areas and whose polymorphisms have been linked to BMI – demonstrated enhanced neural response to food cues [40]. Taken together, genetic data suggest dopamine and opioid receptor genotypes be involved in obesity and different patterns of eating. Genetic polymorphism of the *5HTTLPR* has also been implicated, with S allele carriers showing higher BMI scores than homozygous LL carriers and being more frequent among overweight adolescents [72].

63.6.4 Conclusion

Eating behaviors have been tested extensively using animal models, and a considerable amount of neurobiological research has been generated, although less is known about food addiction per se. Data suggest that animal results may be transferable to human populations, although further research is needed. Certain subgroups of people with obesity (e.g., those with BED) and certain diets (e.g., highly palatable, energy-dense) may share more neurobiological similarities with SUDs. Such findings have important implications, and the extent to which a food-addiction model applies to individuals with obesity and its subgroups merits further investigation.

63.7 Compulsive Shopping or Buying

Classically referred to as "oniomania," compulsive shopping or buying has had a long-standing history (in comparison to more recent phenomena such as IAD and IGD) and was clinically described a century ago. Interest in compulsive shopping or buying has rekindled in recent years (see review: [10]). However, compulsive shopping or buying is not included as disorder in the DSM-5 or ICD-11 [53].

63.7.1 Neural Systems

An fMRI study found stronger ventral striatal activity among individuals with compulsive shopping or buying (versus control subjects) during the initial product presentation phase of a multi-phase purchasing task [72]. During a subsequent price presentation phase, individuals with compulsive shopping or buying showed reduced activation of the insula and ACC. ACC activity was also higher among individuals with compulsive shopping or buying during the concluding decision phase.

63.7.2 Neurochemistry

Beneficial results of citalopram, an SSRI, have been reported in a small 12-week open-label trial, and in a 6-month follow-up, individuals with compulsive shopping or buying continuing citalopram were less likely to relapse than those who discontinued the medication [72]. A subsequent study found those assigned to placebo were more likely to relapse compared to those randomized to continue taking citalopram in a 9-week double-blind, placebo-controlled administration following a 7-week open-label trial [72].

Findings from other SSRIs have been negative. Another study by Koran et al. [36] found no difference between escitalopram and placebo conditions. Double-blind comparisons of fluvoxamine and placebo similarly found no difference in compulsive shopping or buying symptom reduction [10]. As such, data supporting SSRIs in the treatment of individuals with compulsive shopping or buying are mixed, and currently no medication has a formal indication for compulsive shopping or buying.

63.7.3 Genetics/Family History

Compulsive shopping or buying may run in families. Of 18 individuals with compulsive shopping or buying, 3 had one or more first-degree relative with compulsive shopping or buying and 11 had relatives with a SUD [72]. Negative findings have been reported for *5HTTLPR* polymorphisms [72].

63.7.4 Conclusion

Our current knowledge of the neurobiology and genetics of compulsive shopping or buying is limited, but preliminary research suggests altered neurofunctional responses to shopping stimuli. Further research is needed to determine the role of various neurotransmitters, the efficacies of specific medications, and the underlying biology.

63.8 Conclusion

Research in behavioral addictions is challenging due to the heterogeneity of the behaviors, with certain subgroups arguably fitting better in an addiction framework than others [72]. Further complications stem from the arguably normative nature of these behaviors, which has led to debates among researchers as to what constitutes an addiction [4, 72]. Uniformly agreed upon diagnostic criteria and assessment tools will not only facilitate comparisons across studies, but may help to ensure that cut-off points are appropriately generated. Additional research in the domains of neuroimaging, neurochemistry, genetics, and treatment is needed to increase knowledge of behavioral addictions to the level of that for substance addictions. In particular, future studies investigating often underrepresented female populations (especially for IAD and IGD) and studies conducted longitudinally would provide valuable information and more comprehensive understanding.

Keeping these limitations in mind, existing research suggests parallels between behavioral addictions and SUDs. Data are most extensive for GD, and these data led to reclassification of GD as a behavioral addiction in DSM-5 and ICD-11. Although many gaps in knowledge remain, research in IAD, IGD, CSBD, food addiction, and compulsive shopping or buying has accelerated in recent years, with such work yielding important insights.

Neuroscientific approaches to addiction have traditionally been based on the premise that addiction is a process that results from brain changes associated with chronic intake of physical substances. Although the neurobiologies of behavioral addictions remain less well understood than those of SUDs, recent research suggests that similar biological features may lead to the development of behavioral and substance addictions. Given the considerable co-occurrences of behavioral and substance addictions, an improved understanding of their relationships has important implications for not only furthering our understanding of the neurobiologies of these disorders, but also improving prevention and treatment strategies.

Key Points

- Which disorders constitute behavioral addictions remains debated
- Gambling disorder and gaming disorder are recognized by the World Health Organization as disorders due to addictive behaviors
- Similarities and differences exist between individual behavioral addictions
- Similarities and differences exist between behavioral and substance addictions

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The Transdiagnostic Mechanisms of Behavioral Addictions and Their Treatment

64

Hyoun S. Kim and David C. Hodgins

Contents

Abstract

Behavioral addictions such as gambling, video games, shopping, and compulsive sexual behaviors share considerable similarities to substance use disorders. These similarities were officially recognized in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) with the inclusion of gambling disorder in the Substance Use and Related Disorders, the first behavioral addiction to be recognized as such. While our knowledge of behavioral addictions has grown exponentially in the past several decades, evidence-based treatments of behavioral addictions are lacking. Given the similarities between substance and behavioral addictions, we argue that it is possible to develop a treatment for behavioral and substance addictions that targets their underlying similarities (i.e., transdiagnostic mechanisms). In this chapter, we provide an overview of the transdiagnostic mechanisms of behavioral (and substance) addictions as well as the empirically supported intervention possibilities that target them. Specifically, we identify six transdiagnostic mechanisms: deficits in motivation, urgency, deficits in self-control, maladaptive expectancies and motives, deficits in social support, and compulsivity. We conclude with

H. S. Kim (✉) · D. C. Hodgins
Department of Psychology, University of Calgary, Calgary, AB, Canada
e-mail: hyoun.kim@ucalgary.ca

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a discussion on transdiagnostic treatments (i.e., treatments that apply the same underlying intervention principles to a class of disorders) and propose a recently developed pragmatic transdiagnostic treatment of addiction called the Component Model of Addiction Treatment (CMAT; Kim, Hodgins (Front Psych 9, 2018)). The CMAT may have several benefits over disorder-specific treatments, including providing treatment for emerging behavioral addictions (e.g., gaming, shopping, compulsive sexual behaviors). Clinical applications of the CMAT are discussed.

Keyword

Transdiagnostic treatment · Behavioral addictions · Substance use disorder · Component model · Mechanisms

64.1 Introduction

Traditionally, the concept of addictive disorders was limited to psychoactive substances. However, with the publication of the 5th edition of the Diagnostics and Statistical Manual of Mental Disorders (DSM-5) [2] and the 11th edition of the World Health Organization's International Classification of Diseases (ICD-11) [23], the concept of addiction was expanded to include non-substance-related addictive behaviors. Specifically, gambling disorder was included in the Substance Use and Related Disorders section of the DSM-5, and as a disorder due to addictive behaviors in the ICD-11. Gaming disorder was also recognized as an addiction in the ICD-11 with its inclusion alongside gambling disorder in the disorders due to addictive behaviors section. Gaming was also included in the DSM-5 appendix as requiring further investigation (i.e., Internet gaming disorder). In other words, the DSM-5 and ICD-11 recognize the existence of behavioral addictions. It is anticipated that additional behavioral addictions will be added in the future as research evidence accumulates supporting their validity [63]. For example, while compulsive buying and sex addiction were not included in the DSM-5 or ICD-11, with more empirical evidence, these behavioral addictions may also warrant inclusion in future editions [43, 55].

The past several decades have seen remarkable growth in the empirical investigations of behavioral addictions. While fewer than 300 studies were published on this topic in 1990, this number increased over eightfold with over 2500 articles published in 2013. These articles examine a wide array of issues related to behavioral addictions, including their risk factors and correlates with other psychiatric disorders [8]. What can be concluded from the extant literature is that there is a considerable overlap across addictive behaviors, including both substance and behavioral addictions in etiological (e.g., onset, natural course), phenomenological (e.g., cravings, preoccupations), and clinical (e.g., treatment strategies, comorbidities) factors [24].

Despite the increased empirical interest, our knowledge regarding the optimal treatment of behavioral addictions remains sparse. Indeed, gambling disorder is the only behavioral addiction that currently has validated evidence-based treatments. For example, both motivational interviewing (MI)/enhancement therapy and cognitive behavioral therapy have demonstrated efficacy as evidence-based psychological treatments for gambling disorder [74]. In contrast, the evidence base for the treatment of other behavioral addictions, including Internet gaming disorder, is less developed [63]. This is an important gap as behavioral addictions are relatively common psychiatric disorders with prevalence rates of up to 22% ([63]).

We have recently argued that a potentially limiting factor in the development of behavioral addiction treatment is the tendency to create disorder-specific protocols [38]. For example, there now exists separate treatment protocols for gambling disorder, gaming disorder, and compulsive sexual behaviors, to name only a few. Unfortunately, the creation of disorder-specific protocols is problematic on several grounds. The

first and foremost limitation is that there are dozens of behaviors that have been purported to be behavioral addictions [35]. Thus, a disorder-specific treatment approach would necessitate the creation of dozens of treatment protocols for each "unique" disorder, with significant overlap in treatment content of each. It would also necessitate clinicians to learn and become competent in dozens of treatment protocols, which may not be feasible due to time and costs. The creation of disorder-specific protocols also further perpetuates the notion that each potential behavioral addiction is a new psychiatric disorder when the empirical evidence suggests considerable similarities across behavioral addictions. These similarities may warrant conceptualization of behavioral addictions as a group of disorders that represent a common underlying pathology rather than as unique disorders.

The similarities between addictive disorders have been noted since the 1980s with the general theory of addictions [34], and they have been expanded upon in subsequent years (e.g., [25, 61, 68, 75]). For example, Shaffer et al. [68] posited in their syndrome model of addiction that addictive disorders can be thought of as a syndrome of shared signs and symptoms that reflect common underlying risk factors. Orford [61] outlined a set of primary and secondary psychological processes, occurring within a sociocultural context, that lead to a strong attachment to "appetitive" activities (e.g., drinking, gambling, exercise) with impairments of self-control. Griffiths [25] also posited that all addictions can be conceptualized by their similarities rather than their differences. Specifically, according to Griffiths [25], all addictions share six core characteristics: (1) salience, (2) mood modification, (3) tolerance, (4) withdrawal, (5) conflict, and (6) relapse. More recently, seven constructs were derived from expert consensus to be important in understanding the neuropsychological dysfunctions underlying addictions. These include aspects of the positive valence system (reward valuation, reward expectancy, action selection, reward learning, habit), the cognitive control system (response selection/inhibition), and impairment of control (compulsivity) [75]. Given the considerable overlap across addictive disorders, we contend that it is possible to develop a unified treatment model that can be applied across not only behavioral addictions but also substance addictions that target their underlying similarities (i.e., transdiagnostic mechanisms).

Indeed, treatments that target shared mechanisms are not novel and have been developed for anxiety disorders [4] and eating disorders [18]. These treatments target core etiological and maintaining factors shared by a group of disorders, such as avoidance and high neuroticism seen in anxiety disorders and preoccupation of body weight and shape seen in eating disorders. Herein, we suggest that it is also possible to develop a treatment that capitalizes on the underlying similarities between behavioral and substance addictions. In the following section, we provide an overview of the transdiagnostic mechanisms of behavioral and substance addictions along with their intervention possibilities: deficits in motivation, urgency, deficits in self-control, maladaptive expectancies and motives, deficits in social support, and compulsivity (Table 64.1).

The following transdiagnostic mechanisms were identified based on our review of the literature. Specifically, the transdiagnostic mechanisms were selected if they were important etiological and maintaining factors across behavioral and substance addictions, and there existed empirically supported interventions to modify them. It is important to note that other transdiagnostic mechanisms may be identified in the future based on empirical support for their importance across addictive behaviors as well as support that they are amiable to change.

Table 64.1 Transdiagnostic mechanisms of addictions and their interventions

Transdiagnostic mechanism	Intervention	Technique/Skills
Deficits in motivation	Motivational interviewing	Decisional balance Asking about the future Asking about the time before the addiction Asking about values Confidence and importance ratings Query extremes
Urgency	Mindfulness-based interventions	Mindful breathing Body scan meditation Urge surfing
Deficits in self-control	Problem-solving Working memory interventions	5 steps to problem-solving Cognitive training
Maladaptive expectancies and motives	Cognitive-behavioral interventions Coping skills interventions	Thought records Increasing Pleasant activities
Deficits in social support	Self-help programs Assertiveness training	12 step groups/SMART Recovery Expressing negative emotions Asking for support Refusal skills
Compulsivity and maladaptive perseveration of behavior	Stimulus control Cue exposure intervention	Identifying high-risk situations Cue exposure training

64.2 Transdiagnostic Mechanism of Behavioral and Substance Addictions and Their Intervention Possibilities

64.2.1 Deficits in Motivation

The first transdiagnostic mechanism is motivation to change. At least a modicum of motivation is necessary for clients to engage in treatment, even if the motivation is externally derived, reflecting pressure due to family, friends, or more formal influences such as legal mandate. It is increasingly recognized that the first step in treatment is addressing motivation. Furthermore, addressing motivation as needed throughout treatment leads to better engagement, lower attrition, and better outcomes [56]. Motivational interviewing (MI) is a style of interacting with clients that helps them engage in the treatment process, focus on refining their change goals, and identify personal motivations to change and resolve any ambivalence about their decisions. A recent "review of reviews" showed that evidence for the efficacy of MI is strong across a range of addictive behaviors [15].

A related and important issue in treatment is the issue of treatment goal. Treatment goal, whether abstinence or harm reduction, will likely depend on multiple factors, including client preference. MI helps clients to identify and refine their change goals, without imposing any specific goal, which may help enhance motivation. An important consideration in the treatment of behavioral addictions is that the strict focus on abstinence that traditionally is found in substance use disorder treatment is not necessarily applicable for behavioral addictions. Take gambling, for example, does abstinence from gambling preclude any type of gambling, including the purchase of an occasional raffle ticket, or only cessation of the problematic types for the client? Evidence suggests that certain types of gambling can continue non-problematically after a person "quits gambling" [39]. For other behaviors, specifically everyday behaviors such as shopping, work, sex, and eating, cessation may not be feasible at all. Moreover, it is clear that clients with both behavioral and substance addictions shift their goals over time, often not sharing their goal with the treatment provider [69]. At the same time, there is some evidence

that with greater problem severity, adoption of an abstinence goal is associated with better outcomes [69]. A common clinical stance, consistent with MI, is to help the client identify their personal goal in specific terms and to support the client in striving toward that goal but also encouraging revisiting the feasibility of the goal as treatment proceeds.

Miller and Rollnick [52] emphasized that although a range of MI therapeutic techniques are available, the spirit in which MI is offered is an essential ingredient. MI is a client-centered, collaborative interaction in which the client is encouraged to identify and describe reasons, needs, and desires to change their behavior and to talk about their ability and commitment to take action. These verbalizations are termed "change talk," and recent process research shows that the amount of change talk generated in MI is linked with subsequent successful change [46]. Therapists strategically reflect the change talk that they hear to encourage clients to provide examples, elaborate, and expand on their reasons, desires, and need for change. Clients are also invited to describe their ambivalence toward change, including reasons that they would prefer to continue their problematic behaviors and reasons that change would be difficult. This discussion is labeled as "sustain talk," and a greater proportion of change talk versus sustain talk is also linked with successful change [46].

Keeping in mind that the collaborative and client-centered spirit of MI is central, a variety of exercises are available for use in individual therapy and in groups to have clients generate change talk and explore their ambivalence [52]. The Decisional Balance exercise is a frequently used method for helping the client engage in this discussion. It involves using a 2 × 2 grid to capture and summarize the clients' discussion of the benefits and disadvantages of changing and not changing (i.e., pros and cons). The goal is to use the grid as a clinical tool to engage clients in clarifying their goals and generating change talk. The therapist reflects what is said and asks for more detail and examples, which serve to increase the amount of change talk even more. (Table 64.2 lists this technique and other common MI exercises.) Some exercises elicit change talk and some help resolve ambivalence by underscoring the discrepancy between the clients' addictive behavior and their goals and values. In individual therapy, the goal is to continue the discussion until the client is subtly or overtly expressing a

Table 64.2 Exercises to enhance motivation

Exercise	Brief description	Key questions
Decisional balance exercise	Client describes their reasons for changing and not changing using a 2 × 2 grid (pros and cons of changing and pros and cons of not changing)	What are the good things about your involvement with… And the not so good things? What would not be good about changing? And good about changing?
Asking about the future	Clients describe a discrepancy between their current behavior and future goals	Where do you see yourself going in 5 years?
Asking about the time before the addiction	Clients describe a discrepancy between their current behavior and desired goals	What was life like before you began to…?
Asking about values	Clients describe a discrepancy between their current behavior and values	What is important to you? When you make a decision, what values do you consider?
Confidence and importance ratings	Clients are asked to rate the importance of change and their level of confidence in being able to change if they wanted to, using a 0 to 10-point scale.	In terms of importance, you rated…. This is (above a zero, moderate, high). Why not lower? What would need to happen to make it higher? In terms of your confidence, it is (higher/lower) than your importance. Why is it …?
Query extremes	Clients are asked about the worst- and best-case scenarios if they overcome or do not overcome their addiction.	What is the worst thing that might happen if you continue to…? And the best is you do not?

desire to move to actively tackling the problem. For example, in a subtle shift, the change talk might shift to discussion of steps already taken to change ("I googled to see how to cancel my online account") or envisioning what change might look like ("Friday nights might be difficult to fill. I think I will need to join a sports team"). More overtly, the client may ask what the possibilities are for change. In the group context, the therapist must observe the group as a whole to determine when to shift into the next more action-oriented topic.

64.2.2 Urgency

Urgency is a facet of impulsivity that is characterized as the tendency to act rashly during intense emotional experiences [13]. People may act rashly under intense positive emotions (i.e., positive urgency) and/or during intense negative emotions (i.e., negative urgency). For a significant proportion of individuals, the function of engaging in addictions is to alleviate negative affect. Indeed, the ability of both behavioral and substance addictions to regulate affect has been suggested to be an important component of all addictive behaviors [25, 61]. There is empirical evidence to support the notion that negative urgency may be an important transdiagnostic mechanism across addictive disorders. Negative urgency has been found to be a robust predictor of both behavioral and substance addictions (see [38]) and is elevated among people with comorbid behavioral and substance addictions [19]. Negative urgency has also been found to have important treatment implications. Although negative urgency increases the risk of relapse, it is a facet of impulsivity that can be modified during treatment [26]. As such, negative urgency may constitute an important transdiagnostic mechanism that may need to be addressed in treatment.

Mindfulness-based strategies effectively target negative urgency. Mindfulness is generally defined as the ability to pay attention to the present moment purposefully and non-judgmentally [3], and it has been conceptualized as being both a trait and a state [37]. Importantly, there is evidence to suggest that mindfulness-based interventions can increase trait levels of mindfulness, even when people are not engaging in mindful practice (see [21]). In recent years, mindfulness-based interventions have gained empirical support in the treatment of a variety of psychiatric disorders, including addictive disorders [12]. For example, mindfulness-based approaches have been applied to a wide array of behavioral and substance addiction with preliminary support for their efficacy [66]. Mindfulness-based interventions provide skills to help clients cope with difficult emotions in the present moment rather than reacting to their internal states. By staying in the present moment, the intensity and duration of negative emotions are lessened, which reduces the likelihood of turning to an addictive behavior as a maladaptive coping mechanism. Indeed, a potential mechanism for the treatment effects of mindfulness is a reduction in behavioral reactivity and improving emotion regulation skills (i.e., negative urgency; [33]).

As previously mentioned, mindfulness can be cultivated through mindful practice. Formal practices of mindfulness include mindful breathing [11], in which clients purposefully focus their attention on their breath and observe their breath without trying to change it. It is common for clients to shift their attention to thoughts that may arise during mindful breathing practice, especially when they are newly developing mindfulness skills. When clients notice that their attention has wandered from focusing on their breath, they are encouraged to acknowledge their thoughts and gently and non-judgmentally shift their attention back to their breath. The mindfulness breathing exercises are typically 10 minutes in duration and can be guided or unguided. Body scan mediation is another common mindfulness-based practice. In this practice, clients bring their focused attention to physical sensations (e.g., tingling, tightness, pulsing) that they may be experiencing in their body. This can be done systematically, by beginning to examine sensations starting from the head and moving purposefully down to the toe, or simply noticing a physical sensation that may arise. Similar to the mindful breathing exercise, it is common for cli-

ents to experience their mind wandering, and when this occurs, they are encouraged to purposefully reorient their attention to bodily sensations. With continued practice, clients are able to purposefully attend to their breath and physical sensations for longer periods of time. Importantly, clients also develop the skills to purposefully shift their attention to different aspects of their affective and physical states in their day-to-day lives, thus lessening behavioral and emotional reactivity. Mindfulness training is typically done as weekly or twice-a-week sessions and can be conducted in both individual and group settings. It is helpful to debrief with clients regarding their experiences, including whether they noticed any thoughts that arose during the practice, the process of reorienting their attention to their breath, and whether they found the practice easy or difficult. Additionally, clients are often assigned to practice 10 minutes of mindfulness practice daily as homework.

Mindfulness-based interventions may particularly be beneficial in helping clients manage their urges and cravings. Urges and cravings are robustly associated with addiction and are a risk factor of relapse [67]. Mindfulness-based strategies are effective in reducing cravings, which may be a potential mechanism that leads to the overall treatment outcomes for addictions [66]. The experience of urges and cravings can be broken down into thoughts, physical sensations, and behaviors [50]. Through the practice of "urge surfing," clients develop the skills to tolerate their urges and cravings rather than reacting to them by engaging in the addictive behavior. Specifically, clients first acknowledge that they are experiencing an urge or craving. Thereafter, clients use the same skills developed in the mindful breathing and body scan exercises to purposefully shift their attention and observe their urges and cravings as they are experienced. With focused breathing, clients are able to release the tension associated with their urges and cravings, thereby reducing their emotional and behavioral reactivity. This cycle of focusing on the experience of urges and cravings combined with focused breathing is repeated until the intensity of the urge and cravings subside.

64.2.3 Deficits in Self-Control

Self-control is the ability to direct ones' actions toward a goal [5], both in the shorter term and in the longer term. Poor self-control is a component of impulsivity, and in addicted individuals, it is reflected in delay discounting, shortened time horizons, and self-control resource depletion [38]. In addition, deficits in self-control are associated with executive functioning deficits commonly seen in addiction [24]. Executive functioning is the ability to organize, plan, problem-solve, and coordinate thoughts and actions toward goal-directed behavior, thus facilitating self-control [9]. As such, executive functioning involves top-down cognitive processes such as inhibitory control and working memory [14].

A variety of treatment techniques are available to address deficits in the capacity to self-regulate. A well-established treatment intervention is training in problem-solving [57]. Generally, problem-solving consists of five structured steps [53]. The first step is to adopt a problem-solving orientation to situations that cause distress. Rather than catastrophizing or focusing on the hopelessness or unfairness of the situation and reacting impulsively, clients are encouraged to refocus on whether a problem exists that could be solved. To recognize whether a problem exists, people are taught to examine signs of physical (e.g., nausea) and emotional distress (e.g., sadness, anger). The next step is to identify the problem by determining what exactly the problem consists of, including people that may be involved. It is sometimes helpful to break down the problem into more manageable components. The third step is to brainstorm all possible ways that the problem can be resolved. The goal of this step is not to come up with the best solution, but all potential solutions to the problem. This step can be facilitated by reflecting on similar situations that the client may have successfully solved in the past and gathering information from both social networks and self-help resources. Once all possible solutions have been identified, the next step is to consider the potential benefits and consequences associated with each identified solution. Next, the client

chooses the plan of action that is most likely to solve the problem and is associated with the fewest negative consequences. The last step is to assess whether the solution was successful in resolving the problem. It is helpful to note what worked, what did not, and what could be changed next time. If the solution did not solve the problem, then clients can implement the next best option or brainstorm additional solutions.

Problem-solving training helps clients approach challenges as issues to be solved rather than reacting emotionally and impulsively. The relapse prevention model, first proposed by Marlatt in the 1980s, provides a broader framework for helping clients to think about both preventing and coping with high-risk situations associated with the problematic behavior [47]. This model was designed to be relevant to both behavioral and substance addiction. It typically is introduced to clients toward the end of treatment to help them plan for posttreatment challenges. However, it incorporates perspectives and skills already emphasized in the treatment program and involves four components: (1) identifying high-risk situations; (2) learning coping skills; (3) practicing coping skills; and (4) creating lifestyle balance. Numerous clinical guides and worksheets are available to help clinicians with implementing relapse prevention (e.g., [47]). The model can effectively be introduced and discussed in the group context as clients develop individualized relapse prevention plans.

Less well established, but promising, is working memory training as a treatment for addictions [7]. Although meta-analytic evidence exists that computerized cognitive training in older adults can transfer to non-training but similar tasks (near transfer), and to less similar tasks (far transfer) [58], the utility of working memory training in the treatment of addiction is only just emerging [73].

64.2.4 Maladaptive Expectancies and Motives

The beliefs that people hold in regard to addictive behaviors may lead to and maintain their addictions. Two dysfunctional beliefs have been identified that are important to address in treatment [6]. The first is permissive beliefs. These are maladaptive beliefs that provide a justification for engaging in the addictive behavior, such as *no one will find out if I do it just this time.* The second dysfunctional belief is called anticipatory beliefs. These beliefs relate to what people believe engaging in the addictive behavior will do for them, for example, *going to the casino will make me feel better.* Anticipatory beliefs may be closely related to people's motivations for engaging in addictive behaviors, specifically coping motives. Although three motives have generally been identified in regard to addictive behaviors (enhancement, social, and coping), engaging in addictive behaviors to cope with negative emotions is associated with the severity of addictive behaviors (see Kim and Hodgins [38]). Furthermore, coping motives have been found to underlie comorbid addictions [30, 44] and thus represent a transdiagnostic mechanism that can be targeted in treatment.

Cognitive behavioral interventions have shown efficacy in reducing maladaptive expectancies in addictive disorders [6, 41, 45, 49]. One well-known technique used in cognitive behavioral therapy is a thought record. Thought records help clients identify dysfunctional thoughts, their triggers, and develop skills to reframe dysfunctional beliefs to more adaptive and realistic beliefs [6]. There are generally five components to a thought record. The first is the date and time that a client identifies the occurrence of a dysfunctional thought or belief. Second is the context in which the dysfunctional thought occurred. Here, clients are asked to provide as much context as possible, including who they were with (if anyone), the location, and any other relevant details. This aspect of the thought record helps clients to identify potential triggers for their dysfunctional thoughts. The third component is to note emotional experiences associated with the dysfunctional thoughts, including the intensity of their emotional experiences. This is an important component of the thought record as dysfunctional thoughts are more likely to arise during periods of negative affect. The next step is to identify the dysfunctional thought, including labeling the

specific type of the dysfunctional thought (e.g., permissive or anticipatory) if possible. Clients are then taught skills to connect the dysfunctional thought to specific emotions. Indeed, a key principle of cognitive behavioral therapy is that our thoughts, emotions, and behaviors are all interconnected. Clients are then taught skills to change the dysfunctional thoughts to more helpful and realistic ones. To help this process, clients can ask themselves the following questions: (1) what is specifically dysfunctional about this thought? (2) Is this dysfunctional thought accurate? (c) What evidence do I have to support it? For example, a client who identifies the anticipatory thought, *going to the casino will make me feel better* may challenge this thought with *going to the casino might make me feel better in the short term, but will lead to more negative feelings in the long term* or *last time I went to the casino to make myself feel better, I ended up spending my rent money, which caused me more problems.* After the dysfunctional thought has been challenged, clients are asked to re-examine the intensity of their emotional experiences. More often than not, clients will report a reduction in the intensity of their negative emotions. The last component of the thought record is to identify helpful actions, which are behaviors that reduce the likelihood of engaging in the addiction, such as calling a supportive friend or family member, going for a walk, and/or engaging in relaxation exercises. The thought record can be completed both in individual sessions and in group treatment. In group treatment, clients volunteer to work through a personal example. Group members can be involved by asking for their input if a client is having difficulties with reframing their dysfunctional thoughts and/or asking group members what thoughts and/or emotions they may experience in similar situations.

Coping skills interventions can also be used to target maladaptive expectancies and motives. Coping skills training helps clients build skills to cope with difficult life events in a more adaptive manner, that is, being able to cope with difficult situations without the use of the addictive behavior [53]. One component of coping skills training is increasing pleasant activities [53]. If addictive behaviors constitute a maladaptive coping mechanism for negative emotions, then a possible intervention strategy is to increase positive emotions. Increasing pleasant activities serves several purposes. First, it is common for clients to find an abundance of time when they are in active recovery from their addiction. Thus, increasing pleasant activities helps to fill the void left by the addictive behavior and helps to prevent negative emotions such as boredom. To increase pleasant activities, clients, first, brainstorm a list of activities that they find pleasurable. The activities can be social events or activities that clients can do on their own such as reading a book. The activities can also involve monetary costs or can be free, such as going for a walk in the park. Once clients have identified a list of pleasant activities, they are asked to commit to engaging in the activities by scheduling them throughout the week. Clients often find it helpful to schedule a variety of positive activities throughout the week.

64.2.5 Deficits in Social Support

Lack of social support and interpersonal difficulties are strongly associated with addictive behaviors (see [38]). Additionally, the lack of social support, or the wrong type of support such as enabling, is associated with worse treatment outcomes, including increasing the risk of relapse [17, 76]. In response to this, several intervention strategies have been developed to increase social support and improve interpersonal relationships, which have demonstrated efficacy in the treatment of addictions [32, 51]. A common intervention to address deficits in social supports is joining self-help support groups such as 12-step programs or Self-Management and Recovery Training (SMART) Recovery. These mutual support groups are of great therapeutic benefit as they provide clients with a support network consisting of others who are also in recovery as well as potential access to a sponsor who can offer support during times of crisis. There exists self-help support groups for a variety of behavioral addictions (e.g., gambling, shopping, sex, eating), and there is evidence to suggest that these

support groups lead to improved outcomes [36]. In addition to mutual self-help support groups, family- and couple-based therapies such as the community reinforcement and family training approach [51] and behavioral couples' therapy [60] have been developed and show promise in the treatment of addictions.

Interventions that teach communication skills are an important component in addressing deficits in social support. Indeed, communication skills have shown to increase satisfaction and quality of interpersonal relationships [10] as well as treatment outcomes in addiction treatment [65]. To this end, clients are taught skills to communicate assertively. Assertive communication consists of being honest, direct, and expressing your thoughts, feelings, and wishes in a way that respects your own rights as well as the rights of others. Assertiveness is the most effective form of communication and is associated with improved interpersonal relationships, increases in receiving support, and increases in self-esteem and self-confidence [62].

When applied to the treatment of addictions, assertiveness skills can be used to express negative emotions, asking for support, refusal skills, and more (Table 64.3). For example, when expressing negative emotions, assertive communication first involves describing the behavior of the person that is causing the negative emotions. It is important to reference a specific behavior that is external to the person rather than resorting to blaming. The next step is to state the effect that the behavior is having on yourself. Thereafter, a request can be made to stop the behavior and state a positive reaction if they comply with the request. The same general steps can also be used to ask for social support. The development of refusal skills, such as the broken record technique is also an important component of addiction-specific communication skills [53]. In the broken record technique, clients develop skills to respond to a request to engage in an addictive behavior by politely declining. If the first refusal is not successful, clients once again repeat the refusal and so forth much like a broken

Table 64.3 Assertiveness skills in addictions treatment

Assertiveness Skills	Steps/Tips	Example
Expressing negative emotions	1. Describe the behavior of the other person that is causing you negative emotions. 2. State your feelings about the behavior. 3. Make a request to change the behavior. 4. State a positive reaction.	You are asking me again to go to the casino with you. I am upset by that since I told you, I have stopped gambling. I would appreciate it you don't ask me to go to the casino or any other place where there is gambling. If you stop asking me to go to the casino or any other place where there is gambling, then we can continue spending time together. If you keep asking me to gamble with you, we can't hang out together.
Asking for support	1. State exactly what you need help with. 2. Express how you are feeling about the problem. 3. Make a specific request how your support person can help.	I am supposed to be attending my first 12-step meeting tonight and I am feeling anxious and scared. Would you be able to come with me just for the first few sessions while I become comfortable? It would really help my anxiety if you came with me.
Refusal skills	1. Be direct and honest. 2. Keep it brief. 3. Be polite. 4. Speak slowly.	*Kate:* John, let's go to the mall this weekend, we haven't gone together in a while. *John:* Sorry Kate, but I'm trying to reduce my shopping *Kate:* Oh come on, it will be just like old times. Going once won't hurt right? *John:* No, I can't go to the mall with you. *Kate:* I promise I won't tell anyone. *John:* No, I can't go to the mall with you. *Kate:* Come on, I will pay. *John:* No, I can't go to the mall with you.

record. The following five steps can be used to start practicing communicating in an assertive manner [1]:

1. *Prepare.* Write a brief assertive message, focusing on a behavior external to the person, how their behavior has affected you, the change you are asking for, and the consequences of changing and not changing the behavior.
2. *Ask yourself the following questions*:
   (a) Am I violating someone else's personal rights?
   (b) Is it an ongoing concern of mine?
   (c) Is my message free from judgments and blame?
   (d) Will I likely get my needs met?
3. *Practice delivering the message.* This can be done in front of a mirror or can be role-played with a social support.
4. *Choose a time to meet with a person*. Pick a quiet, private place and give yourself enough time to have a good conversation.
5. *Communicate your message assertively.*
   (a) Begin by saying something like, "Thanks for taking the time to talk with me."
   (b) Avoid small talk.
   (c) Stick with your message.
   (d) Keep it brief.
   (e) Use assertive body language rather than aggressive or passive posture.
   (f) Don't apologize. Don't blame.
   (g) Thank the person for listening and for any helpful and positive response.

64.2.6 Compulsivity and Maladaptive Perseveration of Behavior

Compulsivity and maladaptive perseveration of behavior are termed loss of control or, more accurately, impairment of control in the addiction literature [75]. The incentive-sensitization theory of addiction provides empirical support for the role of compulsivity in the manifestation of addictive disorders, including behavioral addictions [72]. According to the model, liking, (i.e., the hedonistic aspect) and wanting (i.e., the compulsive aspect) are separate states. Early on, individuals engage in addictive behaviors for the hedonistic effect, but, over time and with repeated engagement, individuals continue to feel compelled to engage in the addictive behavior without "liking" it. The behavior becomes a compulsion that is cue-dependent, triggered by certain situations, people, places, or internal states. Treatment focuses on handling the cues differently.

The relapse prevention model described earlier (see deficits in self-regulation) encourages the use of stimulus control strategies to avoid such high-risk precipitants. Strategies that separate the individual from cues associated with their addictive behavior are often identified and frequently used in recovery, particularly during the initial phases of recovery [27, 31, 69, 70]. Clinically, clients are asked to identify these risky situations based on their personal history and based on self-monitoring of urges to engage in the addictive behavior during the treatment process. Worksheets to facilitate this process are common [47, 53]. Development of a specific and concrete plan to avoid cues is feasible for some situations (e.g., blocking of problematic Internet sites; discarding drug use paraphernalia) but not others (avoiding shopping; avoiding feelings of dysphoria). Instead, coping strategies are required and, as described earlier, relevant coping skills can be trained and practiced in individual and group therapy sessions.

Cue exposure interventions can also be useful. Cue exposure involves repeatedly exposing the person to high-risk situations (conditioned cues), preventing the typical addictive behavior response and training alternative behavioral and cognitive responses. Cue exposure interventions were designed to help clients practice these responses while in the state of arousal that the cues generate. Cue exposure involves training specific coping skills but also attempts to address the compulsivity and impairment of control associated with the addictive behavior. The goal is to weaken the cues as well as provide an alternative well-learned coping response.

Like other exposure models, cues are typically presented, using a graded hierarchy with the cues that elicit the strongest urge reserved for later in the treatment process. Exposures are organized to allow individuals to experience a reduction in self-reported urge while actively attending to the cue. Cue exposure requires individualized sets of stimuli, so it is easier to administer it in individual sessions. However, group models have also been developed [53] that focus on cues common to multiple clients (e.g., negative affect). The stimuli cues can be real (e.g., exposure to a slot machine or pornography website) and enhanced by imaginal imagery (imagine that you are sitting at this machine at the end of a very long and stressful day…), or completely imaginal. Similar to exposure treatment for anxiety, more frequent and longer sessions appear to be more effective [53].

64.2.7 Relapse Prevention and Addiction Substitution

Lapses and relapses are a common process during recovery from addictions [25, 28]. Thus, relapse prevention is an important intervention component in the treatment of addictions. In relapse prevention, we find it is helpful for clients to have an understanding of the difference between a lapse and relapse. A lapse can be thought of as a brief and very limited return to engaging in an addictive behavior. In contrast, a relapse is more chronic and can be considered a return to an ongoing pattern of addiction. However, clients who are involved in 12-step programs may view lapses and relapses as being one and the same. Nevertheless, interventions to prevent lapses and relapses have been well documented. Relapse prevention interventions consist of reducing the likelihood of lapses and relapses from occurring in the first place. If a lapse does occur, skills are then implemented to manage the lapse and prevent it from evolving into a relapse [47]. For example, in addition to identifying high-risk situations (i.e., triggers) discussed earlier, clients develop skills to identify potential warning signs of lapses, including affective, behavioral, and cognitive signs. If a lapse does occur, it is important to normalize to clients that lapses are part of the recovery process and, importantly, prevent lapses from becoming relapses. According to the relapse prevention model [47], lapses are likely to turn into relapses due to the abstinence violation effect, which are dysfunctional thoughts related to the lapse such as *since I watched pornography again, it's impossible for me to quit my sexual addiction.* Clients can use their skills in completing thought records to identify and challenge the abstinence violation effect and reduce the likelihood of experiencing a relapse.

We highly encourage clinicians to not only monitor lapses and relapses but also assess whether clients are increasing their engagement in other addictive behaviors, a concept known as addiction substitution. Addiction substitution occurs when a person who recovers from one addiction (e.g., alcohol), subsequently develops a new onset addictive disorder (e.g., gambling) or relapses to a previous addiction. Addiction substitution is of clinical importance as it may increase the chances of relapse and/or result in the development of a secondary addiction [71] and is thought to be a common process during recovery ([29]). In our experience, people are more likely to substitute to addictive behaviors that they perceive as being "not addictive" such as behavioral addictions and substitute to high-base rate addictions such as alcohol and nicotine [29].

64.3 Summary and Implications

Behavioral addictions are among the more common psychiatric disorders and are becoming increasingly relevant in the fields of clinical psychology and psychiatry. There is now a substantial body of empirical literature, examining various aspects of behavioral addictions, including its etiology and clinical characteristics. Unfortunately, the treatment of behavioral addictions has generally lacked the same empirical and clinical attention. In this chapter, we provided an overview of transdiagnostic mechanisms of behavioral and substance addictions and their

intervention possibilities. We believe that a transdiagnostic approach would have tremendous utility in the field of addictions, including the treatment of emerging behavioral addictions. To this end, we have recently developed a transdiagnostic treatment model of addictions, called the Component Model of Addiction Treatment (CMAT; [38]), that targets the shared underlying mechanisms (which we refer to as component vulnerabilities) reviewed in this chapter.

64.3.1 Component Model of Addiction Treatment

The CMAT was designed as a pragmatic transdiagnostic treatment model for both behavioral and substance addictions. Although several theories and models that conceptualize addictions based on their similarities have been proposed, the CMAT was the first treatment model of addictions based on the common transdiagnostic mechanisms. Similar to that of other transdiagnostic treatment approaches, the CMAT may have some important benefits for the treatment of behavioral and substance addictions when compared to disorder-specific protocols. First, behavioral and substance addictions tend to co-occur. For example, 40% of people experience problems with more than one addictive disorder, consisting of both behavioral and substance addictions [40]. As the CMAT targets underlying mechanisms found across addictive disorders, the CMAT may lead to improved outcomes for not only the primary addiction but also for comorbid addictive disorders. Second, the CMAT may be used by clinicians to provide treatment for both traditional addictive disorders (e.g., alcohol, cannabis, gambling) as well as emerging ones (e.g., video gaming, shopping, sex). A unified treatment approach to substance and behavioral addictions would not only be more efficient for clinicians but would also meet the treatment needs for people who are experiencing problems with behavioral addictions. Third, the CMAT may reduce the likelihood of addiction substitution, given that the CMAT was designed to target the underlying commonalities across addictions. Indeed, addiction substitution is more likely when people engage in self-help compared to seeking professional treatment [29]. A decrease in the likelihood of substitution following treatment may be due to clinicians addressing some of the underlying mechanisms that led to the addiction.

64.3.2 Clinical Applications of the CMAT

Although the CMAT is a working model, we believe it can be delivered as an individual or group treatment. While psychoeducation should remain an important aspect regardless of the modality, it may be of particular benefit when delivering the CMAT in a group format. This is because some clients may question why they are in a group with someone who is seeking help for behavioral addictions, when they may be seeking treatment for a substance use problem. Thus, psychoeducation should focus on the commonalities across addictions rather than on the specific diagnosis. This is a similar approach used in transdiagnostic group treatment for anxiety disorders [59]. The focus on commonalities not only helps people to understand both behavioral and substance addictions from a transdiagnostic perspective but also helps clients come to a common understanding that they are all here to overcome their addiction, rather than seeing themselves as being different, thus building group cohesion.

In regard to the different transdiagnostic mechanisms, we believe it is important to address all the identified components. However, treatment should be tailored based on the client's specific needs. Some clients may have greater deficits in motivation, and thus more clinical attention would need to be focused on enhancing motivation and readiness for treatment. Others may be motivated to engage in treatment but may have difficulties in managing intense negative affect. As such, clinical attention may need to focus on helping the client develop the skills to identify and manage their difficult emotions. A careful biopsychosocial assessment, consisting of both a clinical interview and self-report measures, can assist in treatment planning, by identifying which transdiagnostic

mechanisms may require greater clinical attention, as well as to identify other relevant factors that may need to be taken into account during the course of treatment.

With the exception of psychoeducation and motivational enhancement, we do not propose any specific sequencing to the treatment. Indeed, there are several ways that a clinician can sequence treatment. First, the sequencing of treatment could be based on clinical assessment and judgment, regarding which transdiagnostic mechanism is most likely contributing to the maintenance of the addiction. Second, the sequencing could be dependent on client preference, which takes a collaborative approach to treatment and may help to engage clients in treatment and enhance motivation. Third, the sequencing of treatment could be made on identifying which transdiagnostic mechanism may be the most likely to lead to immediate treatment improvements. Regardless of how clinicians proceed in treatment, we strongly suggest that the treatment of the transdiagnostic mechanism be linked together rather than treating them as separate components. For example, maladaptive expectancies can be tied to urgency by examining the link between thoughts and emotions, using cognitive behavioral therapy principles. In addition, the clinical interventions associated with some of the components require skill development over time and over multiple treatment sessions, which is most efficiently achieved through blended sessions. For example, mindfulness and cognitive restructuring require practice and reinforcement over multiple sessions.

Although the CMAT conceptualizes addiction as representing a common underlying disorder, we, like Shaffer et al. (2014), acknowledge that addictive disorders also present with unique manifestations, which may require clinical attention. For example, cognitive fallacies related to odds of winning are unique to gambling and have been shown to be an etiological and maintaining factor for gambling disorder [22]. As such, the treatment for clients presenting with gambling disorder may need to address these specific dysfunctional thoughts [20]. A unique and frequent comorbid condition of compulsive buying is hoarding [54]. Specifically, the acquisition aspect of hoarding behavior may be particularly important in the expression of compulsive buying and thus may need to be addressed in treatment [16]. For compulsive sexual behavior, treatment may need to include strategies to reduce the likelihood of sexually transmitted infections [64]. Last but not least, for gaming disorder, more clinical attention may be needed in developing social skills. This is because some people may turn to video games to meet social needs [48], given the increasingly immersive nature of gaming to the exclusion of non-gaming relationships [42].

While we believe the CMAT has significant promise in the treatment of addictions, it is in need of empirical investigation to test its efficacy. While the interventions included in the CMAT are empirically supported, delivering the interventions from a unified and transdiagnostic conceptualization of addictions is not. To this end, we are currently in the process of developing a treatment protocol with the aim of pilot testing the CMAT in individual and group formats. Additionally, we are aiming to pilot the CMAT in Canada and Brazil to determine the CMAT's cross-cultural utility. The CMAT was conceptualized to be an evolving treatment model, with the ability to include newly identified transdiagnostic mechanisms and their interventions. Empirical studies of CMAT will also help to determine which transdiagnostic mechanisms may be particularly important in the treatment of addictions.

64.4 Conclusion

There has been a recent interest in addressing transdiagnostic mechanisms in the treatment of several psychiatric disorders [75]. We believe that the field of addiction will benefit from a similar treatment approach. Indeed, a transdiagnostic treatment model of addiction may have significant advantages over specific disorder treatments and will ultimately aid in improving the treatment of millions of people experiencing problems with behavioral and substance addictions. To this end, we provided an overview of transdi-

agnostic mechanisms of behavioral and substance addictions, and the CMAT is the first attempt at developing a unified transdiagnostic treatment model of addiction. With time, it is our goal to develop the CMAT into an empirically supported treatment for addictive disorders.

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65 Psychological Management of Gambling Disorder With or Without Other Psychiatric Comorbidities

Enrique Echeburúa and Pedro J. Amor

Contents

Abstract

This chapter deals with the new developments in the treatment of disordered gambling with or without other psychiatric comorbidities, as well as with the challenges for further research. Abstinence versus moderated gambling as therapeutic goals is an issue that raises many concerns and that needs to be addressed. Current psychological treatment for gambling disorder (GD) involves a number of different options, including inpatient treatments, individual and group cognitive-behavioral options, Gamblers Anonymous, and intervention in relapse prevention. Most of the treatment is delivered on an outpatient basis. The most evidence-based approaches for GD are cognitive-behavioral therapy and motivational enhancement therapy. Also, psychopharmacological therapy may reinforce psychological therapy and have incremental benefits when patients have comorbid disorders. A relevant issue related to treatment intensity and the

E. Echeburúa (✉)
Department of Clinical Psychology, University of the Basque Country UPV/EHU, San Sebastián, Spain
e-mail: enrique.echeburua@ehu.eus

P. J. Amor
Department of Personality, Assessment and Psychological Treatment, National Distance Education University (UNED), Madrid, Spain

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emergence of a plethora of so-called brief interventions. Responsible gambling may be a therapeutic option for young gamblers or people without a severe dependence. Further information is required about treatment for online gambling addictions and for dealing with specific populations (e.g., women and young people). Finally, the interventions should be tailored to the needs of the patients.

Keywords

Gambling disorder · Comorbidity · Internet gambling · Psychological management · Effective treatments · Relapse prevention

65.1 Introduction

Gambling disorder (GD) is a relatively common and often disabling psychiatric condition characterized by intrusive urges to engage in deleterious gambling behavior in terms of time invested and money wagered, which results in significantly negative effects on gamblers' daily lives and on quality of life. Unlike the DSM-IV, in the DSM-5, GD has been placed in a new category on behavioral addictions. This reclassification of GD alongside other chemical addictions is more appropriate because there are more commonalities between them and they are treated using similar methods [17].

DSM-5 criteria for GD focus on preoccupation with gambling, need to gamble increasing amounts of money, and repeated unsuccessful efforts to control gambling. From a clinical perspective, two elements are the most representative of GD: continuous or obsessional chasing of losses and family, job, and social disruption by gambling.

Men are more likely to be gamblers than women and also more likely to develop gambling-related problems than them. However, there is evidence that gambling problems have increased among women in recent years. In addition, GD is associated with poorer measures of mental health in women compared to men. Women are more likely than men to gamble in order to relieve feelings of depression and anxiety and to escape dysphoria. Whereas men frequently begin gambling early in life, report slow emergence of problems, and seek help well after developing problems, women start gambling later in life, then rapidly develop dependence, and seek help more quickly [16].

The prevalence of GD varies considerably across different studies. Anyway, about 0.8–1.5% of the adult population can be classified as probable pathological gamblers, while the prevalence of problem gambling is 2.5%. In addition, pathological gamblers often suffer from comorbid disorders, such as mood disorders, generalized anxiety, posttraumatic stress disorder, substance addictions, or abnormal personalities, such as borderline and antisocial personality disorder [8].

Finally, patients with dual diagnoses are highly prone to adverse outcomes in several domains: increased rates of hospitalization, violence, victimization, homelessness, nonadherence to treatment, and poor overall response to treatment [24].

65.2 Psychological Intervention for Gambling Disorder

The interventions for GD that have been reported in the literature are quite similar to methods of treating other addictions and include approaches that are behavioral, cognitive, pharmacological, addiction-based and multimodal, and self-help groups, such as Gamblers Anonymous (GA). Often, these approaches are combined to varying degrees in most treatment programs or counseling settings.

65.2.1 Treatment Goals for Gambling Disorder

Abstinence versus moderated gambling is an issue that raises many concerns and that needs to be treated. Like in the case of chemical addictions, the gold standard for disordered gamblers' recovery is total abstinence. Abstinence is closely associated with recovery of pathological gamblers [13].

However, complete abstinence from gambling may not be necessary for successful treatment in problem gamblers who have behavioral problems and negative consequences of gambling, but they are not still dependent on gambling. In these cases, evidence supports strategies aimed at reducing harmful negative consequences incurred through involvement in risky behaviors. Controlled gambling can be defined as gambling in the absence of the subjective sense of impaired control and adverse financial consequences, based on self-rating and confirmation from a partner or significant other. Strict abstinence goals may discourage problem gamblers from seeking treatment.

Irrespective of the need of going on with clinical trials comparing these therapeutic goals, both targets are necessary for different kinds of patients [12].

65.2.2 Effective Treatments for Gambling Disorder

Current treatment for GD involves several options, including intensive individual and group cognitive-behavioral options and pharmacotherapy. Most of the treatment is delivered on an outpatient basis. Inpatient care is generally limited to patients with severe acute crises, treatment failures, and severe comorbid disorders, particularly depression and attempted suicide.

65.2.2.1 Behavioral Therapies

Behavioral approach considers gambling behavior as having three components: antecedents (financial pressure, gambling cues, positive or negative emotions, interpersonal factors, urges to gamble), overt or covert behavior itself (money spent in gambling, coping strategies to deal with anxiety or depression, thinking about gambling or about how to attain money), and consequences, both positive (autonomic arousal, opportunities to socialize, escape from personal problems, monetary gain) and negative (anxiety and depression, low self-esteem, work and relationship conflict, financial loss). Anyway, gambling-based arousal is the central factor in the reinforcement process. Approach to gambling in regular gamblers is triggered by a wide range of environmental features: driving the car, leaving work, the sight of money in the wallet, and so on. Gambling is also highly reinforcing because of the variable pattern of reinforcement and the tension relief [30].

Behavioral therapy considers pathological gambling a learned behavior and relies on techniques such as stimulus control, systematic exposure, and skill development (e.g., relaxation techniques and improving stress management and social skills) to reverse the learned behavior and the association between arousal and conditioned elicitors. Reduction in gambling is expected if patients can successfully develop and use alternative coping responses to deal with urges to gamble. Behavioral counseling, in which the gambler is given verbal reinforcement for desired outcome behaviors, and in vivo exposure, in which the gambler is exposed to gambling behaviors but is not allowed to gamble, are also mentioned in the literature [30].

Stimulus control involves limiting access to money, not visiting venues that offer gambling, and not spending time with people associated with heavy gambling. As treatment advances, the control of stimuli is gradually faded, except avoiding gambling friends. Recovering gamblers are also encouraged to take themselves off mailing lists from the casino, to meet with a financial planner, to cancel all credit cards, and to turn over control of money to another person. Self-exclusion from gaming venues can be an adjunct to treatment. Actually, participants tend to comply with the commitment of abstinence and have more positive outcomes when they are also involved in complementary treatment or self-help groups [40].

Exposure with response prevention is focused on making patients experience the desire to gamble and teaching them how to resist it in a gradually more self-controlled way. The aim of systematic exposure to cues and situations of risk is to make the cues lose their power to induce urges and gambling behavior. If responses are prevented or controlled, the stimulus-response relationship will weaken. In addition, patients are taught alternative strategies to cope with their

anxiety. Exposure tasks take place 6 days a week for a minimal time of 15–20 min. Patients cannot drink alcohol or take other drugs during the exposure tasks. Only stimuli relevant to the individual should be included if generalization is to occur in the natural environment. The characteristics of the application of this technique are shown in Table 65.1. This type of therapy is designed to deal with cravings and urges for gambling by increasing confidence in the ability to impose self-control over gambling.

Apart from some pioneering studies, a behavioral controlled investigation with a waiting list control group was carried out by Echeburúa et al. [11]. They compared the effectiveness of cognitive and behavioral techniques in a Spanish sample of 64 men and women who met DSM-III-R criteria for pathological gambling. Participants were randomly assigned to one of four treatments: individual stimulus control and in vivo exposure with response prevention, group cognitive restructuring, a combination of the first two, and a waiting list control group. At 12-month follow-up, the most favorable outcome was associated with the first two groups, which reported therapeutic success rate (abstinence or one or two gambling episodes in which the amount gambled did not exceed the amount gambled in the week prior to treatment) of 69% and 37%, respectively. The behavioral therapy was found to be more effective than the group cognitive restructuring in terms of reducing gambling frequency.

Table 65.1 In vivo exposure therapy for gambling disorder

Exposure	Characteristics
1st week	The co-therapist (a relative or a close friend) is together with the patient when he is practicing exposure to a slot machine
2nd week	The co-therapist goes with the patient to the gambling site but stays outside waiting for him when the patient is practicing exposure exercises
3rd week	The co-therapist stays at home when the patient goes to the gambling site to practice exposure exercises. If the patient is in a jam, he can phone the co-therapist
4th week	The co-therapist no longer takes part in the exposure task

More recently, Smith et al. [50] evaluated the differential efficacy of cognitive therapy and exposure therapy through a randomized controlled study (N = 87). Both groups experienced comparable improvement at 12-week and 6-month follow-up. Therefore, cognitive and exposure therapies are both effective treatments for problem gambling.

In sum, according to the meta-analysis of Pallesen et al. [42], interventions involving developing relaxation skills, exposure to gambling cues, and direct behavioral action are effective in improving gambling urges, time and money spent, and abstinence. In addition, behavioral change is related to cognitive change after treatment.

65.2.2.2 Cognitive-Behavioral Therapies

Excessive gambling can be driven by distorted and maladaptive cognitions, such as illusion of control, superstitious thinking, or misperception of probability. Two major beliefs (gambling outcomes can be correctly predicted and controlled) appear to describe the problem gamblers' irrational cognition. Disordered gamblers believe that they are able to control random or chance events by relying on superstitious behavior or methods. This illusion of control is stronger as gamblers become more familiar with a game. Thus, they can believe that a big win is imminent and persist despite mounting losses, with an unrealistic hope that they will recover their losses if they persevere with the gambling (the gambler's fallacy) [34].

Cognitive therapy aims to help patients challenge and overcome irrational thoughts that are believed to initiate and maintain the undesirable behavior. Subjects are taught to be aware of the link among thoughts, behavior, and emotion. Many patients do not understand the concepts of probability and randomness, believing that they can exert some control over whether they win or lose. Treatment typically involves teaching subjects strategies to correct their erroneous thinking by providing corrective information through education, logical discussion, or behavioral experimentation. Thus, the therapist will ask the gamblers to describe what they are saying to

themselves when gambling. If the erroneous perceptions and understanding of randomness in the gambler can be corrected, then the motivation to gamble should decrease dramatically. Cognitive therapy also aids gamblers in coping with urges to gamble, managing negative emotions, and training in problem-solving techniques [34].

Randomized clinical trials have focused on combined cognitive and behavioral approaches (CBT) (cognitive correction, problem-solving training, and assertiveness training) [7, 36].

CBT is effective in treating pathological gambling and the associated problems [3, 45]. Both individual and group CBT appear effective for reducing gambling [41]. *Individual* CBT may be enhanced if patients receive compliance-improving interventions, such as a reinforcement of self-efficacy, reminder phone calls, assessment feedback, and a weekly decisional balance exercise to complete. *Group* CBT may be enhanced if individuals have interactive written exercises. In this way, that mapping may serve to individualize the group treatment, leading to greater effect [39].

However, the CBT studies have not yet determined the optimal number of sessions needed to reduce gambling symptoms and maintain improvement [22].

Furthermore, an individual eight-session manualized form of CBT has also been compared, either delivered by a professional counselor or completed alone by the patient in a self-help workbook (WB) with a group referred to GA. Although participants in all groups reduced gambling, CBT in both conditions was better than only GA in terms of days gambled and number of gambling criteria met. Nevertheless, the number of GA meetings attended was significantly associated with gambling abstinence [44]. Additionally, Campos et al. [3] compared the differential efficacy of two CBT modalities through WB for the treatment of GD: WB with therapist guidance or WB only. Although both groups reported fewer gambling symptoms at treatment completion and at follow-up, WB with guidance increased abstinence from gambling compared to WB only.

Lastly, the mindfulness-based and CBT-based treatment as usual interventions appear to be effective at reducing GD behavior and associated distress [38]. In this study, these intervention modalities were more effective than the manualized form of CBT to generalize the improvements in quality of life, mental functioning, and certain mindfulness facets.

65.2.2.3 Motivational Enhancement Therapy

Another approach adopted to help problem gamblers focuses on the use of short-term brief motivational enhancement therapy and telephone counseling, mailed self-help workbooks, and online resources. Brief treatment is defined as that using less professional resources or time (four or fewer sessions) than usual face-to-face interventions (typically, six to twelve sessions of therapist contact). This therapeutic modality may be an important innovation to helping people with gambling problems who fail or refuse to seek treatment in traditional therapeutic settings and may enhance patients' sense of control over their own recovery [30].

Motivational interviewing (MI) is often a 50-minute face-to-face or telephone session used to build commitment to change [55]. MI focuses on patient's intrinsic motivation for change and on patient's strengths to enhance self-efficacy. MI strategies act in some way to resolve ambivalence and promote greater commitment to change.

This approach has proven to be effective, at least with those with less severe gambling problems [29]. In the latter study [27], at a 24-month follow-up, 77% of the entire sample was rated as improved, but gamblers receiving the workbook and a telephone motivational support reported less frequent gambling and lower severity scores than workbook-only group. In other studies of the same group [28], patients who received the MI plus workbook gambled less and spent less money than workbook-only group.

A combined MI and CBT program applied in group or individual format [41], or even adapted to a Web-based format [4], can improve GD behaviors, as well as gambling correlates. Moreover, the addition of MI to CBT can reduce

treatment attrition and improve outcomes [53]. Grant et al. [20] compared a six-session CBT program, combining imaginal cue exposure plus the negative mood induction (focused on the negative consequences of gambling while the urge is active) with GA. The 64% of participants assigned to behavioral program maintained abstinent at 1-month follow-up as opposed to only 17% of patients assigned to GA.

However, these motivational approaches, which are more attractive to gamblers and may result in an increase of treatment seekers, cannot be so effective with severe pathological gamblers or patients with comorbid pathology. More research is needed to determine the efficacy of these programs when compared to more established CBT.

Finally, in a randomized clinical trial, a high dropout rate (83%) was found when applying any of the three forms of Internet-based intervention (personalized feedback on their *gambling* status by email, an email plus CBT workbook, and the same CBT program emailed with personalized guidance) in non-help-seeking problem gamblers who were recruited because of their disordered gambling [37]. Although some improvements were identified in the three treatment groups (without statistically significant differences among them), the group that had a higher percentage of dropouts was the one that included the guidance of a professional.

65.2.2.4 Gamblers Anonymous

Modeled after the traditions and spiritual principles of Alcoholic Anonymous, Gamblers Anonymous is the primary self-help group and uses an abstinence-based treatment program. GD is conceptualized as an illness which can be arrested but never cured, so people affected by this problem have a permanent predisposition for losing control over their gambling.

The therapeutic rationale for GA is that the twelve steps to recovery will lead gamblers to attain abstinence. The group format is intended to provide a sense of common purpose and understanding, emotional and spiritual support, and hope. Anonymity allows for members to feel safe in sharing openly with other members [30].

The efficacy of GA has not been demonstrated in controlled studies. Relapse rates tend to be quite high. Stewart and Brown [51] found that total abstinence was reported by only 7.5% of members surveyed one year after their first attendance and by 7.3% at two years. Attrition rate is also high. People attending GA have better gambling outcomes than those who do not, even though they are engaged in professional treatment concurrently [44].

The therapeutic effectiveness of GA has also been explored with respect to participation by the gambler's partner. There is a trend for higher abstinence rates for gamblers whose partners are present at meetings compared with gamblers whose partners do not attend.

There is a particular need for studies of the role of GA in recovery and treatment outcomes. Another study found that there were not any differences on key gambling variables (e.g., frequency, abstinence rates, money wagered) at 12 months between a program of CBT and twelve-step therapy [52]. If there is a high dropout rate from GA, as the literature suggests, then it is important to investigate its causes and strategies for reducing it.

In sum, GA may be increasing in popularity, but whether participating in meetings makes a significant and lasting impact is still not well known.

65.2.3 Relapse Prevention

A challenge in the treatment of pathological gambling is preventing relapse. Many personal and environmental factors interact to influence the risk of relapse for any individual trying to recover from an addiction. Relapse prevention is focused on training patients to identify high-risk situations for relapse, such as social pressure, negative emotional states (e.g., anxiety, depression, and anger), and interpersonal conflicts, and providing them adequate strategies for coping with problematic situations. Pathological gamblers are deficient in the number of coping skills they have available and in their ability to flexibly choose the skill most appropriate to the stressful, or

potentially relapse-triggering, situations they face. Relapse prevention techniques increase the likelihood of engaging in adaptive coping behaviors.

Successful recovery also involves the development of new skills (e.g., cognitive reframing) and lifestyle patterns that promote positive patterns of behavior. The integration of these behaviors into day-to-day activities is the essence of relapse prevention.

The problem-solving approach is oriented to increasing the gamblers' abilities to cope with urges or cravings and to deal with anxiety, depression, or personal crises for which gambling is an escape. For example, substance abusers with a gambling problem utilize significantly more avoidance and impulsive coping styles.

Echeburúa et al. [13] evaluated the efficacy of providing relapse prevention strategies as a follow-up to behavioral treatment focused on total abstinence from gambling. Sixty-nine pathological gamblers received behavioral treatment (stimulus control and exposure with response prevention), followed by random assignment into one of the three conditions: individual relapse prevention, group relapse prevention, or no treatment control group. The results related to the 12-month follow-up relapse showed a success rate higher in both individual (83 percent) and group (78 percent) relapse prevention than in the control group (52 percent). There were no differences between both experimental modalities. These results raise the need of relapse prevention programs in the treatment of pathological gambling. This study reported a dropout rate of 14.5%. On the other hand, most relapses were observed in the first three months after treatment. The main triggers of relapse were inadequate money management, negative emotional states, alcohol abuse, craving, and social pressure [14].

65.2.4 Pharmacotherapy

Pharmacotherapy is a relatively new approach to the treatment of GD and may be effective for reducing gambling urges and behavior. A variety of medications have been examined with varying results. Actually, there are no approved medications for the treatment of pathological gambling [23].

Neurobiological studies suggest the involvement of serotonin, norepinephrine, and dopamine in GD because these transmitters are strongly associated with reward pathways. The norepinephrine system has been associated with arousal and novelty seeking, dopamine with reward and motivation, and serotonin with impulsivity and compulsivity [32].

The medications target one or more of these neurotransmitter systems. The current pharmacological strategies for treating GD suggest the use of serotonin reuptake inhibitors (SSRI), opioid antagonists, and mood stabilizers.

SSRI antidepressants can reduce urges to gamble or prevent from compulsive behaviors. The rationale for this medication is the phenomenological association between GD and compulsivity. These medications are also helpful if anxiety disorders are associated with GD [47].

Opioid antagonists (naltrexone) can block feelings of euphoria related to gambling behavior and result in reductions of gambling urges and thoughts and in improvement in psychosocial functioning. The rationale for this medication is the similar neurological pathways for GD and substance addictions and the commonalities between clinical symptoms of both disorders. This class of medication, dosed at 50 mg/day, should be considered a first-line treatment for GD [23]. Naltrexone may be particularly helpful for those with strong gambling urges at treatment onset and/or a family history of alcoholism [47].

In turn, mood stabilizers, such as lithium or topiramate, can reduce the use of gambling to regulate negative mood (most of all, if bipolar tendencies are present), but some recent controlled trials have failed to show any significant treatment effect for topiramate on the primary or secondary outcome measures.

Another avenue of approach is the use of medication to treat comorbid conditions. In practice, this is probably the most frequently cited reason for putting gamblers on medication. Comorbid disorders for which medications are commonly prescribed include depression, bipolar disorder, and attention-deficit hyperactivity disorder.

In sum, certain medications, such as opioid antagonists [1], may be beneficial in treating this disorder. Pharmacotherapy research needs to be expanded to determine if this approach has an important role in the treatment of pathological gamblers and plays an adjunctive role to psychological treatments [2]. We still do not know if medications provide therapeutic effect by ameliorating the pathological gambler's cravings, ruminations, or negative feelings. Heterogeneity of GD treatment samples may also complicate identification of effective treatments. In addition, some studies have reported high placebo response rates [47] and high rates of study dropout (30–50%) [43].

65.3 Issues in Treatment

Only a small proportion of the individuals who are suffering from GD (about 6 percent) seek formal treatment. The satisfactions provided by their addiction, a desire to handle the problem by themselves, and shame have been identified as contributing factors to resistance to treatment. Motivation becomes adequate when people identify gambling as a destructive agent in their life. Natural recovery from problem gambling can occur in about 35%, but most disordered gamblers report a chronic course, with symptom severity fluctuating over time [22].

Therapists have been confronted with the problem of treatment compliance. For pathological gamblers, compliance is an issue because they are often ambivalent about giving up their gambling or altering long-standing patterns of coping, no matter how ineffective. Some people do not seek treatment, some drop out after one or two sessions, and some can decide to terminate treatment after a few weeks thinking that their problem has been solved. It is a challenge to identify the characteristics and the reasons of individuals who refuse treatment, drop out, or simply do not show up for the first session. There are no obvious solutions to these matters, but motivational enhancement therapy, behavior contracts, and flexible treatment goals might improve treatment compliance.

Despite the growing trend toward harm reduction strategies and controlled behavior approaches for addiction problems, most gambling treatment programs, like those that treat substance abuse, favor abstinence. Some programs, however, particularly those dealing with problem gamblers in their early stages, aim at reducing and controlling rather than stopping gambling. Anyway, clinical trials comparing treatments with varying treatment goals are necessary [33].

A relevant issue relates to treatment intensity and the emergence of a plethora of so-called brief interventions. A distinction should be drawn between minimal intervention or advice in a primary care setting and brief intervention within a specialist context (one to three sessions). It is difficult to know if there are remarkable differences between brief and extended interventions for pathological gamblers. For instance, there are important differences between treatment-seeking populations as distinct from those that are selected as a result of opportunistic screenings. Anyway, it is relevant to investigate the active ingredients of brief interventions which seem to be, at least, relatively successful [22].

Advances in family therapy for treating substance abuse problems have been adapted for gambling disorders, such as a self-help workbook of the Community Reinforcement and Family Therapy (CRAFT) model (focused on the training of family members to use behavioral principles to reinforce non-gambling behaviors) [31] or a coping skills training program for those with a pathological-gambling partner [48]. Further research is warranted to improve the design and targeting of these approaches.

65.4 Internet Gambling

Internet gambling can be defined as any type of wagering that takes place by using the Internet. Common forms of online gambling are online poker, online casino, sports betting, and online bingo, though there are some other ways to gamble using the Internet that hold strong potential for additional growth, e.g., gambling by mobile devices and gambling on the Internet games [35].

Men are more likely to gamble using the Internet than women. Emotional states, maladaptive cognitions, and life events can serve as triggers for Internet abuse. The pervasiveness of Internet gambling sites on the Web makes it an especially risky form of gambling. One of the most attractive features of Internet gambling is its convenience (e.g., playing comfortably at home and at a convenient time is reported to be the most important reason for playing online poker). The anonymity of Internet gambling presents an opportunity for the development of gambling-related problems. For example, because of anonymity, people may gamble under the influence of alcohol or drugs, be underage, or even gamble from the school or workplace. Solitary gambling, like Internet gambling, where people can gamble at their own pace with no outsiders interrupting or any other distractions, is also a risky factor. Computers and the Internet create isolation and a sense of fantasy. In summary, a cursory consideration of numerous risk areas logically suggests that the Internet might increase the speed of the negative effects of gambling or exacerbate gambling-related problems [25].

Minors might gain access to a credit card and gamble with other people's money. This raises concerns that children and adolescents' participation basically is unrestricted. In addition to being illegal, such an occurrence would be problematic because early exposure to gambling is linked with the development and persistence of gambling-related problems [6].

Appropriate treatment for online gambling addiction is still being researched. Treatments that are effective for gambling addiction work well for online gambling addiction. It is important to consider the individual needs when devising a treatment plan to tackle an online gambling addiction. Every person is different and could be addicted for different reasons.

Stimulus control involves for the Internet gambling addicts to engage in opposite activities, use of timers to end online sessions, set time limits, prioritize tasks, and record Internet usage to abstain from Internet abuse.

Group therapy is commonly suggested as a treatment option as well. If patients are attending support groups such as GA, they can use that group to help cope with their online gambling addiction.

Online gambling addiction, gambling addiction, and Internet addiction, which are all closely related, can create problems outside of the individual. They can cause damage to one's finances, marriage, and even their entire family. In these cases, financial counseling, marriage counseling, and family therapy are all beneficial treatment options.

In conclusion, a combination of individual, family, and group therapy may be the best option, although individualization should be emphasized. Medication (e.g., ISSRs) may be needed to treat associated anxiety or depression [2]. Anyway, our understanding of Internet gambling is still quite limited. More evidence-based research is required for treatment options regarding this topic.

65.5 Treating Comorbid Gambling Disorder and Severe Mental Disorders

65.5.1 Treatment of Gambling Disorder with Affective and Addictive Disorders

There are several studies on the efficacy of treatments when there is dual pathology, especially between GD and mood disorders or alcohol/substance abuse. Psychological treatments effective in treating *comorbidity between GD and depression* are CBT and imaginal desensitization plus motivation interviewing [9].

Pharmacological treatments, such as opioid antagonists [21], memantine that was associated with diminished *gambling* and improved cognitive flexibility [19], citalopram [56], and sustained-release lithium for bipolar spectrum disorders [5], may reinforce psychological therapy.

On the other hand, psychological approaches may be effective in treating *comorbidity between GD and alcohol/substance abuse*: CBT, motivation interviewing, Internet-delivered self-help

CBT, 12-step therapy, solution-focused therapy, and dialectical behavior therapy [9]. Anyway, when there is comorbidity between GD and other problems (i.e., anger and substance abuse), it is advisable to treat them concurrently in order to optimize treatment outcomes.

65.5.2 Treatment of Gambling Disorder with Schizophrenia

There are higher rates of pathological gambling in schizophrenic populations (10%) than in the nonschizophrenic population (1–5%) [26]. These patients also have greater alcohol use severity, higher depression scores, and more outpatient mental healthcare utilization.

Apart from some case reports (e.g., [49]), there is only one controlled trial that tested the clinical effectiveness of a cognitive-behavioral program specifically adapted for pathological gamblers with chronic schizophrenia (N = 44), with posttreatment and 3-, 6-, and 12-month follow-up assessments [15]. In this research, psychological treatment comprised a 20-session program including a) psychoeducation about the nature and the features of the disorder; b) stimulus control of money and avoiding routes of risk as well as gambling friends; c) gradual exposure in vivo with response prevention, focused on experiencing the desire to gamble and learning how to resist this desire in a gradually more self-controlled way; and d) relapse prevention, focused on training the patient to identify high-risk situations for relapse, such as social pressure, negative emotional states, and interpersonal conflicts, and providing him/her adequate strategies for coping with problematic situations.

Adaptation of CBT for these individuals dually diagnosed with GD and chronic schizophrenia took into account several aspects: the active role of the therapist to help patients fulfill the self-reports; the presence of a co-therapist (a family or staff member) in order to enhance motivation for treatment, to encourage patients to carry out in vivo exposure tasks, and to check information provided by patients; and the implementation of the program in the stabilization phases of the schizophrenia. This modified CBT (stimulus control and gradual in vivo exposure with response prevention) has proven to be an evidence-based psychosocial intervention for patients with these dual diagnoses [15].

In this study, individuals dually diagnosed with GD and chronic schizophrenia have benefited from medication and supportive psychological treatment to cope with GD. Thus, the improvement rate in the experimental group was 73.9% (with all patients being treatment completers), versus 19% in the control group at the 3-month follow-up.

Predicting relapse in GD in individuals with chronic schizophrenia after treatment can be useful in targeting patients for aftercare services. The therapeutic failure rate was 43%, and it was associated with the age of first episode of schizophrenia, the number of episodes, and the age of onset in gambling behavior [10].

Finally, a qualitative study identified unique patterns of responses specific to individuals with schizophrenia or schizoaffective disorder. Specifically, gambling as filling a need for activity and gambling as a means of connecting with the society/world were the notable reasons for engaging in problematic gambling [54].

65.6 Concluding Remarks

Behavioral and cognitive-behavioral therapy appear to be the most successful treatment approaches in different formats (individual, group, and self-directed), regardless of the type of gambling behavior practiced [18]. Both individual and group CBT appear to be effective in the treatment of GD and its correlates. Group therapy is not only just cost-effective; it also enables gamblers to learn from and support each other. Individual therapy may be more suitable for those who can afford therapy and those who prefer discussing life events on a one-to-one basis [41]. Further research is needed to determine the optimal number of sessions [22].

However, it continues to be controversial which form of CBT is best and for whom and

what is the optimal duration of therapy. Many behavioral interventions often include cognitive components, so it may be difficult to isolate the most potent agent of change. However, the presence of irrational beliefs and attitudes about gambling in pathological gamblers do not always justify confronting them with a cognitive approach. Interestingly, a behavioral approach, which is focused on short-term cessation of gambling behaviors, can also result in a decrease of erroneous beliefs of patients, without treating them specifically [13].

Pharmacotherapy appears to have a role in the treatment of coexisting depression, rather than as a primary treatment for GD. However, research on the pharmacological treatment appears promising, particularly in the case of opioid antagonists [1]. There is growing recognition that multiple treatment components should be considered given the patient's specific configuration of problems. Thus, patients with dysphoria should be evaluated for antidepressant medication, family therapy may be indicated in the presence of extreme family estrangement, and substance abuse counseling may be necessary for those whose addictive behavior also includes alcohol or other drug abuse. Inpatient programs for severe pathological gamblers, with comorbid disorders or attempted suicide (or suicidal ideation), continue to be in use, but more rigorous research on effectiveness is warranted because to date there are no randomized trials [22].

Very few studies have examined the combination of drug and behavioral treatments. Similarly, despite their high rates, there have been very few studies on the treatment of GD in conjunction with comorbid disorders, such as depression and personality or drug or alcohol use disorders. Irrespective of the effectiveness of CBT for pathological gamblers with or without other mental disorders, treatment must be adapted to these different circumstances. Thus, gamblers who have comorbid schizophrenia may require more sessions of therapy (i.e., 20 sessions) and a treatment focused more in behavioral than in cognitive components [15].

As problem gambling significantly affects patients' relationships with their families, interventions for gambling problems have also been directed at affected families. Family interventions are at an early stage of development and evaluation. It will be important to determine their efficacy and cost-effectiveness compared to treatment provided to the gambler alone [30].

Virtual counseling (Internet or computerized therapy) is another treatment option. Presently, there are only a few gambling specialty treatment programs, and one way to expand treatment services is to provide telephone and Internet counseling. Some pathological gamblers may be reluctant to enter individual or group therapy due to stigma, lack of resource availability, or denial. Numerous chat rooms have emerged for GA 12-step fellowship and are available anonymously 24 h a day.

Gambling studies should focus particularly on treatments that have manual-guided treatments. Poor specification of the therapeutic methods used hinders the replication of successful programs. Not only do therapist's manuals guide interventions, but also they facilitate the clarification of the specific contribution of particular treatment components.

Interventions should be tailored to the needs of the patients [10]. Substantial progress has been made in understanding the treatment of this disorder, but there is not yet research basis for matching patients to treatments according to different characteristics (e.g., subtypes of gamblers, different types of gambling, gender of gamblers, or comorbid disorders).

There is growing evidence for the effectiveness of psychosocial interventions, such as motivational interviewing (brief, easy to be administered, and cost-effective) and cognitive-behavioral therapy, to cope with specific needs of people with dual diagnosis [55]. However, there are serious implementation barriers related to service organization, staffing levels, training, and – most importantly – the difficulties of engaging people with a severe mental disorder in treatment.

Programs that combine pharmacotherapy and psychosocial treatments for GD into a single comprehensive package are most likely to have good treatment outcomes, at least regarding treatment retention.

Finally, since the population of mentally ill pathological gamblers is heterogeneous, it would be interesting to evaluate a patient-treatment matching strategy intended to improve the cost-effectiveness of treatment for these dual-diagnosed patients.

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Gambling and Gaming Addictions in Women

66

Joseph Althaus, David Zendle, and Henrietta Bowden-Jones

Contents

Abstract

This chapter provides a summary of contemporary research perspectives on both gambling and gaming disorders in women.

A discussion of the prevalence of gambling in women is given, as is an overview of gender-specific differences in the kinds of gambling that individuals engage in. A description of the nature of disordered gambling in women is then provided, incorporating a summary of gender differences in the progression of gambling disorder. Comorbidities of gambling disorder in women are described, with a particular focus on barriers to treatment among women. Treatment methods are summarised, incorporating a description of initial advances in pharmacotherapy.

The research literature on gaming disorder among women is then treated. Gender differences in both prevalence of gaming and the prevalence of disordered gaming are described. An overview is provided for a nascent literature investigating potential neurobiological explanations for gender differ-

J. Althaus
The National Problem Gambling Clinic, London, UK

The Barberry National Centre for Mental Health, Birmingham, UK

D. Zendle
University of York, York, UK

H. Bowden-Jones (✉)
The National Problem Gambling Clinic, London, UK

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ences in gaming disorder. Limitations of the literature are discussed throughout, with a focus placed on how the literature is hampered by a lack of well-defined screening procedures for determining what constitutes disordered gaming.

Keywords

Gambling disorder · Problem gambling · Gaming disorder · Internet gaming disorder · Behavioural addictions

66.1 Gambling Disorder in Women

Gambling disorder (GD) is a maladaptive pattern of gambling behaviour that persists despite negative consequences. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [1] (DSM-5) includes nine diagnostic criteria, four being required for diagnosis: (1) tolerance; (2) withdrawal; (3) loss of control; (4) gambling preoccupation; (5) gambling in response to negative affect; (6) chasing losses; (7) lying to conceal gambling extent; (8) jeopardising relationships, work, career or educational opportunities; and (9) relying on others for bailouts. *Problem gambling* (PG) is a general term used in research where screening measures identify problem gamblers without clinical interview confirmation.

66.1.1 Definitions and Diagnostic Criteria

Technology has changed how games are played, from socially to alone; they are more available and globalised (local and cultural differences have reduced). The British Gambling Prevalence Survey (BGPS) series showed statistically significant increases in female gambling from 65% in 2007 to 71% in 2010 (disproportionally greater among older women). Gambling rates in the United Kingdom are now similar among males and females. Women prefer lotteries, slot machines, scratch cards and bingo compared to male preference for poker, sports betting, fixed odds betting terminals (FOBT) and casino games. Female PG has doubled from 0.1% to 0.2% in the same period [53].

Targeted advertising has increased female vulnerability to gambling. In France, following the legalisation of online gambling in 2010, studies to 2014 show a significant increase in gambling prevalence among women in the previous 12 months (44.4% in 2010 vs. 54.8% in 2014) and a doubling in female problem gambling in the year (1.4% vs. 2.8%): the proportion of women to men remaining the same (25% vs. 75%) [6, 7].

Gambling preferences may be socially determined, so liable to change with changes in society. British records demonstrate that in the mid-twentieth century, most women (66%) bet in some form, often through illegal street betting. Two out of five women bet on horses in 1951 compared to one out of ten in 2010. The 1960s Betting and Gaming Act legalised and regulated betting shops, introducing austere interiors designed to prevent loitering, which almost certainly discouraged women from using them. By the mid-1970s, less than 2% of women bet at least monthly on horses or dogs. Bingo, popular among male servicemen in the late nineteenth century, expanded into public spaces women were familiar with and was promoted as glamorous and aspirational. Legislators had created an environment attractive to women, contrary to that seen with bookmakers [52]. That some women are engaging more in gambling, as barriers to entry and social contexts change, could be seen to represent a resurgent interest in gambling among women – part of a cyclic pattern rather than a new phenomenon.

PG rates among interactive gamblers are three times higher than overall rates (2.7% vs. 0.9%) in Australia. In these gamblers, electronic gaming machines (EGM), interactive poker, casino games and sports betting were associated with increased severity of PG. Interactive gambling may not cause GD but is likely to exacerbate it. Policymakers could focus on gambling most associated with harm [16].

66.1.2 Gender Differences in Development and Course of Illness

International gender-focused research finds differences between male and female problem gamblers in terms of reasons and preferences for gambling, progression, mental health and treatment seeking.

Women gamble to escape loneliness, dysfunctional relationships, violence, isolation and childcare and to self-medicate perceived intolerable levels of stress, anxiety and depression. They engage in a narrower range of gambling activities offered by low-skill, high-absorption games [22]. Men gamble more widely, on fast-moving activities, for excitement and to outperform others [8].

Pathological and problem gambling is seen in a range of sociodemographic groups. The risk of PG for women increases with decreasing socioeconomic status [20]. In an Australian cross-sectional study [5], men and women were found to be equally susceptible to the addictive potential of gambling, the strongest independent risk factor for both genders being positive gambling expectancies (of enjoyment or financial gain) [27]. Other risk factors associated with PG in women include deprivation, marginalisation (in Māori women), violent partners and/or childhood [31] and the interaction of dysphoric moods and 'avoidance' coping [47]. Gender-sensitive public health initiatives are needed, and for female problem gamblers, prevention/intervention should focus on coping skills. Measures targeting positive gambling expectancies may also improve intervention outcomes for both genders.

Women consistently start gambling at a later age than men, progress more quickly to PG or gamble for shorter durations before seeking treatment [40]. This 'telescoping' is also found in women substance abusers [57]. Theories exist as to why, none of which satisfactorily explain the phenomenon. Female preference for more addictive games (slot machines, electronic bingo) does not account substantially for the telescoping effect. Links between psychopathology and gambling disorders, appearing strongly in women with anxiety and depression and in men with alcohol dependence, do not explain gambling progression: studies have not yet proved a causal relationship. In relation to neurocognitive measures, male gamblers score higher on risk-taking measures than female gamblers, although no gender differences are found on impulsivity measures. A few neuroimaging studies have begun to investigate neural mechanisms – women with GD showed increased dorsomedial prefrontal, posterior insula and caudate activation when viewing gambling-related videos, compared to men with GD, but the extent to which these relate to telescoping is unknown [55].

Using data from the BGPS 2010, investigating differences in age of first gambling experience among cohorts of women in the United Kingdom, two patterns are evident. Younger cohorts started gambling at a younger age than older cohorts, and among younger cohorts, age 16 marked a pivotal point in starting to gamble, reflecting the legal milestone for engagement in the national lottery, scratch cards and football pools. There appears to be a further cohort effect in operation: fewer of those aged 25–31 had gambled by age 16 (40%) than those aged 16–24 (50%). Within this cohort, the youngest are gambling earlier still, implicating the Gambling Act 2005, which permitted applications for land-based gambling venues, increased gambling opportunities and vastly expanded advertising [52].

Recent subgroup analysis shows younger women aged 16–34 gamble more frequently, across multiple products, and demonstrate more PG. EGM use is most common among women overall, whilst younger women are more likely to bet on sports and gamble at casinos. There are significant differences in the perception of harm associated with horse and sports betting, young women perceiving these as less harmful than older women and non-gamblers [29].

66.1.3 Comorbidities and Suicide

GD is frequently associated with comorbid psychiatric disorder, including depression, anxiety disorders, bipolar affective disorder, personality disorders and SUDs. Its presence is associated with

greater severity of gambling problems and related consequences, including suicide – the leading cause of death in GD (31%), followed by neoplasia (16%) and cardiovascular disease (12%) [21].

A recent Spanish study demonstrates that female problem gamblers with a criminal history were younger, had greater GD severity and dysfunctional personality traits and showed higher levels of comorbid psychopathology than those without. This population is especially vulnerable and could benefit from public policies that target their mental health needs [30].

The same authors clustered women with GD into subtypes based on clinical and sociodemographic variables, finding those with the most severe GD confirmed novelty seeking as well as impaired self-direction, and psychiatric comorbidity, all of which can interfere with treatment. These findings concurred with studies of males with GD [17].

66.1.4 Treatment Seeking (Including Barriers to Treatment)

Female pathological gamblers, underrepresented in treatment, perceive barriers to seeking professional help more than males. Research identifies lack of social support, poverty, lack of childcare, guilt and shame due to stigmatisation and difficulties in finding appropriate treatment. Women using gambling helplines are more likely to have mental health problems, gambling-related financial problems and prior treatment for mental health than men [26]. Higher levels of comorbid psychiatric disorders, difficult biographical backgrounds (significantly higher rates of childhood neglect, abuse and trauma) [3], 'avoidance' coping strategies [13] and increased feelings of guilt or shame and/or fear of being stigmatised discourage women from seeking treatment [19].

Women earn less than men and thus gamble with a higher percentage of their income in comparison, especially older women (on average, 249% more than men of their income in the month prior to treatment) [33].

Non-gendered Australian research has found that help-seeking for PG is crisis driven, prompted by suicide attempts, court charges, arrests, financial ruin or relationship conflicts [8]. Qualitative research further supports this finding in females. Despite low help-seeking rates, women are at least as likely as men to seek professional and non-professional help for PG. Other research indicates barriers that may differ by gender [42]. [43] found men were discouraged by stigma and attitudes to treatment seeking from calling a helpline. In contrast, others found women more likely to feel guilt or shame [18] and to fear consequences of treatment entry (removal of children or injury from abusive husbands) [48].

Women made up 12.5% of a population in treatment in Austria and Germany, were 10 years older than their male counterparts, had greater GD severity and were more likely to live alone or alone with at least one child (50% of the women vs. 28% of the men), suggesting relative social isolation [28]. Just 10–15% of patients in gambling treatment institutions are women [56].

There is a lack of suitable treatment approaches and settings for women, who may feel greater discomfort in a male environment, especially if suffering from traumatic experiences. Available treatment may be incompatible with financial and time constraints for women, who may also fear losing custody of their children.

66.2 Treatment

Individual CBT results in greater improvements (96% recovered or improved) than self-directed workbooks with Gamblers Anonymous (GA) referral (81%) or GA referral alone (77%) [34]. Men were more likely to be abstinent from gambling than women at the end of an eight-week program, but these differences dissipated by the 12-month follow-up.

In a randomised trial of brief interventions, one short advice session was more effective than single-session motivational enhancement therapy (MET) or MET followed by three CBT sessions. It was the only intervention associated with clinically significant improvements in gambling hab-

its after 9 months. Gender was not associated with response to these treatments [35].

Female gambling addicts need a group setting, not associated with addictions, where they feel heard. *Donne in Gioco,* an Italian female-only therapy group focusing on relationships, narration and metaphor in systemic therapy, places emphasis on the 'here and now', with reference to relationship networks [37].

A Swiss study of the effectiveness of self-exclusion found that the incidence of PG was lower among those who had self-excluded previously than in those who do so for the first time [46]. This finding may motivate Swiss casinos to promote voluntary exclusions.

At the National Problem Gambling Clinic in Britain, where females comprise just 7–8% of all referrals, women have high attrition rates. In addition to practical barriers, cost, distance and waiting times, research demonstrated internal barriers: fear, denial, stigma, feeling misunderstood and a sense of ambivalence – a fear of success of treatment – gambling having offered a temporary sense of control. CBT may not be the optimum model to facilitate emotional processing for those displaying high avoidance of their difficulties, for whom psychodynamic treatment may work better [38].

Women often prefer online therapy, helplines and forums, overcoming practical accessibility issues and concurring with other recent research in the field [23].

Sagris and Wentzel [45] reported that feminist cognitive behavioural strategies, such as challenging beliefs, exploration of roles and myths, using mutual aid to encourage self-help and lobbying for policy change, reduced stigma, shame and loneliness. Women can carry high levels of guilt; provision of anonymous online and telephone treatment and development of self-help resources and tools may be more effective still than stigma-reduction campaigns.

Preventative measures such as public health messages and the promotion of self-regulatory strategies (e.g. to contain EGM gambling) need to be assessed for their relevance and resonance with women problem gamblers. The implementation of responsible gambling features on EGMs (the ability to set precommitment limits, receive personalised gambling feedback and access gambling expenditure records) as well as reforms to EGM design, such as lower maximum bet sizes, would also help to reduce gambling-related harm among women. Screening older women presenting with comorbid mental disorders could detect those with GD, expediting therapy.

66.2.1 Pharmacotherapy

Drug treatments for GD in men and women are in their infancy. The efficacy and utility of a number of drugs have been tested, but currently, no drug is approved for GD. In a recent case series, 50 mg a day of the opioid antagonist naltrexone led to marked reduction in cravings to gamble in all 10 patients (20% women), as tested by pre-and post-commencement Gambling Craving Scale (GCS) at 6-week follow-up. The study provides evidence for the efficacy of naltrexone in PGs who have failed to respond to psychological therapies, although care should be taken when prescribing to those with concurrent alcohol use disorder who show evidence of treatment resistance for PG associated with relapse of gambling [51]. Opioid antagonists are advocated as a treatment modality for PG, and there is scope for a randomised controlled trial to ascertain long-term outcomes and tolerability once cessation has occurred.

66.3 Gaming Disorder in Women

Internet addiction has been proposed as a diagnostic entity and studied for over 20 years [especially in light of work by Kimberly Young (e.g. [54])]. However, there has been debate and disagreement regarding a standardised definition. Prevalence of addictive internet use worldwide varies, and comparability of available studies has been limited by variable diagnostic criteria and assessment tools and differing populations screened.

Increasingly, specific online activities are recognised for their addictive potential: online gambling, gaming, use of pornography, shopping, chatting, repeated email checking and use of

instant messaging and social media. Definitions for such addictions are heterogeneous: they vary, and many are not yet determined. Diagnostic instruments are not sufficiently standardised, aetiological models and preventive and therapeutic concepts are not sufficiently evaluated and long-term randomised controlled trials (RCT) are lacking.

Problematic gaming is most commonly conceived of as a behavioural addiction rather than a disorder of impulse control [10, 25]. Important similarities between behavioural addictions and substance use disorders (SUD) include initial pleasure, progressing to increased use with diminished enjoyment. Shared neurobiological features include activation and neuroadaptation in the reward pathways [15].

66.3.1 Definitions and Diagnostic Criteria

Although recreational for most, gaming becomes excessive for others, leading to various negative consequences: dropping out of or doing badly at school, being repeatedly fired from jobs, impaired personal relationships or neglected personal hygiene.

In 2013, *internet gaming disorder (IGD)* was included in Sect. III of the DSM-5 [1] in a list of conditions requiring future study. This addition suggested that IGD may be identified by the presence of five or more of nine criteria within a 12-month period. These criteria include:

(1) tolerance; (2) withdrawal; (3) loss of control; (4) gaming preoccupation; (5) gaming to escape negative affect; (6) loss of interest in offline relationships, social interaction and entertainment; (7) deception to conceal gaming extent; (8) jeopardising relationships, work, career or educational opportunities; and (9) continued excessive gaming despite knowledge of these consequences.

Gaming disorder (GmD) is to be classified as a disease in the eleventh revision of the International Classification of Diseases (ICD-11) [41], under 'disorders due to addictive behaviours'. GmD is defined as:

> A pattern of gaming behaviour ('digital-gaming' or 'video-gaming') characterized by impaired control over gaming, increasing priority given to gaming over other activities to the extent that gaming takes precedence over other interests and daily activities and continuing or escalating gaming despite negative consequences.

It is differentiated from non-pathological gaming by significant distress or impairment in personal, family, social, educational, occupational or other important areas of functioning and must have been evident for at least 12 months.

Given this recent change in the ICD-11, we will refer to addictive internet gaming or pathological online gaming as gaming disorder (GmD) unless otherwise specified.

66.3.2 Gaming Prevalence and Patterns

Gender differences in specific problematic online activities have attracted attention.

A German study of problematic online behaviours showed more females than males using social networking sites (77.1% vs. 64.8%), whereas the reverse was true for online video games (7.2% vs. 33.6%) [44].

Mirroring this, in [2], researchers found that gender was significantly associated with individual's social media addiction screening scores, with females tending to score higher on measures of social media addiction than males. Conversely, male participants tended to score higher on measures of addiction to video games than females. Similarly, in [9], researchers found that male adolescents were more likely to report gaming. Furthermore, among gamers, males were more likely to report gaming problems than their female counterparts. However, by contrast, in [36], researchers analysed problematic internet activities in a representative sample of Swiss adolescent females. Results were unable to show that problematic internet use was associated differently with levels of either online gaming or social networking. Further work is necessary to deter-

mine the extent to which problematic gaming occurs among males and females when the relative prevalence of these activities among genders is taken into account.

The prevalence of problematic gaming is unclear. According to one recent systematic review of publications from 1991 to 2016, 5.5% of the population met criteria for IGD [32]. However, a recent study of large-scale national cohort sample suggests that only a very small proportion of the general population (between 0.3% and 1.0%) might meet these criteria [39]. This demonstrates the variance in the scientific literature. Prevalence rates of IGD are widely derived from rates observed for internet addiction, so may be inaccurate at best. Finally, no reliable gender-specific prevalence rates exist.

66.3.3 Gender Differences in Risk, Aetiology and Comorbidity of GmD

Despite an interest in GmD by researchers, few studies have focused on gender differences, and conclusions are vague. In females, risk factors may include having had below secondary school education and high anxiety and depression scores [4]. Being alexithymic may almost double the risk of IGD (odds ratio = 1.88, $p = 0.030$). However, significant replication work is required to confirm the robustness of these results. Furthermore, whether alexithymia contributes to the development and/or maintenance of IGD or results from prolonged, repeated, problematic online gaming is not known.

In a recent study of both genders, females with IGD were found to have reduced cortical thickness in the left and right rostral middle frontal gyri (MFG), the left superior frontal gyrus, the left supramarginal gyrus, the right posterior cingulate cortex and the right superior parietal lobule, compared with female recreational game users (RGU). These are small, statistically significant differences in cortical thickness. Low craving scores in female IGD subjects were associated with thick right ($r = -0.290$, $p = 0.018$) and left ($r = -0.359$, $p = 0.003$; Bonferroni corrected) rostral MFG. The authors suggest that females may therefore be more vulnerable to IGD, though causation cannot be demonstrated without longitudinal studies, and further preregistered replication work is necessary to confirm the robustness of these findings [50].

Cravings are an important feature of addiction and constitute a diagnostic criterion for substance use disorders though not for GD or GmD. In a recent functional magnetic resonance imaging study, Dong et al. [11] found that gaming-related cues elicited greater cravings in males with RGU than females with RGU and that related corticostriatal-limbic brain activations correlated more consistently with craving responses in males than females, suggesting potential biological mechanisms for male vulnerability in developing IGD [11].

In a related study, Dong et al. [12] made two distinct and significant observations. First, both male and female IGD subjects showed reduced left dorsolateral prefrontal cortex (DLPFC) activation compared with RGU subjects. Left DLPFC activation (which contributes to executive control) may therefore be a target for treatment (e.g. transcranial magnetic stimulation or transcranial direct current stimulation) in IGD as it is in other addictions [12]. Second, IGD status was associated with increased activation of the caudate in both males and females, post gaming, but RGU males showed higher caudate activation than females. The caudate (being a component of reward circuitry and may promote motivations to pursue rewards) findings led the authors to speculate that this difference may relate to female resilience to developing IGD (compared to males) but that once they develop IGD, gaming may impair executive control and make it harder to stop. However, these notions are speculative and warrant specific examination in future preregistered longitudinal studies [12].

In a population of 472 students aged 13–21, emotional dysregulation was associated with substance and non-substance addictions (GmD, GD, alcohol and drug abuse), but no significant gender differences were found. In the same study,

IGD was associated with poor parental and peer attachment in both genders, females scoring significantly higher on maternal and peer attachment problems. The authors conclude that 'IGD may be related to the need for relational satisfaction in adolescence' [14].

Young people with IGD may have a high level of comorbid symptoms from underlying autism spectrum disorder, ADHD, anxiety and depression, though studies examining gender patterns are lacking [49].

66.4 Screening and Treatment

Various assessment tools have been developed to measure IGD: all are self-report questionnaires with no clinician-administered interviews, many derived from existing internet addiction scales [24]. If internet addiction and IGD are to be regarded as distinct clinical phenomena, then tools for each need to be assessed separately. More research is needed, using the new ICD-11 (GmD) criteria in combination with the DSM-5 (IGD), to produce diagnostic and screening tools which will then need to be validated for a range of clinical populations.

A systematic search for keywords related to gaming disorder in Medline, PsycInfo, and Embase found no published randomized controlled trials for treatments of GmD at the time of writing. There is a dearth of research on treatments for GmD altogether, and no studies have yet looked at gender-specific needs in treatment of GmD. More research is needed into the prevalence of GmD, and clinical tools and parameters need validating. Brain-based biology, socio-economic/health impact, empirically justified intervention and policy approaches all need to be investigated with gender-focused longitudinal studies and controlled trials in cross-cultural populations. Preregistration and the application of open science principles are essential in order to build confidence in the robustness of this work. The way in which gender moderates problematic internet activities, including GmD, warrants specific research.

Key Points

- The prevalence of gambling has increased among women in recent years and is likely to represent a cyclic resurgence in gambling among women, linked to societal change and targeted advertising, rather than a new phenomenon.
- Women consistently start gambling at a later age than men, progress more quickly to PG or gamble for shorter durations before seeking treatment.
- Gender differences in gambling preferences are evident: women prefer lotteries, slot machines, scratch cards and bingo while men prefer poker, sports betting, FOBT and casino games. However, younger women (aged 16–34) are increasingly using EGM.
- Motivations for gambling among women include escape from loneliness, dysfunctional relationships, violence, isolation and childcare and to self-medicate perceived intolerable levels of stress, anxiety and depression.
- The incidence of problem gambling among women has risen in recent years, and is linked to lower socio-economic status, deprivation, marginalisation, violent partners and/or childhood and the interaction of dysphoric mood and 'avoidance' coping.
- Comorbid psychiatric disorders often associated with GD include depression, anxiety disorders, bipolar affective disorder, personality disorders and SUDs – suicide being the leading cause of death in GD (31%).
- Barriers to seeking professional help faced more predominantly by women than men include lack of social support, poverty, lack of childcare, guilt and shame due to stigmatisation and difficulties in finding appropriate treatment.
- There is a lack of suitable treatment approaches and settings for problem

gambling among women, who may feel greater discomfort in a male environment, especially if suffering from traumatic experiences.
- Available treatment for problem gambling may be incompatible with financial and time constraints for women, who may also fear losing custody of their children.
- When it comes to treatment, individual CBT results in greater improvements (96% recovered or improved) than self-directed workbooks with Gamblers Anonymous (GA) referral (81%) or GA referral alone (77%). However, CBT may not be the optimum model to facilitate emotional processing for those displaying high avoidance of their difficulties, for whom psychodynamic treatment may work better.
- Women with GD need a group setting, not associated with addictions, where they feel heard. Women often prefer online therapy, helplines and forums, overcoming practical accessibility issues.
- Preferences for treatment may be partly due to the observation that women can carry high levels of guilt; provision of anonymous online and telephone treatment and development of self-help resources and tools may be effective in this regard.
- Drug treatments for GD in men and women are in their infancy. In a recent case series, 50mg a day of the opioid antagonist naltrexone led to marked reduction in cravings to gamble in ten patients (20% women). However, care should be taken when prescribing to those with concurrent alcohol use disorder.
- Online gambling, gaming, use of pornography, shopping, chatting, repeated email checking and use of instant messaging and social media have been recognised for their addictive potential. However, definitions for such disorders are heterogenous, diagnostic instruments are unstandardised, aetiological models and therapeutic concepts are not sufficiently evaluated and RCTs are lacking. There is a dearth of research into gender differences in gaming disorder.
- Gaming is more prevalent among males than among females, and studies have suggested that males may be more likely to suffer from problematic gaming even when these increases in prevalence are taken into account. However, the overall prevalence of problematic gaming behaviours is unclear. Furthermore, no gender-specific prevalence rates exist.
- Various neurobiological explanations for gendered differences in problematic gaming have been proffered. However, significant preregistered replication work is necessary to confirm the robustness of these explanations.
- There are no published randomised controlled trials for treatments of GmD at the time of writing. There is a dearth of research on treatments for GmD altogether, and no studies have yet looked at gender-specific needs in treatment of GmD. More research is needed into the prevalence of GmD, and clinical tools and parameters need validation.

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Problematic Internet Use

67

Orsolya Király and Zsolt Demetrovics

Contents

Abstract

The Internet has arguably revolutionized our lives in a completely unprecedented way. Despite its countless benefits, threats such as problematic Internet use (PIU) (or Internet addiction) have also emerged. This chapter gives a brief overview of the main research questions, topics, and controversies of the field of problematic Internet use. More specifically, it discusses the concept of Internet addiction and its major criticisms, the development process of diagnostic criteria for gaming disorder (GD) as a specific Internet-use-related disorder, the etiology and theoretical models of general and specific problematic Internet use, the assessment and prevalence estimates of problematic Internet use and gaming disorder, and the main treatment approaches. This chapter closes with conclusions and suggestions for future research directions.

Keywords

Internet addiction · Problematic Internet use · Diagnostic criteria · Etiology · Prevalence · Treatment

O. Király · Z. Demetrovics (✉)
Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary
e-mail: demetrovics@t-online.hu

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67.1 Introduction

The Internet has arguably revolutionized our lives in a completely unprecedented way. It has virtually changed every aspect of our modern lives from communication to entertainment, from doing science to being a parent, and from navigating in an unknown city to cooking from recipes shared by strangers. With the recent omnipresence of smartphones, we basically keep all the knowledge of human kind in our pockets, we are able to speak and see almost anyone on the planet in real time, and we are able to shop, gamble, bank, or work 24/7. Furthermore, this incredible technological advancement not only affected young "tech-savvy" males but literally everybody belonging to both genders, all ages, and all socioeconomic groups across the planet. Nevertheless, the most shocking aspect of this incredible change is arguably its speed. In the 1980s, less than 40 years ago, at the dawn of the Internet, no one could have possibly imagined a world we live in today.

The history of the Internet dates back approximately to the 1970s when the Advanced Research Projects Agency Network (ARPANET) was established. The ARPANET was the supreme network of regional academic and military networks, which allowed information sharing between geographically distant computers [33]. Shortly after this, in the 1980s, the Internet was born as a technology supporting different communities of researchers and developers, as well as other communities for daily computer communications, mostly via email. It was then the 1990s when the Internet has gradually become accessible to the wider public through the large-scale linking of different commercial networks [33]. Growth has been exponential since then, as institutional, personal, and mobile computers were connected to the network in an ever-increasing manner. By now, Internet services and technologies have been incorporated into almost all major areas of modern life.

Besides the undeniable positive impact of the Internet in countless areas, possible risks have also emerged. It was at the end of the 1990s when the first clinical case studies were published about people who used the Internet in such an excessive manner that it resulted in significant impairment to their personal, social, and professional lives [11, 48]. According to the early scientific observations, these cases resembled addictive disorders. The subjects were preoccupied with using the Internet; demonstrated withdrawal symptoms and tolerance; lost control over the activity; lost interest in other social, occupational, and recreational activities; disregarded the negative physical or psychological consequences of Internet use; and were prone to relapse after periods of abstinence or control [13, 48]. For this reason, DSM-IV criteria for substance dependence and pathological gambling [1] were mostly used for clinical diagnosis and in research as well. The term "Internet addiction" (IA), applied in that early period, also mirrors the conceptual similarity with psychoactive substance use dependence and pathological gambling.

67.2 The Concept of Internet Addiction and Its Major Criticisms

IA is an umbrella term referring to a collection of online behaviors (e.g., social networking sites, online games, shopping, porn, gambling) one can be addicted to. Nevertheless, the concept of IA has been heavily criticized. The main criticism concerns the "Internet" component. Starcevic [43] and several other researchers argue that the term IA represents a misnomer. More specifically, being addicted to the Internet implies being addicted to a delivery mechanism, a medium or channel through which specific activities such as gaming, gambling, viewing pornography and related sexual behaviors, shopping, or chatting are accessed or performed. In this sense, it is like saying that a person with alcohol problems is addicted to bottles [16] or a person with gambling problems is addicted to casinos [43]. To address this concern, several researchers have proposed to avoid the concept and the term IA entirely and replace it with concepts referring to specific online activities such as online video game addiction [43].

The second major criticism concerns the "addiction" component. It has been argued and lengthily debated that the addiction framework might not be the best to capture and explain the condition. One reason is that according to some studies (e.g., [27]), behavioral addictions are fairly transient or episodic in nature, characteristic for certain life stages and remitting with the change of circumstances, while substance-related addictions are usually chronic and progressive if not treated [44]. Consequently, it has been argued that alternative theoretical models such as the model of compensatory Internet use [15] may explain these conditions better. This model proposes that problematic Internet use is the consequence of maladaptive coping (i.e., people alleviate dysphoric moods by using certain online applications) or a way of meeting particular needs. Furthermore, it is also a strong concern that the "light" use of the term addiction may depreciate the severity and importance of traditional substance-related addictions and lead to the overpathologization of otherwise healthy everyday behaviors [4, 43]. However, the research activity (e.g., literature reviews, original research) of the WHO working groups leading to the inclusion of gambling and gaming disorders in the eleventh edition of the International Classification of Diseases (ICD-11) as disorders due to addictive behaviors (more details of these processes are presented in the next section) brought to light new evidence supporting the idea that gaming disorder and, perhaps, the problematic use of other specific online activities are correctly considered addictions (see Ref. [5]).

Nevertheless, addressing these criticisms, several alternative terms were proposed and used as well, such as excessive Internet use, problematic Internet use, pathological Internet use, compulsive Internet use, and Internet use disorder (IUD), and similar terms were also applied to the specific online activities such as gaming or social media use (e.g., problematic gaming, compulsive social media use). In this chapter, we will be mostly using the term "problematic Internet use" (PIU) as an umbrella term for the pathological use of specific Internet activities.

67.3 The Development of Diagnostic Criteria: From Internet Addiction to Gaming Disorder

Despite the heavy criticisms, the clinical presence of PIU-related cases and research in this field and in the field of other so-called behavioral addictions such as exercise addiction, work addiction, or cybersex addiction have grown exponentially since the first case studies were published [4, 38]. However, as in the case of many other new disease candidates, terminology, definition, diagnostic criteria, and assessment have been highly inconsistent. Without official diagnostic criteria, researchers and clinicians used several different theoretical frameworks and created countless assessment instruments to identify and interpret problematic cases [30].

Nevertheless, this increased clinical presence and research interest have urged researchers to make efforts to unify the field by reaching some consensus in the aforementioned areas (terminology, definition, diagnostic criteria, and assessment). As a result, during the development of the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; [2]), the American Psychiatric Association charged the Substance Use Disorder Workgroup to review the scientific literature regarding behavioral or non-substance addictions and to make a proposal regarding their possible inclusion. This preparatory work was a long process; it has lasted for several years, in which the workgroup has reviewed the literature in gambling, Internet use, gaming, work, shopping, sex, and exercise. The proposals they made have been changing during this process. At an early stage, the working group proposed the inclusion of Internet use disorder (IUD) in Sect. 3 (entitled "Emerging Measures and Models" including conditions that need further study), but then, they modified this proposal to only include Internet gaming disorder (IGD; as a specific form of IUD) because this was the only Internet activity with enough evidence of clinically significant impairments. The other important proposal made by the working group was to

realign gambling disorder in the same chapter with substance use disorders due to their overlap with respect to etiology, biology, comorbidity, and treatment [39].

The inclusion of IGD in the DMS-5 was in line with the long-proposed suggestion to replace the concept of general IA (or addiction "to" the Internet) with conditions concerning specific online activities (or addictions "on" the Internet) [12, 43]. This approach was then further supported by the inclusion of gaming disorder (GD) as an official diagnostic category in the Substance-Related and Addictive Disorders section of the ICD-11 in 2019 along with gambling disorder.

It is also important to mention that both inclusions stirred heated debate among scholars. Some of the diagnostic criteria for IGD, namely, preoccupation, withdrawal, tolerance, deception, and escapism as well as the name and the content of IGD, were strongly criticized [14, 22]. However, one can argue that this intense debate was useful in moving toward a larger international consensus, which finally manifested in the inclusion of GD in ICD-11 and the development of the GD definition. According to the World Health Organization [47], gaming disorder is "manifested by a persistent or recurrent gaming behavior (i.e., 'digital gaming' or 'video-gaming') characterized by an impaired control over gaming, increasing priority given to gaming over other activities to the extent that gaming takes precedence over other interests and daily activities, and continuation of gaming despite the occurrence of negative consequences. The behavior pattern is of sufficient severity to result in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. These features and the underlying pattern of gaming are normally evident over a period of at least 12 months in order for a diagnosis to be assigned, although the required duration may be shortened if all diagnostic requirements are met and symptoms are severe." If we break down this definition, it only includes those IGD criteria that were more or less consensual (i.e., behavioral salience, loss of control, losing interest in and reducing other recreational activities, continuation of the playing behavior despite negative consequences, and risking/losing relationships and opportunities).

As a conclusion, a growing consensus can be observed among scholars, which supports the idea that although Internet use can be problematic for some individuals, it is very important to specify the online activities in particular that cause the problem. Consequently, the general concept of IA or PIU is increasingly replaced with conditions involving specific online activities. Among these, the most prominent ones are online gaming, the use of social networking sites, and perhaps the consumption of online pornography. In the following sections, we will focus on general PIU and GD.

67.4 Etiology and Theoretical Models of General and Specific Problematic Internet Use

The cognitive behavioral model of pathological Internet use [9] was one of the first to theorize IA and propose a model for its etiology. According to the model, there are distal and proximal contributory causes to the symptoms of pathological Internet use. Psychopathology (e.g., depression, social anxiety) is a distal necessary cause as it might make the person vulnerable to develop and subsequently maintain pathological Internet use. The other key distal contributor is the positive reinforcement the individual gets from using the Internet, perhaps directly interacting with the aforementioned vulnerabilities (e.g., getting more positive feedback from people online than offline). Maladaptive cognitions about the self and the world are proximal causes of pathological Internet use. These include self-doubt, low self-efficacy, and negative self-appraisal in the form of thoughts such as that the person thinks that he/she is worthless offline but good on the Internet or that he/she thinks that the Internet is the only place he/she is respected. Furthermore, it is suggested that these thoughts are guided by a ruminative cognitive style which prevents the individual from taking action and contribute to more severe and prolonged pathological Internet

use. It is also Davis' model that clearly distinguishes specific pathological Internet use (SPIU) and generalized pathological Internet use (GPIU). In the case of SPIU, the person pathologically uses a specific Internet activity such as online gambling or gaming, while GPIU involves a general, multidimensional excessive use of the Internet such as chat rooms and email (note that this is an early model) or wasting time with no direct purpose. Maladaptive cognitions might cause both SPIU and GPIU, while the behavioral symptoms of pathological Internet use (mostly cognitive in nature such as obsessive thoughts about the Internet, diminished impulse control, decreasing interest in other activities, social isolation) reinforce the maladaptive cognitions resulting in a vicious circle and maintaining pathological Internet use.

A more recent theoretical framework of specific Internet use disorders is the person-affect-cognition-execution (I-PACE) model proposed by Brand et al. [6]. The model proposes that specific Internet use disorders are the consequence of interactions between predisposing factors such as personality-related features (e.g., impulsivity, low self-esteem, low conscientiousness); social cognitions (e.g., loneliness, perceived social support, social distrust); biopsychological factors (i.e., genetics, early childhood experiences, stress vulnerability); psychopathology (e.g., depression, social anxiety, ADHD) and motivation for use (specific motives of the specific online activities such as escapism in the case of online games); moderators, such as coping styles (e.g., avoidance) and Internet-related cognitive biases (i.e., expectancies, illusions, implicit associations); and mediators, such as affective and cognitive responses (i.e., cue reactivity, craving, urge for mood regulation, attentional bias) to situational triggers (e.g., confrontation with Internet-related cues, perceived stress, personal conflicts, negative mood) in combination with reduced executive functioning (e.g., decision-making) or inhibitory control. Pavlovian and instrumental conditioning (e.g., positive reinforcement) processes may strengthen these associations within an addiction process. According to the model, the interaction between affective mechanisms (e.g., cue reactivity and craving) and top-down control processes may progressively lead to increased urges to use the specific Internet activity and reduced inhibitory control abilities while specific Internet-related disorders are being developed. The authors also assume that individuals with different types of Internet use disorders have specific personality profiles. Although the components and processes proposed in the model are based on previous theoretical and empirical research, further empirical studies are needed to test the hypothesized mechanisms in a systematic way. Nevertheless, the model may serve as a comprehensive explanatory framework for the development and maintenance of specific Internet-related disorders and, as such, is greatly helpful for formulating clear research hypotheses in future studies.

Majority of research to date is cross-sectional in nature providing a long list of comorbid psychopathologies for both general PIU and specific PIU such as gaming disorder or problematic social media use. According to these studies, major depression, dysthymia and depressive symptoms, general and social anxiety disorders, substance use disorders, low life satisfaction, low well-being, loneliness, low self-esteem, low emotional stability, attention deficit hyperactivity disorder, borderline personality disorder, impulsivity, hostility and aggressive behavior, and sleeping disorders are all related to PIU, usually with low or moderate effect sizes [26, 28, 29]. When reviewing the studies involving clinical samples, Kuss and Lopez-Fernandez [29] concluded that the presence of comorbidities (e.g., mood and anxiety disorders, other impulse control and addictive disorders) appears to be the norm rather than the exception. However, due to the overwhelming degree of correlational research in the field, the directionality and causality of these relations remain unclear. According to the longitudinal studies conducted to date, the relationship between psychopathology and PIU appears to be rather reciprocal, meaning that poor mental health is a considerable precursor to PIU, while PIU is also succeeded by a diminished level in mental health [3, 32]. It is also worth mentioning that experimental design is not suit-

able to explore the etiological and causal processes in PIU (or the field of behavioral addictions more broadly) as opposed to other fields such as the study of media- or video game-induced violent behavior where it is used very often.

67.5 Assessment of Problematic Internet Use and Gaming Disorder

One of the most crucial, most studied, and also most debated topics within the field of PIU is assessment. The very first IA-related publications have already proposed ways to assess the problematic behavior (e.g., [50]), and newer and newer instruments have been continuously proposed since then resulting in an almost unmanageable amount and variety of scales using diverse theoretical backgrounds, diagnostic criteria, and – very often – ad hoc cutoff thresholds for both general and specific PIU [20, 30].

According to systematic reviews, the Internet Addiction Test or shortly IAT proposed by Young in her early publications [49] is the most popular screening instrument for general PIU [30] but also one of the most popular instruments for problematic gaming [20]. It has 20 items that are scored on a 5-point Likert scale. The instrument lacked a psychometric development process both regarding its items and for its proposed cutoff thresholds. Its psychometric properties have been explored in several subsequent studies yielding varying results [23, 30]. Furthermore, results regarding its factor structure are highly inconsistent meaning that models with one to six factors have been reported in studies that subsequently attempted to validate the instrument. Consequently, although the IAT has by far been the most often used instrument in the field, its psychometric properties do not support such a popularity.

The Problematic Internet Use Questionnaire (PIUQ; [10]) and the Compulsive Internet Use Scale (CIUS; [37]) are both frequently used screening instruments demonstrating good psychometric properties. The PIUQ has 18 items, the CIUS has 14, and both are rated on 5-point Likert scales. Both instruments have been translated into several languages and used in cross-cultural research showing adequate psychometric qualities [31, 35].

Another popular instrument used most often in Asia is the Chen Internet Addiction Scale [8]. The scale has 26 items scored on a 4-point Likert scale. The instrument demonstrated good psychometric properties in its original development study, and it has clinically proposed cutoff scores both for large-scale epidemiological surveys (demonstrating a good diagnostic accuracy) and for clinical practice (having a higher sensitivity than specificity to reduce the number of false-negative cases) [25].

The Scale for the Assessment of Internet and Computer Game Addiction (AICA-S; [46]) and the Checklist for the Assessment of Internet and Computer Game Addiction (AICA-C; [45]) were based on criteria for gambling disorder and substance-related disorders and have been used in both epidemiological and clinical research with promising results.

The inclusion of Internet gaming disorder in the DSM-5 as a tentative condition in May 2013 was an important milestone in the assessment of problematic Internet use. Before that, instruments were highly inconsistent, and many of them lacked a proper validation process. King et al. [20] found 18 instruments measuring problematic gaming in the "pre-DSM-5 era," and there were no two instruments among them covering the same diagnostic criteria. The inclusion of IGD in DSM-5 brought along the development of numerous new screening instruments for problematic gaming (rather than general problematic Internet use), which were more consistent and have been developed more carefully than their predecessors. However, even these have several shortcomings that need to be addressed in the future.

The Ten-Item Internet Gaming Disorder Test (IGDT-10; [24]) is a screening instrument that operationalizes the IGD criteria with 10 items (the last IGD criterion is covered with two items) and a 3-point Likert scale using clear and unam-

biguous wording. It has been translated into numerous languages and demonstrated good psychometric qualities both in the original developmental study and in cross-cultural settings [21]. The Internet Gaming Disorder Scale-Short Form (IGDS9-SF; [40]) is a short screening scale operationalizing the IGD criteria as well. The scale has 9 items assessed on a 5-point Likert scale. It has demonstrated good psychometric properties and has been translated into several languages and applied in different cultural settings. Lemmens et al. [34] also developed screening instruments to operationalize the IGD criteria. They tested four different versions, a 27-item and 9-item polytomous scale and a 27-item and 9-item dichotomous scale, and found that all four scales were reliable and valid, but the dichotomous 9-item version appeared to be the most practical for diagnostic purposes. According to a recent review of these instruments, the shortcomings of these scales are problematic wording in the case of the IGDS-SF9, the lack of full IGD coverage in the case of Lemmens and colleagues' scale, and the need for more quality studies in the case of IGDT-10 and IGDS-SF9 [17].

The inclusion of gaming disorder (GD) in the ICD-11 was another huge milestone. We now have a diagnostic definition and criteria which may serve as a gold standard for the assessment of problematic gaming and perhaps also for other Internet-related disorders as suggested by numerous experts in the field [6]. However, the definition needs to be operationalized to be suitable for clinical use and research. The WHO has now established a working group to lead "The WHO Collaborative Project on the Development of International Screening Tools for Disorders due to Addictive Behaviors" [7]. The project aims to develop (i) a lay-administered fully structured diagnostic interview for GD, (ii) a clinician-administered semi-structured diagnostic interview for GD, and (iii) diagnostic research criteria for GD in the upcoming years. The working group comprises experts from all around the world and aims to integrate their knowledge to establish assessment tools that can be applied across the globe.

67.6 Prevalence Estimates of Problematic Internet Use and Gaming Disorder

Estimating prevalence rates of PIU and its specific forms is of primary importance to assess the demand for prevention and intervention programs and to determine the scale of the problem in general. However, majority of the studies that aim to estimate such prevalence rates suffer from severe methodological shortcomings that undermine the reliability of the results. The most important shortcoming affecting the entire field of PIU is the aforementioned lack of diagnostic criteria. Without a consensual definition, it is impossible to conduct reliable assessment. Therefore, the unification of the field is pressing, and both the inclusion of IGD in the DSM-5 and the WHO's efforts are important steps toward such a consensus. Other important shortcomings of epidemiological research include the use of unreliable assessment tools and non-probability sampling. The literature is overwhelmed with studies using convenience samples and reporting "prevalence rates" like those would be the true proportion of clinical cases. This directly leads to the pathologization of non-problematic cases resulting in an unnecessary moral panic concerning Internet use. Furthermore, in the case of disorders, which are relatively rare, screening instruments (even with high diagnostic accuracy and even in representative samples) inherently yield a very high rate of false positives (i.e., cases which score positive on the screening test while not being disordered in the clinical sense) (for a more detailed explanation, see Ref. [36]). Therefore, even proper epidemiological research conducted with large-scale representative samples most probably overestimates the true prevalence rates of PIU.

According to systematic reviews, prevalence estimates of PIU largely vary indicating a high uncertainty in the field of assessment. For instance, a study reviewing epidemiological data between January 2014 and February 2015 reported prevalence estimates ranging from 1% in a representative German community-based sample and 18.7% in a representative sample of

school-based adolescents in Taiwan [41]. Another review of epidemiological research in PIU carried out between 2000 and 2013 found prevalence estimates ranging from 0.8% in Italy to 26.7% in Hong Kong, but it included studies with convenience samples too [28]. Prevalence estimates for problematic gaming usually range between 1% and 9% in representative adolescent samples [22]. Nevertheless, taking into consideration the aforementioned severe methodological (and theoretical) shortcomings and the high rate of false-positive cases yielded by screening instruments, true prevalence rates (cases with valid clinical diagnosis) of PIU and problematic gaming are most probably somewhere around or even below 1%.

67.7 Treatment Approaches to Problematic Internet Use

Given that the behavioral addiction framework is the leading framework to theorize PIU, treatment attempts are also derived from addiction treatment methods (e.g., substance use disorders, gambling disorder). According to a systematic review conducted by King et al. [19], studies reporting PIU treatment most often applied cognitive behavior therapy (CBT), motivational interviewing, reality training, or self-devised psychological interventions. The cognitive behavioral approach claims that problematic cognitions coupled with behaviors play a role in the development, maintenance, and relapse of PIU and therefore focuses on identifying, challenging and changing maladaptive cognitions (e.g., thoughts, beliefs, and attitudes) and behaviors, improving emotional regulation, and learning more adaptive coping strategies that can successfully be used in solving current problems. The therapist helps the client to monitor their Internet use, set clear and attainable goals, and identify and modify cognitive distortions [18].

Monitoring use (e.g., by systematically recording the types and duration of online activities, as well as emotions and outcomes related to them) draws attention to the negative consequences of excessive use such as loss of sleep, relationship conflicts, and neglect of other activities and increases motivation by making the client more aware of the vicious cycle of PIU (i.e., excessive Internet use creates problems that the client seeks to escape from by being online).

The main goal of therapy is to reduce the amount of time spent online to a degree that no longer interferes with the client's healthy functioning. In contrast with substance use disorders where abstinence is often the goal, in the case of PIU, controlled use is usually aimed for given the essential role Internet plays in our modern lives. During therapy, it is very important to reveal the needs certain online activities fulfill in the client's life (e.g., dealing with stress, reducing social anxiety) and to address them by developing alternative ways and improving skills to meet those needs (e.g., social skills training). It is also recommended that clients in the early stages of reducing online time should try to commit to healthy lifestyle choices such as eating and sleeping regularly, engaging in sports, and finding alternative hobbies; to minimize deliberate exposure to situations that initiate Internet use (e.g., muting notifications, using a traditional wristwatch instead of checking the time on their smartphones); and to make Internet use less convenient and accessible (e.g., putting away the smartphone while reading/cooking, blocking the use of certain apps after reaching a preset time limit) [18, 42]. Furthermore, given the high incidence of comorbid disorders, PIU treatment may benefit from therapeutic approaches that combine treatments for co-occurring disorders in order to increase the efficacy of the treatment [29].

Besides monitoring Internet use and setting clear and attainable goals, identifying and challenging faulty cognitions that maintain PIU and replacing them with more adaptive thoughts that promote healthy behavior are some of the main objectives of CBT. Cognitive distortions or Internet-related cognitive biases are important factors in both aforementioned PIU models (the cognitive behavioral model of pathological Internet use and the I-PACE model) that increase the individuals' dependence on the Internet and maintain PIU. According to Davis [9], such cognitive distortions include a negative view of the

self and a positive view about the Internet and one's online presence and are manifested in thoughts such as "I am only good on the Internet"; "I am a failure offline, but I am successful online"; and "the Internet is the only place where others respect me." These faulty cognitions need to be revealed, challenged, and modified during therapy along with increasing the client's self-efficacy and positive self-appraisal.

Although there is an increase in treatment facilities offering interventions for PIU across the globe, reliable data concerning treatment efficacy is still highly limited. Efficacy studies are scarce, and the existing ones suffer from several methodological shortcomings. According to King et al. [19], these limitations include inconsistencies in the definition and diagnosis of PIU, a lack of randomization and blinding techniques applied in the treatment studies, a lack of adequate comparison or control groups, and insufficient information concerning recruitment dates, sample characteristics, and treatment effect sizes. Consequently, efficacy studies with better study design and more thorough reporting are highly necessary and should be one of the important directions for future research in PIU.

67.8 Conclusion and Future Directions

The Internet has changed our lives in completely unforeseeable ways. Having an entirely offline life few decades ago, we suddenly found ourselves in a completely interconnected world, having the possibility to live online if we wish to do so. The Internet offers us everything: we can order food while sitting in front of our desks, we can complete most of our administrative tasks from home, we can work online, we have access to endless forms of entertainment, we can make friends and live a social life, and we even have infinite ways to acquire sexual pleasure. Consequently, it is not surprising that a lot of people are "binge-using" the Internet and a minority of them experience addiction-like symptoms and suffer severe negative consequences due to their Internet use.

Similar to other technological innovations (e.g., television, microwave oven), the sudden popularity of the Internet caused a moral panic (especially in the media), as well as raised enormous research interest while stirring heated debate among scholars. After about two decades of intense research in the field, it appears that consensus was reached in some essential questions such as the existence and the importance of the phenomenon (i.e., excessive use of the Internet causes severe problems in the case of a small group of users, and these symptoms are similar to the symptoms of substance use and other addictive disorders) and the importance of specific Internet activities (e.g., gaming, buying, watching pornography) over general Internet use and also that gaming disorder should be an official diagnosis. However, a lot of questions still remain to be answered, and much more quality research is needed to have a clearer picture. Future tasks include distinguishing the individual characteristics and addiction mechanisms of specific online activities, investigating whether other specific Internet-use-related behaviors (e.g., problematic social media use) should be included in official diagnostic systems, developing unified assessment tools to determine reliable prevalence rates across cultures, carrying out large-sample longitudinal studies and clinical and qualitative studies to understand the etiology (risk and protective factors, causal relations in the development of the disorders) as well as the natural course of PIU, and carrying out efficacy studies for different prevention programs and treatment methods to find the most optimal ways to help those in need.

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68 Conceptual and Methodological Considerations of Gaming Disorder and Internet Gaming Disorder

Linda K. Kaye, Daria J. Kuss, and Hans-Jürgen Rumpf

Contents

Abstract

This chapter provides an overview of the current conceptual and methodological challenges in light of gaming disorder recently being included in the ICD-11 (WHO, Gaming disorder, 2018). This is discussed in reference to the DSM-5 (APA, Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association, 2013) with its more tentative approach of adding Internet gaming disorder (IGD) in the appendix as a condition for further study. The debate is summarised to present the disparities between these two diagnostic manuals, along with a range of other key conceptual challenges which call for a cautious approach when inferring diagnostic efficacy from these clinical manuals. These issues include definitional differences, impact of game classifications and the various behaviours afforded to these based on game type, game function and form of gaming. Further to this, methodological issues are drawn out to highlight the potential limitations of the academic evidence base in this field. As such, this chapter provides a critical review of the conceptual issues with considerations of the practical and clinical implications.

L. K. Kaye
Edge Hill University, Ormskirk, UK

D. J. Kuss (✉)
Nottingham Trent University, Nottingham, UK
e-mail: daria.kuss@ntu.ac.uk

H.-J. Rumpf (✉)
University of Lübeck, Lübeck, Germany
e-mail: hans-juergen.rumpf@uksh.de

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Internet gaming disorder · Gaming disorder · Internet games · Digital gaming

68.1 Introduction

The gaming industry is a multi-billion pound industry, which in 2018 was estimated to reach a market value of $137.6 billion and to attract players in excess of 2.2 billion [66]. Clearly, digital gaming is a highly sought-after pursuit, highlighting its pertinent role in public interest and society. For the vast majority of players, gaming serves as an enjoyable leisure pursuit, in which the average time spent playing per week is approximately 10 hours for those between 11 and 64 years [66]. However, for some, gaming behaviour may become problematic, which may start to have a detrimental impact upon other aspects of one's lifestyle. Theorising the extent of this detriment often involves referring to criteria used within the addiction field, whereby a distinction may be drawn between those who are "excessive" players and those who may be considered "addicted" [6, 7, 16]. However, there remains substantial academic debate surrounding the applicability of addiction criteria to digital gaming [8, 34, 41]. That is, whereas some scholars propose there is efficacy in using diagnostic approaches [30, 53, 54, 60, 64], others highlight that there is not yet a sufficient consensus in the academic community to warrant agreed clinical diagnostic criteria [19, 67], if indeed it is deemed necessary at all. Despite this, health policy has already offered clinical diagnostic criteria for addiction relating to digital gaming. That is, the American Psychiatric Association has listed "Internet gaming disorder" (IGD) in the appendix of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; [1]) as a "condition for further study", but the World Health Organization (WHO) has outlined "gaming disorder" (GD) as an established clinical condition in the recently published ICD-11 [71]. These policy advancements have driven a wide range of research agendas, which have sought to establish the validity of gaming addiction as an independent clinical condition (e.g. [4, 24, 33, 36, 42, 59]). Despite the wealth of research evidence pertaining to gaming addiction, which to date is typically framed in relation to IGD, there are many queries which remain unaddressed within both health policy guidelines and the academic literature. These are highlighted in the following sections.

68.2 Conceptual Definitions

When exploring the diagnostic criteria afforded to gaming disorder [71] and Internet gaming disorder [1], it is clear that there are some variations. Specifically, gaming disorder is characterised by "a pattern of persistent or recurrent gaming behaviour ('digital gaming' or 'video-gaming'), which may be online (i.e. over the Internet) or offline, manifested by (1) impaired control over gaming (e.g. onset, frequency, intensity, duration, termination, context), (2) increasing priority given to gaming to the extent that gaming takes precedence over other life interests and daily activities and (3) continuation or escalation of gaming despite the occurrence of negative consequences" [71]. The ICD-11 further states that this pattern of behaviour should have been severe enough to have a significant impairment on specific important areas of functioning (e.g. personal, social, occupational areas [63]). Normally, criteria should be evident for at least 12 months (either continuously or episodically); however, the required duration may be shortened if all diagnostic criteria and requirements are met and symptoms are of sufficient severity. In contrast, the DSM-5's Internet gaming disorder does not specify the aspects of life of these impairments, but does state that the impairments may be mild, moderate or severe and are based on the amount of time spent playing games and the general impact on overall functioning [1]. Further, it refers to repetitive use of "Internet-based games" leading to the experience of at least five diagnostic criteria within one year. Criteria include preoccupation with Internet games, withdrawal, tolerance, loss of control, loss of interest in other

life activities, continued use of Internet games despite negative consequences, deception about the amount of Internet game use, escapism from negative symptomology and loss (or risk of loss) of relationships, job, educational or career opportunities.

These definitions appear to vary in operational terms, particularly in relation to how clinical diagnosis is established through fulfilling a specific set of criteria. Whilst GD, in its current clinical description, does not specify if two or three criteria should be present, IGD quantifies a set amount of criteria (five or more) which should be met for diagnosis to be taken forward. In the future, diagnostic guidelines for ICD-11 are anticipated specifying the required number of criteria. For this purpose, sound empirical data are needed. Given the different approaches in DSM-5 and ICD-11, one may raise debate over the convergences and divergences. That is, if their measurement criteria are different, how confident can one be in assuming they are both measuring the same construct? For this purpose, crosswalk analyses will be of special importance.

The inclusion of IGD in DSM-5 as a condition for further study was acclaimed by many researchers. It has stimulated further studies and led to the development of a number of measures to assess IGD and to approaches to applying the DSM-5 criteria to other Internet activities [49]. Whilst a number of studies confirm the approach in general, the concept has been criticised. In particular, concerns were raised that individuals could falsely be classified to have IGD. It has been argued that criteria were taken from the substance use disorder area, whilst in fact, IGD criteria are largely based on the DSM-IV criteria for defining pathological gambling. Nevertheless, both share criteria stemming from substance use disorders.

Some researchers have questioned a distinction between gaming-related problems (e.g. interference and impairments in life events) and addiction-related symptoms (e.g. tolerance, withdrawal, mood modification) which are noted to often be conflated within empirical work [8]. It has been suggested that a reformulation of IGD is needed based on findings that these symptoms and problems are relatively exclusive from each other in the majority of adolescent players [42]. Studies in this regard have used latent class analysis techniques as a means of determining distinctions. For example, Colder Carras and Kardefelt-Winther [8] identified four classes of player: "IGD class" (2.2%), "normative class" (63.5%), "engaged class" (7.3%) and "concerned class" (23.6%). These latter two classes would be misclassified based on their reporting of gaming-related problems only. Similarly, Myrseth and Notelaers [50] identified five classes: never symptoms (46.2%), rarely symptoms (22.3%), occasionally symptoms (23.5%), problem gamers (6.9%) and disordered gamers (1.2%). This has prompted recommendations for establishing greater distinction between problems and symptoms, as well as the potential for better formulation of user groups or classes of players who may have distinct phenomenology and patterns of behaviour [8]. This may go some way to help inform clinical practices surrounding diagnosis and treatment where necessary. Alongside this, there are also recommendations for participatory approaches, involving samples of gamers who may be able to help refine and improve content validity of IGD criteria [9].

Another criticism according to the DSM-5 approach refers to the distinction between core addiction criteria including withdrawal, conflict and relapse/loss of control and peripheral criteria like salience, tolerance and euphoria. This is based on the model of Charlton and Danforth [7] and is discussed in a recent paper on the distinction between high involvement and pathological involvement in video games [5]. The authors come to the conclusion that the ICD-11 approach has advantages by being more close to core criteria with a reduced probability to falsely identifying gaming as an addictive disorder.

Recommendation 1
Distinguish between addiction symptoms and gaming-related problems to identify different player classes.

Furthermore, the inspection of the DSM-5 approach – extended to other behaviours like social network use besides gaming and based on factor analyses in three samples – reveals that some of the criteria show quite high endorsement rates [4]. Interestingly, the youngest sample's data were characterised by a different factor structure. Whilst the other two samples' data show a one-factor structure, in the data of a sample of students in vocational schools, a second factor occurred characterised only by the criterion of escapism from negative mood. This might be interpreted in that using specific online activities to relieve negative mood is very common in young cohorts and might not reflect pathological or addictive use. Taken together, criteria of the DSM-5 might lead to false-positive results in detecting gaming disorder. However, additional studies and comparisons with the ICD-11 approach are necessary.

68.3 Game Classifications and Behaviours

Both IGD and GD refer to online and offline games. In the DSM-5, the term Internet gaming disorder was chosen to better distinguish this condition from the term gambling disorder [55]. However, it is explicitly stated in the DSM-5 that IGD could involve offline games. Although it is likely that criteria should work comparable for different kinds of online and offline games, it might be useful to compare subgroups of players and to further specify characteristics of games that are related to addictive behaviour. This raises a number of conceptual challenges in respect of pinpointing the specific behaviours or specific types of games being referred to within these definitions. Although these labels may be attempting to define the same behaviour, arguably, they may be referring to different things. This presents a key limitation of much research in this field, in the general lack of specificity in how GD and IGD relate to the diversity of games themselves and indeed gaming as an activity. That is, within the IGD research specifically, this has predominantly defined the reference point in studies as "online games" or, in some cases, has been even less specific [46, 59, 65]. Arguably, there are a range of forms of "online" gaming which are Internet-mediated and thus by definition would appear under the remit of IGD (e.g. social networking site games).

Typically, the conceptualisation of "online games" would most likely align to hardcore forms of gaming, played for leisure (e.g. massively multiplayer online games (MMOGs)), although recent evidence has provided initial insight into the "perceived addictiveness" of smartphone games [3], with opposite results found in another study [47]. However, online gaming can take many forms. Of specific relevance here is that even for different types of MMOGs, there are observed variations in player characteristics, preferences and behaviours. Particularly role-playing games as a subtype of MMOGs tend to be associated with greater playing times relative to other types of games, such as shooter games and real-time strategy games [51]. Arguably, using a generic reference point such as "online gaming" or "Internet gaming" is too broad to capture the nuances of player characteristics and behaviours for the various types of games on the commercial market. Specifically, this relates to a number of key issues: (1) variety of the types of games, (2) variety of the function of gaming and (3) variety in the form of gaming. These are discussed next.

68.3.1 Game Types

Digital games are highly diverse as is evidenced by the range of game types which exist on the commercial market. To understand "excessive gaming", it is useful to approach this from the perspective that gaming behaviours are framed by not only individual and contextual factors but also the structural components of games themselves [18, 28, 29, 39, 40]. Indeed, previous studies have proposed a taxonomy approach to understanding how the structural components of digital games may be related to gaming behaviours [28]. Within this taxonomy, the structural components are identified as social features,

manipulation and control features, narrative and identity features, reward and punishment features and presentation features. This has been a helpful approach to operationalise within research, which has revealed differences in how these structural components relate to different gaming behaviours [29]. For example, reward and punishment features (e.g. finding rare items and earning points) and manipulation/control features (e.g. mastering controls and managing game resources) were some specifically highlighted features which interact with players' perceptions of the game and the likelihood of problematic patterns of play [31]. In line with the notion that reward features may encourage problematic play, other researchers have highlighted the limiting effect of the "random reward ratio" and instead indicated a more fixed ratio pattern would be a way of designing more ethical multiplayer online role-playing games [35]. Further, in relation to smartphone games, an analysis of player reviews has found that games being described as "challenging" is the most common keyword associated with them being perceived as "addictive" [3]. In general, a recent review article summarised that based on the current literature on structural characteristics of digital games, it is primarily the features of games which take a long time to achieve which are most likely to be associated with problematic play, such as mastering challenges and earning experience points [18], which is in line with the game mechanics of motivation having been found as predictive of addictive MMORPG play [43].

Based on the fact that the empirical literature has revealed structural components of games to be influential in varying gaming behaviours, it seems logical to assume this would also impact upon excessive gaming which may translate to behaviours synonymous with addiction. This presents an issue when scrutinising the currently available literature referring to IGD and GD, given that studies have largely failed to specify the game type within empirical enquiry. As such, an assessment of the available literature therefore suggests that we perhaps know a lot about IGD, but not how this may vary by game type. Considering game type may be widening the debate about diagnostic criteria, and perhaps, the game-type issue is relevant to the understanding of players' problematic experiences of games.

The clinical implications of this are noteworthy and highlight that any associated treatment plans might benefit from specificity in respect of the "game" aspect of "gaming addiction". A way forward with this may be realised through applying the aforementioned taxonomy approach for characterising structural game features in respect of their presence and importance for players of different types of games. Using this taxonomy as a basis, empirical research has found it to underpin different typologies of players [68]. That is, six types of gamers have been found: story-driven solo gamers, social gamers, solo limited gamers, hardcore online gamers, solo control/identity gamers and casual gamers [68]. Therefore, it may be that such an instrument can form a part of a screening protocol, whereby there is at least some additional intelligence as to how the game type interacts with individual and contextual components of gaming behaviour.

Recommendation 2
Use the video game taxonomy [28, 29] to identify game-specific components associated with gaming-related problems and addiction symptoms.

68.3.2 Gaming Function

As well as games themselves being diverse, gaming behaviours can also be rather varied. In part, this can be related to specific game types (as previously noted) but may also be represented by the fact that there may be different functions of gaming for different players [23]. For example, although most players will engage in gaming for leisure purposes, gaming can also function as a professional domain for many. That is, esports is becoming increasingly recognised as a mainstream sport in which athletes (the terminology here being pertinent to distinguish them from

being "players" or "gamers") undergo intense training and compete in professional tournaments, akin to the rituals which are commonplace for other professional sportspeople or athletes. Esports has garnered interesting debate, particularly in respect of it being more typically conceptualised as a professional sport rather than gaming [10, 20]. As such, although the medium of this activity is digital games (e.g. usually through online multiplayer games such as *League of Legends*), the domain itself is considered professional sport, so it is questionable whether the function of gaming should actually be considered under the umbrella of "gaming", which might have implications in light of IGD or GD. A number of empirical questions can be derived from this issue which should be answered in future research: (1) Does IGD or GD occur in professional esports? (2) Is this related to being successful or unsuccessful? (3) How does the motivation to become an esports gamer contribute to developing signs of addictive use?

68.3.3 Gaming Forms

Beyond gaming functions varying between being professional and leisure-related, there are other conceptual distinctions to be drawn out, particularly in respect of the form of gaming. This includes whether gaming behaviour is considered "hardcore" or "casual" [22]. Within this, casual gaming would be typically represented by someone who plays "easier" or "lighter" games, often in short burst rather than longer uninterrupted sessions, which would be more typical in their hardcore counterparts [11, 21, 38]. Variations may also be found in the consoles which are used between these two forms of gaming, in which hardcore gaming may often be more likely to take place on console or PC devices and casual gaming usually on mobile devices [23]. Clearly, there are some variations present in the behaviours afforded to these forms of gaming. In respect of the current literature particularly on IGD, because studies tend to hold a generic reference point as "online games", this may be capturing players across a continuum of both hardcore and casual players. This could benefit from a more specific enquiry in which distinction is drawn out further to more fully establish gaming behaviours between these distinct forms. This is important as it can help provide a more informative account of how IGD and GD may be represented differently in theoretically varied patterns of play or players. Although it is conceivable that IGD and GD would not be so highly prevalent in casual gaming, establishing empirical evidence to ascertain this is still warranted.

This chapter so far has provided an overview of some conceptual-based challenges which exist in relation to the current understandings of IGD and GD. However, from an empirical standpoint, there are also some methodological issues to highlight, which bring into question the validity of measurement tools within this field. These are discussed next.

68.4 Behavioural Measures

Academic approaches to understanding problematic or addictive technology use, including gaming, have typically relied on self-reports of individuals' personal experience with a given technology [13]. One exception here is the work on gambling which, in a number of cases, has capitalised on online behavioural tracking data to understand gambling intensity and "at-risk" users (see [17] for an overview). However, in respect of digital gaming and indeed the vast majority of empirical work on problematic technology use, this approach has been largely omitted. Commentators in this field would argue that this is problematic based on the fact that users' estimates of their technology-related behaviours are often inaccurate [2], and psychometric scales used to measure "addiction" (particularly in respect of smartphones) are not likely to be sensitive enough to predict technology use behaviours [12]. As such, this raises queries surrounding the validity of psychometric scales used within empirical enquiry and screening protocols for assessing gaming-related addictions.

In general, the methodological approaches to assess IGD and GD are characterised by a num-

ber of weaknesses and do not reach the common standards found in mental health [62]. The instruments used in the academic literature as a means of measuring aspects of gaming addiction include the Internet Gaming Disorder Scale-Short Form (IGDS9-SF; [57]), the IGD-20 [58], the IGDT-10 [32], the Game Addiction Scale [45] or adapted scales from those validated for pathological gambling [15], as well as those adapted from Young's [73] more generic classification of "internet addiction" (e.g. Problem Video Game Playing Test [31]). Unfortunately, none of these instruments have been validated against behavioural metrics which correspond to gaming behaviour, so the extent to which these may be entirely valid as a means of understanding facets of gaming addiction is unclear. In particular, garnering user data could be specifically informative for understanding diagnostic criteria relating to tolerance to gain objective measurements on the way.

Recommendation 3
Make use of digital data garnered through gaming platforms and user metrics to gain more objective data to corroborate with existing instruments.

Offering an alternative approach, it has been noted that an area of promise in the study of technology use may be to move away from "addiction" or "problematic use" [33] and instead focus on cognitive usage, such as attentional lapses and mind wandering in respect of specific technology use [12, 13, 48]. This notion is also supported by evidence suggesting that implicit cognitions associated with technology usage may hold some merit in understanding the underpinning processes, which may translate into addictive behaviour [12, 13, 69]. This is further supported by neurobiological and neurophysiological evidence that those labelled as having IGD show poorer cognitive control and are more prone to attentional bias towards game-related cues than healthy controls [25, 44], which has been verified largely in experimental research [52]. This can go beyond self-report, which may only measure expectancies associated with a given behaviour and be subject to judgement-memory relationships which may compromise one's perceptions of one's behaviours [14, 72]. Therefore, obtaining more implicit association measures which may capture attentional bias or cognitive salience may be a worthy candidate for further study in relation to gaming-related addiction. In particular, this may provide corresponding evidence for diagnostic criteria relating to salience or preoccupation.

Recommendation 4
Explore the use of implicit association measures to further explore cognitive and attentional processes underpinning gaming behaviour.

At the same time, it is important to mention that measures based on tracking or implicit associations have practical limitations and cannot be used as easily as self-report questionnaires. Furthermore, the more disguised assessment with new methods might have implications on the motivation to participate in screenings or diagnostic procedures. Therefore, self-report measures might be more appropriate for reaching large groups in epidemiological surveys or for the purpose of case finding for preventive measures. At the same time, indirect technology-based assessments might be feasible and important in clinical settings which will be outlined below.

68.5 Clinical Implications

Based on the commentary provided within this chapter, a number of key issues are presented which hold practical implications for clinical practice. These are summarised in Table 68.1 for ease of reference.

In general, these represent both conceptual and methodological challenges to the current understanding of IGD and GD. In general, the literature suggests that there is insufficient evidence from

Table 68.1 Summary of issues outlined with suggested recommendations and implications

Issue	Recommendation	Clinical implications
Observed distinctions between addiction symptoms and gaming-related problems which often are not accounted for in academic practice or health policy	Latent class analysis approaches which may reveal distinct player classes	More specific or tailored treatment provision which may vary between being more game-focused (gaming-related problems) and more generic (addiction symptoms)
Game types are not specified in health policy	Video game structural taxonomy scale as part of clinical screening	More specific insight into the interaction of game-related components within symptomology to better inform treatment provision
Psychometric gaming addiction scales may be inaccurate and lack validity to actual behaviours	Make greater use of digital data garnered through gaming platforms and user metrics	Clinicians will have objective data to corroborate with existing assessment instruments to ensure adequate validity. Particularly relevant for understanding tolerance
Self-report measures may capture cognitive expectancies and not predict behaviour	Explore further use of implicit association measurements	Clinicians will have additional approaches to assess cognitive saliency or attentional bias as part of screening and/or assessment practices. Particularly relevant for understanding preoccupation or salience

treatment studies which can confirm the long-term benefits of gaming addiction treatment interventions [26, 37]. However, a current randomised controlled trial confirmed short- and long-term efficacy of a cognitive behavioural therapy approach [70]. For preventive and policy measures, the evidence base is relatively sparse [27, 56], and there is clearly a paucity of brief intervention studies [61]. Treatment and prevention approaches may benefit from the aforementioned issues. This may include paying more attention to the nuances of game-specific components, which interact with individual- and contextual-level factors to determine gaming-related cognition and behaviours. Further, the empirical literature itself would greatly benefit from more intricate and objective approaches to garnering users' gaming data to correspond with widely used psychometric instruments in this field. This may help enhance the validity of measurement tools in this area, and this serves to underpin the ongoing empirical work committed to better understanding IGD and GD.

In conclusion, although there is a large quantity of academic work in this field, particularly framed in relation to IGD, there remains a lack of sufficient attention to game-specific enquiry, which may contribute in improving treatment and prevention. Given that different types of games, often based on their structural characteristics, result in varying psychological affordances and playing behaviours, it is pertinent to include further detailed guidance on how these components interact with individual- and contextual-level factors in fostering problematic gaming behaviour. Further, this endeavour may also be supported concurrently by considering how this relates to gaming-related problems (as a distinct category from addiction symptoms), whereby some distinction may be drawn for establishing different classes of players to better establish "at-risk" candidates. Both these recommendations acknowledge the role of empirical approaches to support this, whereby academic evidence can help better inform clinical practices. In addition to this, empirical approaches can also be aided through corroborating objective behavioural tracking data particularly to understand tolerance and preoccupation as two key addiction symptoms which may relate to problematic rather than addictive gaming behaviour. These may therefore support existing screening and assessment practices by ensuring that these are sufficiently valid instruments to use within academic and clinical practice to measure GD and IGD. One could speculate that teasing out the aforementioned nuances may increase knowledge on GD and IGD and thus set up a precedence for more efficacious treatment and intervention provision.

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Compulsive Buying Disorder

69

Tatiana Zambrano Filomensky
and Hermano Tavares

Contents

Abstract

The increasing availability of credit has made buying a frequent behavior in everyone's life. Compulsive buying disorder (CBD) is characterized by loss of control over buying, accruing debts and psychosocial distress. Reported by the founding fathers of modern psychiatry, Kraepelin and Bleuler described it as a monomania and named it oniomania. CBD may have a profound impact upon both individuals and society; however, it remains absent from current diagnostic classifications. There are still doubts regarding the psychopathology and nature of CBD; some regard it as a behavioral addiction or a member of two different groups either the bipolar spectrum or the obsessive-compulsive spectrum of disorders. Conservative estimates describe a prevalence of around 2% in the general population with an extra 6% at risk for CBD. An association with female gender is usually described, but it

T. Z. Filomensky · H. Tavares (✉)
Impulse Control Disorders Outpatient Unit,
University of São Paulo, São Paulo, Brazil
e-mail: unknown_user_491810@meteor.springer.com

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has been recently challenged. The CBD construct is based upon three concepts: emotional activation, urges, and affect regulation. Current and lifetime psychiatric comorbidities are usual among treatment-seeking compulsive buyer, respectively 50% and 90%; the most common are mood, anxiety, and impulse control disorders. Accounts of subtypes of CBD patients describe a thrill and pleasure-seeking impulsive type and an emotionally stricken compulsive type. Selective serotonin reuptake inhibitors (SSRIs) in general and citalopram in particular have been used to treat CBD, but so far, its efficacy remains undetermined. Modulation of dopamine pathways within the brain reward system has been speculated as a promising pharmacological approach. So far, the best evidence-based treatment approaches come from cognitive behavioral models.

Keywords

Compulsive buying · Behavioral addictions · Impulsivity · Compulsivity · Neurobiology · Treatment

69.1 Introduction

Since antiquity, the act of buying has been present in society. The emergence of currency modified cultural and moral values, marking a period in which power went from being determined by the family name to being defined by commerce, gaining momentum with the adoption of monetary systems [85]. The act of buying continued to distract and enrapture people throughout the subsequent millenniums, driving commerce and influencing governmental structure. The lack of control over this behavior aroused the concern that we could be facing a clinical disorder.

Compulsive buying disorder (CBD) was described at the beginning of the twentieth century by two descriptive psychiatrists, Kraepelin and Bleuler. Both founded their descriptions on Esquirol's concept of monomania. Kraepelin, the first to elaborate the syndrome, titled it oniomania – from the Greek words *onios* (for sale) and *mania* (insanity), describing it as a pathological impulse. He underscored the predominance of the female sex and believed that oniomania would be a subclinical variation of kleptomania. Bleuler emphasized the impulsive nature of the disorder and likened it to the insanities of impulse along with pyromania (apparently much more abundant at that period than it appears to be today) and kleptomania [81].

CBD did not arouse the interest of researchers in the following decades, except among those studying consumer behavior [81] as well as psychoanalysts that elaborated case reports [49]. During the early 1990s, three independent clinical case series studies involving 90 individuals were published, after which CBD once again returned to be globally discussed [9, 77], with reports originating from countries such as Germany, Brazil, Canada, France, England, and the United States [81]. This renewed interest was probably fostered by the perception of the profound impact that CBD may have upon individuals as well as on society. Indeed, it is estimated that in the United States, compulsive consuming generates more than US$4 billion in annual purchasing.

Despite being described by researchers and scholars for more than a century, CBD continues to be, inexplicably, undefined and understudied. It is absent from modern classifications in psychiatry, except possibly for classification in the residual category of disruptive, impulse-control, and conduct disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), including the subgroup of impulsive disorders featuring loss of control over specific behaviors, alongside pyromania and kleptomania [1]. CBD could also be regarded as an addiction. Indeed, it was briefly cited in the introduction of the substance-related and addictive disorders chapter in the DSM-5, as a potential addition to the realm of behavioral addictions, currently represented solely by gambling disorder in the aforementioned chapter. The scenario is even bleaker in the case of the International Classification of Diseases of the World Health Organization, since

CBD was not even mentioned on either its previous tenth edition or its latest, the 11th edition. The debate over CBD's classification has made little progress, so far.

The first accounts of CBD classification tended to regard it as an addiction [32]. In accordance with this view, Nataraajan and Goff [66] described two independent factors related to the occurrence of a compulsive buying episode: an urgency or desire to buy and loss of control over buying. Others consider CBD to be an excessive behavior secondary to mood disorders, associated within the frameworks of mania, hypomania, or mixed episodes in bipolar disorder (BD), or as a subsidiary symptom of hoarding, on the obsessive-compulsive disorder spectrum [27]. In one of the few attempts at empirically clarifying this matter, Filomensky et al. [27] investigated 80 individuals undergoing outpatient treatment for either bipolar disorder, OCD, or CBD, regarding impulsivity, obsessive-compulsive traits, hoarding, and mood spectrum of symptoms. Compared to the other two conditions, CBD patients scored significantly higher on all impulsivity measures and especially on the non-planning subdimension. In the hoarding spectrum, they scored higher on the acquisition subdimension, but not for difficulty discarding or cluttering subdimensions. Manic symptoms were distinctive of BD patients, while elevated scores on the contamination/washing and checking dimensions differentiated OCD patients. A discriminant model built with these variables correctly classified 79% of the CBD outpatients, 71% of the bipolar patients, and 77% of the OCD. The authors concluded that given the high impulsivity involved and the intense acquisition desire, CBD, like gambling disorder, was closer to a behavioral addiction.

There is also a stream of researchers who criticize the attempts to classify compulsive consumption as a disorder, stating that it implies medicalization of variations within the spectrum of consuming behaviors [47]. Unfortunately, this view ignores the reality that CBD is a prevalent and severe syndrome and stigmatizes the attempts to recognize, understand, and treat the condition.

69.2 Epidemiology

Studies estimating the prevalence of CBD in the general and in specific populations report rates of approximately 2% to 8%. In spite of the increasing scientific and layman interest in the disorder, there is no evidence to suggest that the prevalence of CBD is increasing. A recent meta-analysis examined 40 studies from 16 different countries (n = 32,000). The pooled prevalence rate in adult population was 4.9% (3.4–6.9%), with a higher estimate for young individuals, specially university students reaching 8.3% (5.9–11.5%), and for individuals approached in shopping sites 16.2% (8.8–27.8%). The usual assumption that highly industrialized developed societies with a higher level of consumption would favor the expression of CBD was somewhat challenged since location, i.e., the United States versus other countries, did not present meaningful associations. Nonetheless, comparisons between jurisdictions and diverse cultural milieu were hampered by considerable sample heterogeneity, mainly due to diverse CBD screenings and varying time frames (current versus lifetime). The female gender was strongly associated with CBD as usual [53, 54].

Indeed, previous reports had already pointed to a male-to-female ratio around 1:4 to 1:5, however, they were almost all conducted in clinical settings [27]. Kraepelin and Bleuler had already proposed the predominance of the female gender in CBD, suggesting that the female compulsive buyer was in search of risk and excitement, much like the risk-seeking behavior in male gambling. For Dittmar and Drury [18], the prevalence of the female gender in CBD appears as a compensation strategy to combat negative emotions and low self-esteem. They state that the gender difference is genuine and should not be attributed to the underrepresentation of males in clinical samples, basing their conclusion in a study conducted in the general population of the United Kingdom, in which 92% of the respondents considered compulsive buyers were women. Conversely, Dittmar [19] carried out another survey about consuming behaviors in adolescents, between the ages of 16 and 18. The results indicated a CBD

prevalence ratio similar to the adult survey but without gender imbalance. The same was observed by Lejoyeux et al. [52] while investigating the occurrence of CBD in medical students. Thus, it seems that this gender imbalance is likely to appear in younger samples. There are also relevant differences regarding the sample source (clinical site versus general population) and the method of data collection (face-to-face interview versus anonymous survey). For example, a study by Koran et al. [43] interviewed approximately 2500 American adults through an anonymous telephone questionnaire. They determined a CBD prevalence rate of about 5% and a ratio of men to women of 1:1, which indicates a rather larger participation of men than usually reported.

Nonetheless, gender differences seem relevant and considerable in CBD in a varied set of aspects such as demographics, psychiatric comorbidities, and features of the buying behavior itself. A Brazilian study [12] investigated gender differences in CBD treatment-seeking individuals. Compared to the female compulsive buyer, the male compulsive buyer was more often of non-heterosexual orientation, had fewer years of education, and was more often diagnosed with sexual addiction and intermittent explosive disorder, suggesting a more severe and impulsive presentation. Conversely, a Chinese study in college students found differences in the mediation of the compulsive buying behavior with mood compensation strategies working as a significant mediator for women, but not for men [7]. Finally, regarding favored purchasing, the differences are also noteworthy, with female compulsive shoppers targeting mainly clothes, handbags, shoes, perfumes, makeup, and jewelry while men prefer electronics and objects that display elevated social status such as expensive suits, watches, electronic gadgets, and cars [4, 9, 55].

69.3 Course and Consequences of Compulsive Buying Disorder

It is believed that CBD begins toward the end of adolescence, around 18 years of age, or at the beginning of adulthood. This is the period in which the adolescent develops more autonomy and emancipation from the nuclear family, when they are likely to acquire credit for the first time [4]. Nevertheless, the perception of buying behavior as a problem occurs later, around 30 years of age, and treatment seeking between 31 and 39 years of age.

Before 18 years of age, uncontrolled buying is generally associated with a more diffuse general pattern of behavioral disinhibition, which can include smoking, alcohol and drug misuse, and premature sex [74]. Besides, 24-hour shopping made possible by online credit card purchasing could be a contributing factor to adolescent onset. Indeed, it has been reported that among computer compulsive users, up to 19% would fulfill criteria for CBD [4]. In view of this fact, it is likely that some compulsive shoppers will enter their adult lives already with a substantial debt.

CBD is commonly associated with severe personal impairment, both financial and familial, as well as other psychiatric disorders, including personality disorders [4, 81]. Although there is a lack of longitudinal studies for CBD, some studies indicate that the course of the disorder can be chronic or recurrent [9, 77]. However, the treatment of CBD can modify the course of the disorder, as shown in a study in which patients who responded to treatment with citalopram maintained states of remission in 1 year [42]. More recently, Black et al. [5] published a 5-year follow-up of 17 CBD individuals. Psychiatric comorbidity had significantly decreased at follow-up, interest and actual shopping also decreased for roughly half of individuals, and 18% reported having overcome CBD. However, CBD revealed a mostly recurrent nature with usual triggers such as urges to shop, boredom, negative emotions, and the desire for positive emotions. CBD severity was significantly associated with mood disorders both at baseline and follow-up, and although on average severity and impulsivity decreased over the course of 5 years, the majority of individuals still had ongoing symptoms of CBD. However, the small sample size of this study compromises the generalization of its findings to CBD individuals in general.

Perhaps, the most meaningful longitudinal study on CBD to date was performed by Zhang et al. [88]. They conducted a survey on residents of two New York counties (N = 548), who were followed from adolescence until their forties with a focus on quality of life and cost of CBD. The main findings were CBD was associated with a significant decrease in quality of life and family income, even after controlling for demographics and concurrent mental health issues. Quality of life and family income had a significant but weak association (16% of variance explained); however, the monetary cost of CBD was not trivial, subtracting an estimated amount of US$138,000 per family income. In other words, CBD weighs upon the individuals and their families in two fronts: well-being and financial health.

69.4 Diagnosis and Assessment Scales

Usually, compulsive buying episodes occur in a solitary manner, routinely, or in the form of purchasing binges. Sometimes to lessen the guilt, compulsive buyers will also buy for their partners, family members, or friends. When buying for themselves, they often – though not necessarily – hide the objects in closets, drawers, or the car trunk. Many of such purchases may never be used. There is no pattern to stores or commercial places in which these episodes of excessive spending occur; however, buyers do have their "favorite" shopping places, catalogues, and online sites. A study that evaluated excessive Internet use among compulsive and non-compulsive buyers concluded that buying through the Internet is more common among compulsive buyers. The same applies for purchases made through the television [60].

In 1989, O'Guinn and Faber defined compulsive buying as an addictive behavior characterized by "a response to an uncontrollable drive or desire to obtain, use, or experience a feeling, substance, or activity that leads an individual to repetitively engage in a behavior that will ultimately cause harm to the individual and/or others," underscoring the chronic and repetitive nature of CBD [81]. Valence and colleagues (1988) proposed that CBD was a three-pillar construct defined as 1) a strong emotional activation when exposed to a shopping environment and shopping opportunities, 2) tension and buying urges elicited by the exposure to such stimuli, and 3) shopping and buying as means to obtain affect regulation, shortly lived because it is usually followed by post-purchase guilt [84] Moreover, it is likely that later negative consequences (indebtedness, family and friends' reproaches, etc.) enhance the negative affective state, which in turn will lead to stress-relief-seeking behavior through further shopping and buying, thus closing a cycle of self-reinforced behaviors. Both groups of researchers developed their own scales based on these roughly equivalent approaches to CBD. One study pointed to the complementary nature of these scales, reflecting the interrelated aspects of both models. Although subtle, the difference between shopping (perusing showcases and malls and analyzing objects in display) and actual buying (the exchange of money for the acquisition of a desired object) seems relevant. Indeed, it appears that Valence's approach has a better focus over shopping behavior and its effect over affect regulation, while Faber and O'Guinn's perspective seems to better capture the extremes of uncontrolled buying, associated behaviors, and consequences. Thus, their scale may be better suited for the assessment of clinical samples. In both cases, the models suggest that CBD cannot be characterized solely by impulsive purchasing, which for that purpose has to be combined with attempts at emotional self-regulation by shopping and buying.

In 1994, McElroy and colleagues proposed the following diagnostic criteria for CBD, emphasizing the inability to resist the impulse to buy:

A. Maladaptive preoccupation with buying or shopping or maladaptive buying or shopping impulses or behavior, as indicated by at least one of the following:
   1. Frequent preoccupation with buying or impulses to buy that is experienced as irresistible, intrusive, and/or senseless.

2. Frequent buying of more than can be afforded, frequent buying items that are not needed, or shopping for longer periods of time than intended.

B. The buying preoccupations, impulses, or behaviors cause marked distress, are time-consuming, significantly interfere with social or occupational functioning, or result in financial problems (e.g., indebtedness or bankruptcy).

C. The excessive buying or shopping behavior does not occur exclusively during periods of hypomania or mania. These criteria are currently the most employed, despite the scarcity of studies endorsing their validity and reliability. Although the lack of official and specific diagnostic criteria for CBD remains, McElroy's criteria have been internationally adopted, and it has been the diagnostic reference for almost all studies conducted on CBD until now.

It is important to differentiate normal from uncontrolled buying. Essentially, the distinction is not based on the quantity of money spent in relation to the income level, but on a subjective feeling of irrepressible urges to buy, the experience of being out of control while buying (e.g., feeling as if one's behavior was led by an external force), the extent of worry, the degree of distress suffered by the individual, and the appearance of adverse and negative consequences. At any moment of their lives, people may experience an occasional shopping binge, particularly in special occasions such as birthdays or holidays. However, isolated episodes of unrestrained buying should not be confused with CBD's impulsive, harmful, and recurrent purchasing.

Several researchers have developed instruments for the investigation and diagnosis of CBD, or for severity assessment. The Minnesota Impulsive Disorders Interview (MIDI), developed by Christenson et al. [9], is a semi-structured interview, which evaluates the presence of CBD, kleptomania, trichotillomania, intermittent explosive disorder, compulsive sexual behavior, pathological gambling, and compulsive exercise. Grant et al. [34] report that based on McElroy's criteria for CBD, the MIDI presented a sensibility of 100% and specificity of 96%.

Faber and O'Guinn's [22] previously mentioned scale, the Compulsive Buying Scale (CBS), is a 7-item self-report one-dimension scale with high internal consistency (Cronbach's alpha = 0.95) that seems to reliably distinguish normal from compulsive buyers, with estimated sensitivity of almost 90% and 85% of specificity.

Monahan and colleagues adapted the Yale-Brown Obsessive-Compulsive Scale (YBOCS – 1989) to measure the severity of CBD. The YBOCS-Shopping Version (YBOCS-SV) evaluates cognitions and behaviors associated with CBD. It has been mostly used to assess the effects of treatment in clinical trials. The mean pre-treatment score for CBD patients was 21 (range 18–25), which was grossly larger than the mean score of 4 (range 1–7) for healthy controls. Unlike the other scales that base their approach on the impulse control disorder framework, due to its original source, the YBOCS-SV is able to tap into compulsive aspects of CBD [26].

In that sense, the Richmond Compulsive Buying Scale is unique in its attempt to combine both impulsive and compulsive aspects of CBD. The authors also tried to address another conceptual limitation due to a tautological flaw in the definition of psychiatric disorders by which a behavioral syndrome constitutes a disorder because it implies negative consequences and the reason why it causes negative consequences is because it is a disorder. Thus, Richmond's CBS focuses on behavioral aspects of buying rather than shopping and purposefully avoids tapping into negative consequences. It has convergent validity with Faber and O'Guinn's CBS, and its 6-item simple structure makes it feasible for population surveys [13, 14].

Finally, the Compulsive Buying Follow-up Scale (CBFS) was developed with the goal of providing periodic assessment of individuals undergoing CBD treatment and identifying clinical recovery. It contains six multiple-choice questions and can be used as either self-report or interview format, tapping into compulsive buying frequency, time and money spent buying, craving

for shopping, debts in relation to one's income, and emotional distress due to compulsive buying. The CBFS presented significant correlations with all scales cited above as well as measures of depression and anxiety, with sensitivity to change and accuracy for detecting clinical recovery. Its simple structure makes it useful for repetitive assessments in clinical sites [14].

69.5 Psychiatric Comorbidity and Relationship with Other Mental Disorders

The association of CBD with other psychiatric disorders is the rule rather than the exception, with comorbidity most often seen with mood, anxiety, hoarding, substance use, eating, and other impulse control disorders [3, 4, 9, 55, 62, 65, 68, 77].

A bicentric study analyzed data from US and German treatment centers and found that approximately half of the sample had at least one current psychiatric comorbidity, mainly an anxiety disorder, and that 90% fulfilled criteria for at least one Axis I diagnosis during the lifetime. The main diagnoses were mood disorder (74%), anxiety disorder (57%), and impulse control disorder (21%) of which intermittent explosive disorder was most common [59].

It is not uncommon for CBD patients to build up collections of similar items varying one single aspect, e.g., color, size, or design, to zealously stock and hoard them, not allowing other people to interfere with them. For this reason, a relationship with obsessive-compulsive disorder (OCD) has been speculated. However, there have been few studies on this topic. Only one study found a relevant association, reporting that seven (35%) out of 20 patients consecutively admitted for CBD treatment had a lifetime diagnosis of OCD [55]. Conversely, CBD has been described as a frequent comorbidity among OCD and eating disorder patients [24, 25]. In OCD, the association with CBD has been related to an impulsive subtype, with more depression and alcohol-related symptoms ([21, 51]). A more recent and larger study conducted in multicenter study treatment-seeking OCD patients (N = 993) found that 7.5% of participants had comorbid CBD. CBD was associated with female gender, hoarding symptoms, poorer insight, social phobia, binge eating disorder, Internet use disorder, and kleptomania [40]. The hoarding behavior seems to be the psychopathological link between the two disorders [27] and for both of them a marker of a compulsive trait and severity [30]. For CBD, severity goes hand in hand with psychiatric comorbidity; thus, presence of hoarding behavior is associated with mood, anxiety, and eating disorders [45].

With regard to personality disorders, very few studies have investigated Axis II disorders in the population of compulsive buyers. The two most important studies revealed that the disorders most observed were from clusters B and C: borderline, obsessive-compulsive, and avoidant personality disorders. The first study demonstrated that around 60% (N = 46) of the compulsive buyer patients presented with at least one of the personality disorders mentioned above [77] and the second around 73% (N = 30) [62]. More recently, a study with a large sample among patrons of a shopping mall (N = 1409) investigated the relationship between CBD and borderline personality disorder (BPD); 26% of CBD individuals fulfilled criteria for BPD. This relationship was mediated by self-esteem, impulsivity, and general psychiatric distress, again with a modulation effect from gender with distress and self-esteem being more relevant, respectively, for men and women [53, 54].

Finally, a relationship between Parkinson's disease and behavioral addictions, or hedonic impulsive behaviors, including shopping and buying, is an ever-growing issue. Whether it remains controversial if behavioral addictions are more frequent in de novo Parkinson's patients, there is no doubt about the relationship between high incidence of those disorders and treatment with dopamine agonists. However, with CBD being such a prevalent disorder in the general population, the prevalence ratio between Parkinson's patients and non-Parkinson's individuals does not seem particularly imbalanced, quite different from gambling, binge eating, and hypersexuality with their

frequencies varying from two to five times higher for Parkinson's patients [31]. Nonetheless, clinicians should be aware of the increased risk of precipitating maladjusted, hedonic, impulsive behaviors (including buying) for patients undergoing treatment with dopamine agonists. Having previously experienced difficulties with those behaviors is certainly a risk factor for developing behavioral addictions when initiating treatment with dopamine agonists. This risk could be greater for dopamine agonists with a higher affinity for the D3 receptor; for instance, the frequency of such behaviors in Parkinson's patients treated with pramipexole as an add-on agonist was as high as 32% [78].

69.6 Psychopathology Dimensions

The compulsive buying phenomenon could be approached from three concentric strata. The first and most inner one is related to temperament traits and basic drives. The second one comprises attempts at self-regulation and construction of a self-image, and lastly, the most external strata relate to the interface between the individual and societal and culturally bound values.

In the inner stratum, the feature that most clearly comes to light is impulsivity. The evidences of an association between CBD and impulsive traits of personality and impulse control disorders are abundant [63, 64]. This seems to be a feature shared between all the so-called behavioral addictions, with evidences pointing to impulsivity as a preceding factor, like in gambling disorder [70]. Unfortunately, the cross-sectional nature of almost all studies on CBD precludes causality assumptions between impulsivity and loss of control over buying. Moreover, there is still an open question which is what is fueling the loss of control and driving the behavioral response? The recurrent association with hoarding symptoms hints that these patients are led by an acquisition drive [27]. The evidences of an association between buying and eating point to a potential common root, a primal drive toward perusing the environment in search of valuable resources that must be collected and stored either in one's own body as energy reserve (i.e., fatty tissues) or in one's wardrobe or kitchen cabinet. Along those lines, De Mattos and colleagues (2018) reported that mild to moderate (17.6%) and severe (18.6%) binge eating disorder were common in treatment-seeking CBD patients, as well as hoarding symptoms. Additionally, the relationship between severity of binge eating and CBD seemed mediated by hoarding, specially by the clutter dimension.

Advancing to the second stratum, the self-regulation one, a study investigated inhibitory control in CBD. Compared to normal controls, CBD individuals had poorer performance at a go/no-go task and had an even worse performance after a negative mood induction experience [67]. Negative emotions such as anger, anxiety, boredom, and self-criticism have been related to compulsive episodes of buying [56]. When pressured by an intense negative affective state, the CBD patient feels the need to quickly perform a purchase, regardless of the nature of the purchased object, or they may feel a need to purchase an object to which they are particularly fixated, e.g., a nail polish flask and a CD of their favorite artist [81]. The consummation of buying is accompanied by immediate relief of the negative affective but is often shortly followed by unpleasant feelings such as guilt or regret. Several authors underscore this narrow association between buying and the need to regulate negative affective states [10, 23, 60].

In the cognitive sphere, compulsive buying episodes have been associated with means of identity building, "all or nothing" attitudes toward money, hindsight appraisal of purchasing, and gift buying as a way to garner affection and avoid embarrassment [26, 57]. Difficulties at self-regulation and identity building have been assigned as core features of narcissistic personalities and usual features of CBD as well. Indeed, studies have found positive associations between narcissism and compulsive buying. Furthermore, the relationship between impulse control and buying behavior was negatively mediated by materialism, defined as a tendency to consider material possessions and physical comfort as

one's primary source of well-being [75]. On a multilevel approach to personality and individual differences, extrinsic life aspiration factors like financial success, attractive self-image, popularity, and conformity to societal expectations were able to predict CBD beyond basic personality traits [69], which points to the third stratum, the one related with societal norms and values.

Materialism as a life perspective is largely encouraged in our postmodern, consumer-driven behavior societies [73]. As a matter of fact, in comparing full-fledged CBD and moderate risk buyers, Jung and Yi [39] found that narcissism differentiated both groups, but not materialism, suggesting that the latter had a wider unspecific determination over consumer behavior. However, social-cultural factors alone cannot be blamed for CBD occurrence, but it is important to consider their influence. The easy access to growing amounts of credit is a worldwide phenomenon, and in the last decades, there have been a shift in advertising strategies from focusing on the qualities of the purchase to how good purchasing makes you feel [4].

An almost universal selling strategy is to anticipate the pleasure of the acquisition through credit card shopping or other option and to delay the "pain" of payment, to which impulsive individuals may be particularly vulnerable. Indeed, several measures of compulsive shopping have a strong correlation with credit card use and credit card minimum payment [22]. The credit card has become a cultural icon, going beyond a mere form of modern "plastic cash," something particularly noticeable in developing economies, and most appealing to vulnerable women as a promise of more autonomy in societies largely dominated by men [4].

69.7 Subtypes of Compulsive Buyers

Based on the profile of psychiatric comorbidities and the abovementioned psychopathology dimensions, researchers have tried to define subtypes of CBD. De Sarbo and Edwards [16] described two subtypes of compulsive buyers: one group in which the principal trigger of a compulsive episode was the materialism and desire for objects with a tendency to be more impulsive and the second group in which the compulsive episode was more motivated by internal emotions such as low self-esteem and little control over the desire to buy. This second group presented with a higher propensity to develop depression. Likewise, another study pointed to two distinct groups among compulsive buyers: one group in which the motivation for the purchase was guided by positive reinforcement related to pleasant aspects of the purchase and the other in which the purchase occurred as a result of emotional suffering associated with financial problems, interpersonal relationships, and emotional questions, revealing a group with significantly higher levels of debt [83].

Therefore, like previously described for pathological gambling, CBD seems to encompass a double nature, an impulsive side related to purchase cravings and lack of planning and a compulsive side characterized by the avoidance of negative emotions and attempts to control one's affective state; both combined lead to loss of control over buying. The determination of the subtype depends upon which side prevails [80, 87].

69.8 Neurobiology, Genetics, and Risk Factors

Family studies of compulsive buyers show a heavy concentration of mood, anxiety, and eating disorders, substance use, and other impulse disorders, including CBD itself. Evidence also exists showing that traumatic childhood events such as sexual abuse are factors that predispose the development of CBD [4, 55]. A study of 370 gynecology patients investigated the relationship between five traumatic experiences in childhood (before the age of 12) and CBD. The results indicated that childhood trauma is associated with compulsive buying behavior, particularly when the trauma was emotional in nature or involved witnessing violence [76]. However, there are no data on how childhood trauma and early adversities can build a specific vulnerability to consum-

ing behavior or if it would be an unspecific vulnerability factor for various psychiatric syndromes.

There are few neurobiological studies of CBD, and most are concentrated on the loss of regulation over the serotonergic, dopaminergic, and opioid neurotransmission. Due to the diagnostic doubt that haunts CBD, researchers who note similarities between CBD and OCD use selective serotonin reuptake inhibitors (SSRIs), as it is a common and effective treatment for OCD, but so far, its efficacy in CBD and the role of serotonin transmission in CBD remain undetermined [4, 42]).

Potenza [71] proposes that compulsive purchases, pathological gambling, and other self-indulgent behaviors are related to factors involving low dopaminergic activity, the so-called brain reward deficiency syndrome (BRDS). Thus, the preferred biological tools to intervene in CBD would be those directly or indirectly modulating dopamine transmission, through opioid and glutamate modulation, in the brain reward system. Few reports have suggested the benefits of treating CBD with the opioid antagonist naltrexone, raising speculations about the role of β-endorphin and opioid receptors in CBD [33]. A preliminary study with memantine, an antagonist of the N-methyl-D-aspartate receptor, resulted in reduced glutamate excitability, in addition to improving the compulsive buying behavior of patients with CBD [35]. In any case, proposals regarding neurotransmission remain up to now speculative, with no studies so far having directly examined the neurotransmitters involved in CBD, through either plasma levels or cerebrospinal fluid.

Comings [8] found a significant correlation between the polymorphism of the D1 receptor gene and Tourette's syndrome, pathological gambling, alcohol abuse, and CBD, corroborating the BRDS hypothesis. Another study investigating the polymorphism of the promoter region of the serotonin transporter gene did not find any association with CBD. However, it is important to note that this study involved a small sample and studied only the association with alleles of small effect [17]. A recent study carried out by De Neve and Fowler [15] identified an association between the polymorphism of the MAO-A gene and a higher probability of credit card debt. The MAO-A is implicated in the metabolism of serotonin and has one or both of the variant alleles of low efficacy associated with higher probability of addiction and impulsivity.

One study using functional magnetic resonance imaging in nonclinical samples observed activation of the nucleus accumbens when the subjects anticipated an advantageous purchase. This is the same structure overstimulated by drug addictions, which confirms the involvement of brain reward system in buying behavior. Conversely, disadvantageous offers, i.e., excessive prices, activated the insula and deactivated the mesial prefrontal cortex, indicating the involvement of different circuitries in the decision-making process related to purchasing. Interestingly, other studies have associated the insula activity with the experience of physical pain and its emotional component [41].

To date, so far, only one neuroimaging study has been conducted on CBD patients. Authors compared 26 normal controls to 23 female undergoing psychotherapy because of CBD in a functional magnetic resonance imaging study in which participants were exposed to photographs of consumption products and their prices and then they had to decide whether they were going to buy it or not. During the photographs' exposure, there was a significantly higher activation of ventral striatum for subsequently bought versus not-bought products; this discrepancy was even higher for CBD patients. Moreover, regardless of acquisition, i.e., bough or not bought, the activation of the ventral striatum was always higher for the CBD group compared to controls. Similar to the previous neuroimaging study, the activation of the insula was related to a decision of not buying, with a significant higher activation for the control group. Finally, regarding the prefrontal cortex structures, the anterior cingulate cortex (ACC) was also more activated when the decision tended not to buy, with a stronger activation for the control group as well. Conversely, when the decision tended to buying, then, the activation of the ACC was higher for the CBD group.

Interestingly, a high activation of the ACC has been related to decision-making under conflict and depressive mood. As to the other prefrontal structures, the ventral medial and dorsolateral prefrontal cortex were highly activated while participants decided whether to buy or not a product, but no differences were observed regarding CBD patients and the control group [72]. These findings are strikingly similar to other neuroimaging studies conducted over substance and gambling addiction [48].

Another interesting line of research is cue reactivity. One study investigated cue reactivity through electrodermal response toward pictures of consuming products in 66 females assessed for "pathological buying tendencies" (CBD-related symptoms). Both visual analogue ratings of cravings and electrodermal response had a positive and significant relationship with CBD-related symptoms [79]. Another study investigated cue reactivity using analysis of EEG coherence. Widespread EEG coherence differences were found according to preferred and non-preferred products [46]. On both studies, authors concluded that the relationship of the cue-reactivity measures to specific buying stimuli reinforces the perception of the addictive nature of CBD.

69.9 Treatment

69.9.1 Psychotherapy

Recently, Leite et al. [49] conducted a systematic review of psychotherapeutic treatment for CBD, encompassing original articles from 1985 to 2012. Twenty-three valid contributions were located ranging from motivational interviewing, psychodrama, psychoanalysis, family therapy, behavioral therapy, and cognitive behavioral therapy (CBT). Of all possibilities, cognitive behavioral therapy presented the most promising results regarding CBD remission and decrease of impulsive behaviors. Indeed, over the past years, studies regarding the treatment of CBD established important advances, as what existed were previous case reports aligned to the theoretical orientation of the authors. Still, controlled studies evaluating treatment efficacy for CBD, independent of therapeutic modality, remain scarce.

CBT remains as the most tested and studied treatment modality. The first studies were by Lejoyeux and Bernik, both of which suggested that cue exposure and response prevention may be useful in treatment [81]. Bernik and colleagues reported on two cases treated with clomipramine for panic attacks, who also presented with CBD. The medication did not improve compulsive buying behavior; however, both responded well to 3–4 weeks of buying cue exposure and response prevention, although no posttreatment information was provided.

A pilot study carried out by Mitchell et al. [57] involved 28 patients with CBD diagnoses for the treatment with CBT and 11 controls on the waiting list. At the end of 12 weeks, the results showed significant advantages of cognitive behavioral therapy, with subjects outperforming the waiting list controls in terms of the number of compulsive buying episodes and time spent buying. This improvement was maintained over the following 6 months. In 2008, Mueller et al., inspired by the Mitchell et al. [57] study, treated 31 compulsive buyers with a 12-week CBT intervention and compared them with 29 control patients on the waiting list. The treatment sessions specifically dealt with problems related to compulsive buying, restructuring of negative thoughts and emotions regarding buying, control over buying behavior, and problem-solving skills. Throughout the next 6 months, the patients continued to present with improvements when compared with the control group.

Imaginary desensitization was also used to treat a female compulsive buyer with a treatment package that also included motivational interviewing, financial planning, leisure, and cognitive restructuring. The final evaluation was positive, showing a reduction in compulsive episodes [20]. Another uncontrolled study reported on a cognitive behavioral group intervention with an emphasis on cognitive restructuring. Specific sessions were devised to deal with the most common cognitive distortions related to buying such as buying as a way of coping with emotions and building an identity and "all or nothing" type of

thinking. Nine patients participated; they all reported improvement of both cognitions and behaviors related to CBD [26].

Recently, Muller et al. [65] conducted a randomized controlled trial to assess the efficacy of group CBT compared to wait list combined with guidance for self-help delivered over the phone as a control group. The CBT program included motivational intervention, stimulus control, cognitive restructuring, response prevention, problem-solving, and financial counseling. After 6 months of treatment, the CBT group was better than the control group and retained most of the benefits attained with treatment.

Despite the undeniable enthusiasm with CBT for the treatment of CBD, as well as for other addictive behaviors, doubts remain as to what are its most valid components. The studies conducted so far have failed in choosing more rigorous control conditions beyond wait list, such as support therapy devoid of other specific techniques. In its current state, CBT is pretty much a *potpourri* of techniques, sometimes loosely correlated with considerable variation among its components according to who and where it is conducted. The field is in dire need of dismantling studies that could clarify which techniques are working and what they do. Nonetheless, some common denominators can be derived from previous reports of successful CBT including the exploration of behavioral, cognitive, and emotional aspects related to buying behavior, focus on internal and external triggers for buying, the structural analysis of the buying behavior, and its specific consequences [26, 57]. For these purposes, the most commonly reported techniques are cognitive restructuring, coping skills training, relapse prevention, and financial planning [28, 38, 58, 61].

Finally, family or couple's therapy has been cited in few studies as an add-on therapy to the regular treatment, but the field is still missing controlled studies. Guimarães et al. [36] conducted one of the few studies in this regard. They propose that adding family or couple's therapy to the treatment combo provides the strategic advantage of creating a specific space for debating family-related issues that may contribute to maintenance and facilitation of the compulsive buying behavior, such as secret keeping, payment of debts, and nonassertive communication, i.e., quarreling, nagging, and pleading [29].

69.9.2 Psychopharmacology

Similar to psychotherapeutic treatments, controlled clinical trials for CBD are scarce. Lejoyeux et al. [50] suggest that depressive compulsive buyers have an increased chance of improving their compulsiveness when treated with antidepressants than compulsive buyers without depression. A clinical trial with ten patients evaluated the use of fluoxetine in nondepressed compulsive buyers over nine weeks. Nine of the ten patients showed improvement, suggesting that it is not necessary for patients to be depressed in order to benefit from antidepressants [4].

Two more randomized controlled clinical trials with fluoxetine were carried out soon after. The first treated 37 compulsive buyers over the course of 12 weeks and did not find a difference between fluoxetine and placebo [68]. The second studied a sample of 23 CBD inpatients without depression [3]. The participants were randomly distributed to fluoxetine (n = 12) or placebo (n = 11). At the end of 9 weeks and applying the scale of global clinical improvement, 50% of the patients in the fluoxetine group and 64% of those in the placebo group were classified as showing "great" or "very great" improvement. The positive response of the placebo group points to the need to undertake more randomly controlled trials with longer follow-up periods [4, 9].

A clinical trial with citalopram showed favorable results in the double-blind discontinuation study carried out by Koran et al. [42]. Twenty-four patients with CBD were selected, and after 6 weeks of treatment, 17 patients presented with a significant reduction in spending and purchases and an improvement in global functioning. Then, these patients were randomly assigned to either citalopram or placebo maintenance for nine more weeks. The seven patients that took citalopram did not relapse, while five of the eight patients who took the placebo relapsed. After 1 year, 73% of the seven patients who took medication remained in remission from compulsive symp-

toms even after having interrupted medication. The authors suggested that citalopram treatment might have modified the natural course of the disorder. On the other hand, another study with a similar design using escitalopram found no significant effect [44].

Grant [33] reported on the successful treatment of three patients with naltrexone, and recently, memantine was tested in nine CBD patients with encouraging results [35]. Indeed, there is an interest with the potential therapeutic effects of glutamate pathway modulation for addictive behaviors [82] that is yet to be confirmed. Among the alternatives, topiramate shows promise, given that it has showed moderate to considerable effect over substance addictions like alcohol and maybe cocaine [11] and a moderate but definitely significant positive effect for binge eating disorder [6, 13, 14] and maybe for gambling disorder [2, 11]. Given the similarities between gambling and CBD and the putative shared mechanisms with binge eating, topiramate is speculated as a natural candidate for CBD pharmacological treatment. So far, only case reports have been published [37, 86]. A double-blind placebo randomized clinical trial has been registered (https://clinicaltrials.gov/ct2/show/NCT02138058) and recently completed, but the outcome report is still pending.

69.9.3 Self-Help/Community Resources

Other treatments have been elaborated as complementary to those more traditional ones that could be useful. These include self-help books about CBD for individual clarification or group discussion. The Debtors Anonymous group, which was created with the same perspective of Alcoholics Anonymous, is a self-help group coordinated by laymen who have the same difficulties and who provide support and encouragement for those with substantial debt. Simplicity Circles, which exists in some American cities, is a group of volunteers who encourage people to adopt a simple lifestyle, resist consumerism appeal, and abandon CBD. Finally, couple and financial counseling may be beneficial as relationships and financial status of the family become stranded because of chronic CBD [4].

Key Points

- CBD is a disorder marked by both impulsive and compulsive features, associated with excessive acquisition that leads people and their relatives to both subjective and objective social harm that has in financial indebtedness its main external sign, but which is not limited to it.
- CBD has been regarded as either an impulse control disorder or a behavioral addiction.
- Regardless of classification controversies, CBD is one of the most prevalent psychiatric disorders, with estimates ranging from 4% to 8% of the general population.
- Surprisingly, CBD has not been officially recognized by current codes of psychiatric classification, i.e., DSM and ICD. The recent classification of gambling disorder as the first recognized behavioral addiction in the DSM-5 opens the opportunity for the future recognition of CBD, as well as other behavioral addictions.
- CBD is comorbid with a wide range of psychiatric disorders, mainly mood disorders, anxiety disorders, and other addictive behaviors.
- Studies on the neurobiology on buying behavior and the loss of control over it are still in its infancy, but they all point to the involvement of structures from the brain reward system and from the prefrontal cortex, notably those involved in decision-making.
- Likewise, the knowledge on psychopharmacological treatment of CBD is incipient. The best evidence-based treatment up to now is CBT coupled with family support when needed.

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Sex Addiction

70

Meyen Hertzsprung and Stephen Amadala

Contents

Abstract

This chapter reviews the concept of 'sex addiction' and discusses what we know of its history, nosology, neurobiology, prevalence and comorbidity, as well as assessment and treatment approaches. Excessive sexual behaviour has been documented clinically in the western world since the eighteenth century. Most recently, a classification of Compulsive Sexual Behaviour Disorder was included as an impulse control disorder in the latest revision of the International Classification of Diseases (ICD-11, 2018). While both its inclusion and classification remain controversial, the hope is that this recognition would spur further research in the area.

Keywords

Sex addiction · Compulsive sexual behaviour Sexual behaviour assessment · Sex addiction treatment

M. Hertzsprung (✉)
M Hertzsprung Psychological Services, Calgary, AB, Canada

S. Amadala
Alberta Health Services, Calgary, AB, Canada
e-mail: stephen.amadala@albertahealthservices.ca

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70.1 Introduction

Phenomena of excessive sexual behaviour have been documented clinically in the western world since the eighteenth century. It became known in the early twentieth century as 'Don Juanism', characterized by excessive sexual appetite and protracted promiscuity. It became codified in the tenth revision of the International Classification of Diseases (ICD-10 2007) as Excessive Sexual Drive (F52.7), and included in the most recent revision as Compulsive Sexual Behaviour Disorder (ICD-11, 2018 [56]). Its inclusion and classification in the ICD-11 as an impulse control disorder are already controversial [26], as many discussions of whether and how to conceptualize a particular constellation of 'excessive and maladaptive' [37] sexual behaviour has been from the beginning.

In the 1970s, 12-step recovery groups addressing 'out-of-control' sexual behaviour began to arise independently and spontaneously throughout a number of cities in the United States. Most of these groups were formed by members of Alcoholics Anonymous (AA) groups and followed the 12-step format and principles. These groups placed excessive sexual appetites/behaviour within the rubrique of 'addiction' [32]. However, it was the publication of Patrick Carnes' *Out of the Shadows* in 1983 that signalled the emergence of 'sex addiction' into the world of science and media, and the first inpatient treatment programs for 'sex addicts' were introduced.

'Sex addiction' was a grassroots term that seemed to capture the experience of those struggling with 'out-of-control' sexual behaviour, and emphasized commonalities between AA members' experience with sex and their experience with alcohol. Although the term was controversial, by the late 1980s, extensive media coverage popularized the idea of 'sex addiction', and for a time it seemed like every few years various celebrities would admit to 'sex addiction' and enter treatment.

In the 1990s, widespread access to the Internet lent a new dimension to 'sex addiction'. Suddenly 'an essentially unlimited range of sexually explicit texts, still and moving images, and audio materials' were available for immediate and secret consumption [20]. As if the task of definition and classification were not complicated enough, technology further added to the complexity of what was described as compulsive sexual behaviour. Currently, the Internet continues to be the arena of ever-varied forms of cybersex.

The use of the Internet itself has become the focus of considerable attention in the literature, as it can also become problematic. Hertlein and Piercy [29] noted that high levels of general Internet use account for lower levels of family communications and social interactions, and higher levels of depression and loneliness within families. Moreover, among adolescents, the use of online pornography in particular is associated with increased conduct problems and depressive symptoms, and lower levels of social integration and emotional bonding with caregivers [21].

It can be tricky to differentiate between general Internet use and online sexual behaviour. Young [57] identified three subtypes of 'Internet addiction': (1) excessive gaming, (2) online sexual preoccupation and (3) email/text messaging. All three subtypes can and often do have a sexual component to them. Role-playing games often involve sexual encounters between fantasy avatars, and email/text messaging can and has been the means for sharing sexual preoccupations.

'Cybersex' includes activities that may be described as 'passive' (viewing pornographic texts or images) as well as 'interactive' (webcam, sexting). Interactive components in particular defy straightforward classification. Dryer and Lijtmaer [18] take a psychodynamic approach to the meanings of cybersexual encounters, noting that interactive components lend to these encounters a unique kind of 'techno-intimacy'. Their paper highlights the specific dynamics of this 'twilight zone' of techno-intimacy: ways that constitute simultaneous virtual *and* real sexual 'relationships', wherein the individual is able to be both 'there' and 'not there'. This twilight zone bears further exploration, as virtual/real relationships have also become portable with the increasing sophistication of smart phones.

Thus, online sexual behaviour could be a subset of Internet addiction, or it could be a technological variant of sex addiction [47]; both of these also need to be distinguished from online 'affairs' or Internet infidelity [33]. Indeed, as technology advances, the task of delineating boundaries around 'sex addiction' becomes more complicated.

Coleman et al. [14] summarize the various conceptual models proposed over the years to explain problematic sexual behaviour: Money's focus on disruptions in psychosexual development, Carnes' addiction model with its emphasis on family of origin dynamics and trauma, Kafka's model of a dysregulated drive resulting in adverse consequences, Braun-Harvey and Vigorito's sexual health model with a focus on interpersonal/intrapersonal conflicts regarding sexual values, and their own comprehensive biopsychosocial and sex positive model.

Controversy is bound to surface when any class of behaviours is medically pathologized, including sexual behaviours that many consider 'normal' [43]. Kafka's formulation of a hypersexuality disorder diagnosis [37] for inclusion in the Sexual Disorder section of DSM5 was disallowed, despite his framing the diagnosis as a dysregulated appetitive drive, rather than as an 'addiction'.

As already mentioned, the ICD-11 (WHO, 2018) includes a diagnosis of Compulsive Sexual Behaviour Disorder in the section for Impulse Control Disorders:

> Compulsive sexual behaviour disorder is characterized by a persistent pattern of failure to control intense, repetitive sexual impulses or urges resulting in repetitive sexual behaviour. Symptoms may include repetitive sexual activities becoming a central focus of the person's life to the point of neglecting health and personal care or other interests, activities and responsibilities; numerous unsuccessful efforts to significantly reduce repetitive sexual behaviour; and continued repetitive sexual behaviour despite adverse consequences or deriving little or no satisfaction from it. The pattern of failure to control intense, sexual impulses or urges and resulting repetitive sexual behaviour is manifested over an extended period of time (e.g., 6 months or more), and causes marked distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. Distress that is entirely related to moral judgments and disapproval about sexual impulses, urges, or behaviours is not sufficient to meet this requirement.

Krause et al. [40] point out that the definition is meant to preclude overpathologizing: the diagnosis cannot be applied if there is no impairment in control, nor if the psychological distress is solely based on moral judgments. The disorder is not classified as an addiction due to the lack of definitive information about its phenomenology and its neurobiological underpinnings. As with any other type of diagnosis, self-identification is discouraged. Still, its inclusion in the ICD-11 is an important acknowledgment that problematic sexual behaviour is a clinical problem with potential serious consequences if left untreated.

From the early to mid-2000s, increasing attention has been paid to the effects of 'sex addiction' on couples and families. The term 'codependence', widely used with respect to partners of alcohol and drug dependents, came under criticism as a term that pathologized normal reactions to extreme situations [53]. Rather, partners of 'sex addicts' are invited into treatment as those who have suffered a traumatic experience upon the discovery or disclosure of the 'addict's' compulsive sexual behaviours (e.g. [5]).

Indeed, therapeutic work with partners has become a specialty in itself. The Association of Partners of Sex Addicts Trauma Specialists (APSATS) is dedicated to the professional training and certification of 'Partner Specialists' and 'advocate for ethical care and relational healing for partners, addicts, families and communities impacted by sexual addiction and betrayal trauma' [2]. In addition, an entire literature on managing disclosures of problematic sexual behaviour to partners continues to develop (e.g. [48]).

70.1.1 Relationship with Paraphilias

Paraphilias are characterized by intense, repetitive, deviant, sexually arousing fantasies, sexual urges and behaviours lasting at least 6 months and marked by personal distress or indications of

significant psychosocial impairment related to sexual behaviour. In contrast, compulsive sexual behaviour is characterized by excessive repetitive expression of culturally adapted normophilic sexual behaviours.

70.2 Assessment

Treatment begins with a comprehensive assessment and diagnosis. It is important to clarify what precipitated the visit, the behaviours of concern, their frequency, the circumstances under which the behaviours occur, and the sex and age of partners involved. What is the timeline of the behaviours? When were the behaviours at their worst, and what were the factors that contributed to their exacerbation? What has helped reduce the behaviours or the distress? What has been the impact of the behaviour on various aspects of functioning? Particularly important would be a review of current relationships and the impact of the behaviours on family and friends.

With regard to history, the clinician must assess any experience with sexual or physical abuse or neglect, as well as review the medical history, including any treatments for sexually transmitted illnesses. The clinician must inquire into other addictive behaviours and their relationship with sexually acting out behaviours. In addition, assessing for any legal involvement, past and present, would be important, as well as mental health function and any comorbid psychiatric disorders.

A number of screening and assessment instruments are available, including the Sex Addiction Screening Test (SAST); the PATHOS, a short screening interview analogous to the CAGE for alcohol use; the Compulsive Sex Behavior Inventory; and the Sexual Compulsivity Scale. Carnes [9, 10] developed the SAST, a 25-item dichotomously answered self-administered questionnaire. The SAST has demonstrated a single factor with high internal consistency in a sample of 191 sexually addicted, in comparison with 67 nonaddicted, males. A cutoff score of 13 (out of 25) is likely indicative of the presence of problematic sexual behaviour in heterosexual males. The SAST was revised in 2010 (SAST-R, [12]).

The PATHOS (derived from the SAST and SAST-R) has been developed as a brief screening instrument to assist clinicians with identification of individuals who may have ‘sex addiction’ [13]. A score of 3 out of 6 indicates the need for further assessment.

PATHOS questionnaire items are as follows:

1. Do you often find yourself preoccupied with sexual thoughts? (**P**reoccupied)
2. Do you hide some of your sexual behaviour from others? (**A**shamed)
3. Have you ever sought help for sexual behaviour you did not like? (**T**reatment)
4. Has anyone been hurt emotionally because of your sexual behaviour? (**H**urt Others)
5. Do you feel controlled by your sexual desire? (**O**ut of Control)
6. When you have sex, do you feel depressed afterwards? (**S**ad)

70.3 Etiology and Neurobiology

We do not have quality evidence supporting the etiology of ‘sexual addiction’. Most of the literature about etiological mechanisms is based on theory: endocrine dysfunction, incomplete monoamine hypothesis, developmental processes and a courtship disorder, social learning theory and psychodynamic theories. Little is known about the brain pathways that regulate sexual behaviour and cognition. Dopamine, serotonin and androgenic hormones appear to play a critical role [36]. Functional imaging with PET and MRI has corroborated that the amygdala, mesencephalic tegmentum and septal nuclei are activated during sexual response [1]. PET scans of healthy volunteers during orgasm and ejaculation showed strong activation of dopaminergic mesodiencephalic junction and ventral tegmental area; the latter region of the brain is also activated with the ‘rush’ experienced by heroin addicts [44].

Neurobiological correlates of addiction start with the brain reward circuitry: specifically, the mesolimbic reward system ([17].), a region significant for understanding the origins of how addictive behaviours emerge. There is a paucity

of literature on brain imaging during conventional or pathological sexual functioning. Reward circuits such as the dopaminergic and endogenous opiate systems have been implicated in the process of sexual behaviour in much the same way as substance use [23]. The role of the reward system in these disorders is derived from research into Parkinson's disease, whereby treatment with dopamine agonists leads to vulnerability to impulse control disorders such as pathological gambling, hypersexuality, compulsive shopping and compulsive eating [54]. Addiction has usually been defined as dependence on a drug that can 'hijack' the reward system. Any stimuli (drug or behaviour) that transform the basic drive required for survival (like feeding, thirst, reproduction) into actions of craving/seeking behaviours or repetitive out of control behaviours may make it plausible that addiction can occur even in the absence of drug taking [38]. Thus, behavioural addictions may share many of the same pathways associated with chemical dependence. Hence, the theory that, 'if one can alter neurocircuitry with illicit drugs and pharmacology, then one can alter it with behaviour as well' [31].

70.4 Prevalence

The prevalence of compulsive sexual behaviour is unknown due to the lack of large-scale community data and consensus on diagnostic criteria. Researchers estimate rates as ranging from 3% to 6% [4, 35–37, 41]. Erez et al. [19] found the lifetime prevalence rates of sexual impulsivity, a possible dimension of Compulsive Sexual Behaviour, was found to be higher for men (18.9%) than women (10.9%) as per data from the US National Epidemiologic Survey on Alcohol and Related Conditions.

70.5 Comorbidity

One of the consistent findings of studies of those with sexual compulsion was that the great majority have a lifetime comorbid mood, anxiety, psychoactive substance use and/or other impulse disorder diagnoses [16, 49]. In 103 men seeking treatment for compulsive pornography use and/or casual sexual behaviours, 71% met criteria for a mood disorder, 40% for anxiety disorder, 41% for a substance use disorder and 24% for an impulse control disorder [39]. Estimate rates of co-occurring compulsive sexual behaviour and gambling disorder range from 4% to 20% [3, 25].

ADHD (inattentive subtype) was identified as a co-occurring psychiatric diagnosis in those with problematic sexual behaviour [6]. There is a high correlation between 'sex addiction' and substance use disorders, up to 80% in some studies. This tends to complicate the task of diagnosis and treatment.

With respect to personality disorders, Raymond et al. [45] found that the most commonly co-occurring personality issues are Cluster C personality disorders (39%), followed by Cluster B personality disorders (23%). Reid (2012) [46] found that men with compulsive sexual behaviour exhibited higher levels of emotional dysregulation, stress vulnerability and interpersonal sensitivity; these characteristics generalized to hypersexual women. They concluded that personality traits associated with emotional problems, difficulties coping with stress, and interpersonal sensitivity may constitute a precipitating or perpetuating risk factor in the onset or maintenance of compulsive sexual behaviour in adult men and women; and that treatment interventions targeting affect regulation, stress coping, interpersonal coping, interpersonal sensitivity, impulsivity and manipulative tendencies are warranted for both men and women.

Neuropsychiatric illness [54] may induce acute changes in sexual behaviour; similarly, medications, typically dopaminergic agonists [36], may also contribute to hypersexual behaviour. In these circumstances, the hypersexual behaviours tend to be a mixture of normophilic and paraphilic like sexual behaviours (e.g. inappropriate touching and exposing oneself, but not to strangers).

70.6 Treatment Approaches

70.6.1 Psychosocial Approaches

Patrick Carnes, whose autobiographical book *Out of the Shadows* [8] brought 'sex addiction' to public attention, has also been instrumental in the development of the most widely published therapeutic approach to compulsive sexual behaviour [28]. Carnes uses an addiction framework, and his 'Task-Centred Approach', outlined briefly in his introductory workbook *Facing the Shadow* [11], guides the 'recovering addict' through 30 tasks that generally work well in conjunction with a 12-step recovery program such as Sexaholics Anonymous. Each task has a list of 'performables' meant to operationalize the task. For example, the first task is to 'break through denial' and includes the following performables: make a problem list, make a secret list, make a list of excuses and rationales, complete a consequences inventory (list of consequences in various life areas), make a list of people hurt, find a therapist, find a sponsor and make full disclosure to therapist and sponsor. The first seven tasks are meant to guide the 'addict' through early sobriety; tasks 8–19 provide longer-term guidance in individual recovery, and dovetail with tasks 19–30, which focus on 'family recovery'.

While most of the 'performables' can be directly linked to 12-step recovery (e.g. find a sponsor, complete a powerlessness inventory, share your first step), many others can also serve as a menu of helpful worksheets regardless of therapeutic approach, and can easily be used within the context of relapse prevention and cognitive-behavioural therapy (e.g. identify your relapse scenarios, complete a fire drill plan).

Carnes was instrumental in the establishment of the Society for the Advancement of Sexual Health (SASH), a non-profit organization dedicated to promoting an integrative approach to sexual health research, education and intervention that addresses the full spectrum of sexual health, from problematic attitudes and behaviours to the pursuit of fulfilment, freedom and pleasure [50]. SASH holds a conference yearly and offers a certificate for 'Advanced Training in Problematic Sexual Behaviour'.

Carnes founded the International Institute for Trauma and Addiction Professionals (IITAP), 'a global leader among practitioners who treat addictive and compulsive behaviours, whose certifications, training and continuing education programs offer a cutting-edge advantage for practitioners wanting to grow their practice and gain new insights' [30]. Carnes also founded Gentle Path Press, which publishes many of the materials used for training, as well as books recommended through his Task-Centred Approach.

When conceptualized as an addiction, there are many possibilities of extending already established therapies that help with addictive behaviours, such as Motivational Enhancement Therapy, cognitive-behavioural approaches, emotional awareness and mindfulness-based approaches. Participation in 12-step recovery groups is also routinely recommended in conjunction with psychosocial treatment.

Perhaps the most comprehensive therapeutic process used to address problematic sexual behaviour is described by Coleman et al. [14], who focus on identity formation and the development of intimacy in relationship. They begin with a thorough diagnostic assessment, recognizing that at times all that is needed is brief psychoeducational therapy to help people understand their behaviour patterns and resulting consequences and to motivate them to adapt healthier sexual practices. The diagnostic assessment would also allow for exploring and prioritizing possible comorbidities, whether physical or psychiatric.

When intensive therapy is indicated, Coleman et al. [14] recommend that the following areas be addressed, in loosely chronological order: (1) establishing and maintaining appropriate behavioural and emotional boundarie; (2) understanding patterns and dynamics present in the family of origin and developing and practicing more functional patterns; and (3) identifying the effects

of trauma, and then learning how to manage emotions and developing new ways of relating to the self and to others. Work in these areas lay the foundation for continued growth in the following areas: (1) identity formation, (2) self-esteem development, (3) intimacy development and repair, (4) authenticity, and (5) integrity and positive sexuality.

Their approach requires the judicious use of various psychotherapeutic approaches (behavioural, cognitive-behavioural, family and systems, exposure-based therapy, acceptance and commitment, life review) and modalities (individual, couple, group). Although each of these approaches and modalities has long and respectable histories as evidence-based treatments, so far there is little research evidence to empirically support any one treatment approach specifically for problematic sexual behaviour.

70.6.2 Pharmacological Approaches

Pharmacological treatment uses two main categories of medications: specific serotonin reuptake inhibitors (SSRIs) and antiandrogens [27]. Patients with problematic sexual behaviour may present with dysphoric mood symptoms that may warrant antidepressant medications. This usually occurs in the initial phase of abstinence.

There are no randomized control trials for treatment of patients with antidepressants. However, case reports and open-label studies [34, 51] indicate that SSRIs may be of use in the treatment of 'sexual addiction'. This is based on the rationale that serotonergic dysfunction may underlie the condition. Madeo [42] showed in a randomized control trial with citalopram that, in healthy adult males, four weeks of treatment significantly increased the time to orgasm compared to men on placebo. However, the medications did not dampen sexual desire or penile tumescence measurements, suggesting that SSRIs may have differential effects on dampening libido and sexual function in men who are not depressed, or who do not have compulsive sexual behaviour.

In a randomized control trial, gay and bisexual men with 'sexual addiction/compulsivity' who were treated for 12 weeks with citalopram (20 mg–60 mg a day) reported significant reductions in sexual drive, frequency of masturbation and viewing of pornography in comparison to those treated with placebo [55]. In summary, there is some evidence supporting the use of the SSRI citalopram for 'sex addiction', especially in gay and bisexual men.

Naltrexone is an opioid antagonist approved for use in treating alcoholism and opioid dependence. It works by dampening dopamine release, thus reducing the euphorigenic effects of fantasizing and tension building, which are considered the initial steps in compulsive sexual behaviours. There are no randomized trials of opioid antagonists for 'sexual addiction'. Some open-label trials show that high doses of naltrexone reduced frequency of masturbation, sexual fantasies and nocturnal emission [7].

Antiandrogen medications currently used for the treatment of excessive nonparaphilic sexual behaviour are cyproterone acetate (a synthetic steroid similar to progesterone that acts both as a progesterone and an antiandrogen) and medroxyprogesterone acetate. Medroxyprogesterone acetate diminishes libido in men and thus makes it easier to control problematic sexual behaviour. The rationale of using hormone therapies in men with 'sexual addiction' is based on eliminating sexual compulsivity and obsessions by stopping the production of testosterone. This approach is usually reserved for treating paraphilias in men that involve sexual offending involving children and violence [24, 52]. Antiandrogens diminish sex drive in women; hence, the use of antiandrogens in women to control hypersexuality may be of benefit.

Goodman [22] has presented a psychotherapeutic stage model integrating pharmacotherapeutic, behavioural and psychodynamic approaches. In this staged model, in the first stage (initial behaviour modulation), individuals who engage in compulsive sexual behaviour learn how to modulate their behaviour through a combination of inner motivation, psychological support and affect-regulating medication; the second stage (stabilization of behaviour and affect) addresses the question of relapse preven-

tion, with a distinction between high- and low-risk forms of sexual behaviour. Patients are taught to engage in 'healthier' forms of sexual behaviour.

70.7 Conclusion

'Sex addiction' as a concept carries a lot of controversy. There have been a number of attempts to define the features of 'sex addiction' in the last three decades. The inclusion of a Compulsive Sexual Behaviour Disorder diagnosis in the ICD-11 gives hope of providing a reference for clinicians in the recognition and treatment of this disorder and of furthering research in this field [40]. Although it has been noted that there is frequent comorbidity with attention deficit, and various substance use and personality disorders, there remains a paucity of research about the prevalence and incidence of the disorder [15]. Treatment of the disorder encompasses a variety of approaches, including psychotherapeutic models, involvement in 12-step programs, and pharmacotherapeutic interventions (especially for concurrent psychiatric disorders), alone or in combination. All of these approaches could benefit from more empirical research attention. In sum, the field is wide open for continued research efforts, whether in definition, nosology, incidence and prevalence, assessment and treatment.

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The Association Between Binge Eating, Obesity, and Addiction

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S. Yarnell-Mac Grory, Brian Mac Grory, Luming Li, Blake Werner, S. Murray, N. Avena, and M. Gold

Contents

S. Yarnell-Mac Grory (✉)
Yale School of Medicine – Department of Psychiatry, New Haven, CT, USA
e-mail: stephanie.yarnell@yale.edu

B. Mac Grory
Brown University, Providence, RI, USA
e-mail: brian_macgrory@brown.edu

L. Li
Psychiatry, Yale University, New Haven, CT, USA
e-mail: luming.li@yale.edu

B. Werner
Yale University, New Haven, CT, USA
e-mail: robert.werner@yale.edu

S. Murray
Icahn School of Medicine, Mount Sinai, NY, USA

N. Avena
University of Florida College of Medicine, Gainesville, FL, USA

M. Gold
Washington University, St. Louis, MO, USA

Abstract

Obesity has become a worldwide pandemic with an estimated annual cost in related illnesses and loss of productivity over $100 billion and rising. Though not recognized as a psychiatric disorder, obesity has been linked to serious physical, psychological, and social consequences. Some forms of obesity are characterized by the compulsive consumption of food, inability to restrain from further intake despite negative consequences, a desire to cut back, and increasing amounts of food needed to reach satiety, resembling a form of tolerance.

These symptoms are remarkably similar to DSM criteria for substance use disorders: preoccupation, escalation, tolerance, denial, and a series of medical, psychological, and social consequences that relate directly to continued

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use. Research in both animals and humans has demonstrated food-related changes in the brain itself that are very similar to changes caused by drugs of abuse leading to the hypothesis that some forms of obesity and a related contributing behavior, binge eating, may manifest secondary to or along with a "food addiction." This chapter seeks to describe the common elements and possible intersection of binge eating disorder, obesity, and addiction.

Keywords

Obesity · Binge eating · Food addiction · Overweight · Overeating · Eating disorder

71.1 Introduction

This chapter seeks to describe the common elements and possible intersection of binge eating disorder, obesity, and addiction. The Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) currently recognizes anorexia nervosa, bulimia nervosa, binge eating disorder (BED), avoidant/restrictive food intake disorder, other specified feeding or eating disorder, and unspecified feeding or eating disorder due to the serious impairments and severe negative outcomes associated with these conditions [4]. While these recognized eating disorders largely pertain to restriction of food intake or behavioral compensation for overconsumption, persistent excessive caloric intake resulting in obesity is not currently recognized as a psychiatric disorder. However, obesity has been linked to serious physical, psychological, and social consequences.

Obesity and overeating may represent an addictive process. Some forms of obesity are typified by the compulsive consumption of food, cravings, requiring increasing amounts of food to reach satiety (resembling a form of tolerance), a desire to reduce consumption, and significant difficulty curbing further intake despite negative consequences, including potentially serious medical and psychological issues [59, 61]. These symptoms are remarkably similar to DSM criteria for substance use disorders: preoccupation, cravings, escalation, tolerance, denial, and a series of medical, psychological, and social consequences that relate directly to continued use [4, 31], supporting the hypothesis that some forms of obesity and a related contributing behavior, binge eating, may manifest secondary to or along with a "food addiction."

The concept of food addiction is a highly debated one [5–7]. One argument against the notion that food is addictive is, of course, that everyone eats. How can something that sustains life be considered addictive? A recent systematic review assessed the evidence around "food addiction" and found that certain foods, such as processed foods with high added sweeteners and fats, have greater addictive potential [32]. This fits with prior hypotheses suggesting that only certain foods should be considered addictive, specifically those high in sugars and fats. Foods associated with "addictive" properties tend to be typically calorie dense and highly palatable and foods that people tend to overconsume the most [19]. Studies using animal models have provided a great deal of empirical support for the concept of food addiction. These studies found that, similar to substance addictions, the consumption of such food types increases dopaminergic activity in the brain's mesolimbic reward circuits which leads to increased intake over time. Furthermore, when animal subjects consumed these foods for significant periods of time and were then deprived of them, they experienced symptoms of withdrawal [8]. More recently, tools have been designed to assess food addiction in humans, and studies incorporating such tools are beginning to provide additional evidence of this construct. For example, more than half of obese individuals with binge eating disorder included in one study met the criteria for food addiction [27]. Using fMRI scanning, individuals with greater food addiction scores have also been shown to have greater activation in motivation-related brain regions when anticipating highly palatable food – similar to drug-addicted individuals when viewing cues associated with a drug [28].

Disordered eating, such as that seen in binge eating disorder, bulimia nervosa, and some cases

of obesity, poses a number of complications for the medical community. First, these conditions can be physically compromising; secondary side effects including type II diabetes, high blood pressure, and associated arthritis (from heavy-weight load) are particularly important consequences of disordered eating and weight gain, as well as public health concerns. Furthermore, disordered eating can, in some cases, even be fatal; however, their etiology is not well characterized. Expert speculations regarding the underlying risk factors for the development of disordered eating include a range of psychological, biological, and societal influences. Given the growing evidence of neurochemical and behavioral similarities between overconsumption of certain foods and substance addiction and the urgent need to develop effective treatments to combat obesity and overeating, it may be time to consider food addiction as a possible contributing factor to these issues, as well as a target for treatment.

71.2 Neurobiology

71.2.1 Feeding and Reward

Feeding behaviors are controlled by more than homeostatic mechanisms. As it has been pointed out, "if feeding were controlled solely by homeostatic mechanisms, most of us would be at our ideal body weight, and people would consider feeding like breathing or elimination, a necessary but unexciting part of existence" [54]. The fact that this is not the case suggests that there is a role for the reward systems in the brain in promoting motivational, hedonically driven feeding. Thus, excessive food intake may be explained more by dysfunction in the reward circuitry than strictly dysfunction in the homeostatic mechanisms controlling feeding habits. Studies in both humans and animals have supported the hypothesis that brain reward circuitry may be dysregulated in cases of obesity, disordered eating, and, more recently, food addiction.

The neurocircuitry underlying eating behaviors is quite complicated. Of the multiple regions of the brain involved in the processes of food procurement and ingestion, there are four regions that stand out as also being implicated in substance use disorders and drug addictions: the amygdala/hippocampus, insula, orbitofrontal cortex, and striatum. These areas of the brain play key roles in learning the rewards associated with food, allocating attention and effort toward procuring food, setting incentive for food, and integrating internal homeostatic information about energy stores and gut contents [11].

Sensory input from the mouth is relayed to the same cortical areas of the brain that receive satiety signals from the gut [53]. The gut hormones ghrelin, leptin, insulin, and peptide YY interact with limbic structures and the thalamus to integrate hypothalamic energy control signals [45]. The hypothalamus has direct connections to the nucleus accumbens, which is the control center for reward behaviors such as exercise, sex, and feeding. Mesolimbic dopamine (DA) directly acts upon the nucleus accumbens, thereby controlling motivational and hedonic feeding as well as serving as the point of action for endogenous opioids, serotonin (5-HT), and acetylcholine (ACh). (It should be noted that these are some of the same neurotransmitters and pathways that control motivation and reinforcement of behaviors typically associated with substance addictions.) The endogenous opioids modulate DA release, thereby affecting the reward process. Similarly, ACh in the nucleus accumbens has been associated with satiety, though the precise mechanism of action needs further investigation [9]. 5-HT is also associated with the sensation of satiety and can be associated with weight loss and fat intake [36]. Given the interplay between all of these neurotransmitters and the nucleus accumbens, it is possible that dysfunction at any of these key points could result in disordered eating. This also explains why many of the pharmacological therapies for eating disorders frequently target these neurotransmitter systems.

71.2.2 Obesity

Obesity, defined as a body mass index >30, has increased dramatically over the last three decades and was estimated to affect over 39% of the US population as of 2016 [35]. Obesity is classified

as a medical condition as it places a patient at increased risk for cardiovascular disease, diabetes, cancer, and other diseases. By conservative estimates, the health sequelae from obesity result in a 5–20-year reduction in life expectancy, as well as accrue healthcare costs totaling $147–$210 billion annually [15]. The seriousness of these health consequences highlights the urgent need for strong prevention efforts and the development of effective treatment approaches for individuals with this condition [61].

The cause of obesity remains largely unknown but, similar to eating disorders, is likely multifactorial (Fig. 71.1). It has been suggested that the behavioral phenotype of overeating may be influenced by an interplay of genetics, development, and environmental factors [14]. While separable in theory, the interplay of one's genes; the time, place, and culture in which one lives; and the development of one's obesity through non-homeostatic mechanisms are likely all simultaneously involved and thereby relevant to the problem [21].

Within genetic theories, the "thrifty genotype" hypothesis suggests that the neurocircuitry underlying food procurement and bodily storage evolved at a point in human history in which food was scarce as a means of promoting survival in times of famine [61]. However, recent advances in technology have allowed for the creation and modification of foods, which artificially enhance palatability beyond what would be found in nature, especially with regard to sugar, fat, and caloric value [23, 59] [23]. Foods that are both high fat and high sugar do not exist in nature, but calorie for calorie, these foods are valued more than foods containing only fat or carbohydrate resulting in supra-additive responses in the striatum during food valuation and are associated with greater recruitment of central reward cir-

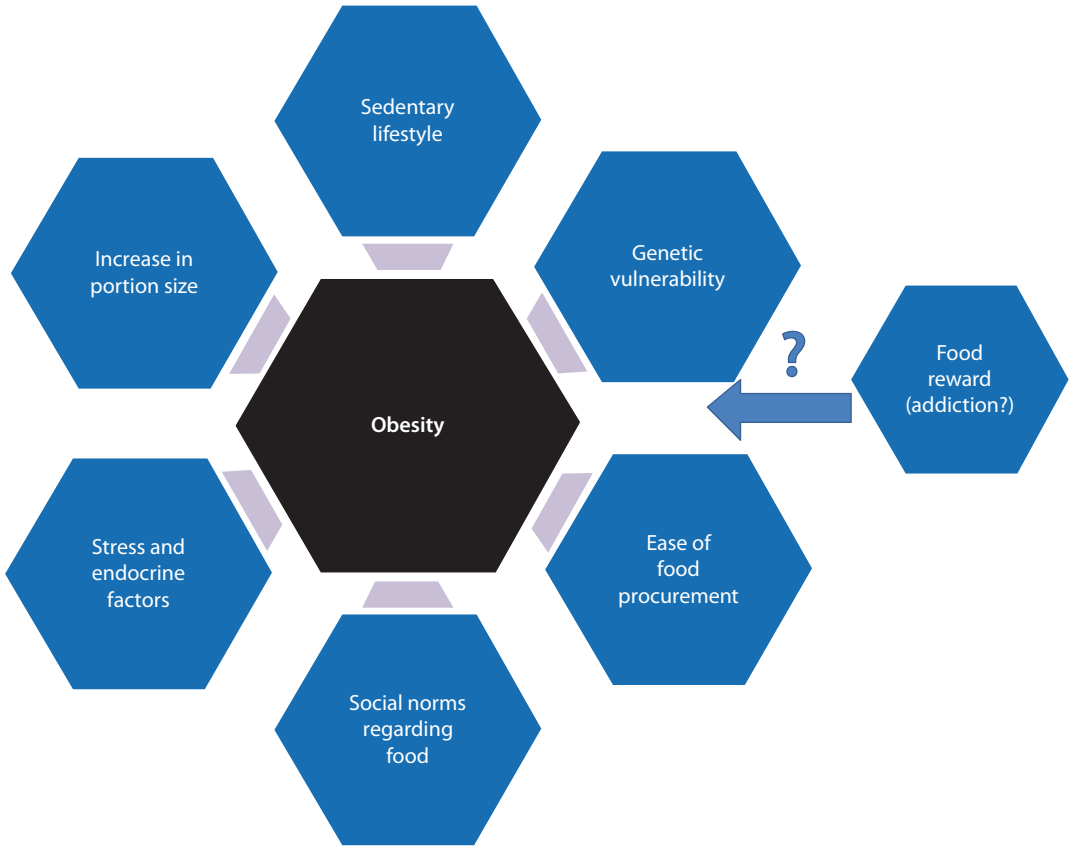

Fig. 71.1 Theorized contributions to the obesity epidemic

cuits [23]. Moreover, these calorie-rich, highly palatable foods are abundant and easily accessible in the typical Western diet. This combination of factors may lead to the activation of reward circuitry, which evolved to reinforce feeding behavior and desires to engage in pathologic overconsumption, which would have been advantageous in a time of famine but now, in a context of abundance, appear maladaptive [14].

In contrast, the "developmental origin" hypothesis suggests that our exposure to certain nutrients and calorie contents in utero may imprint upon our developing brain and influence food choices when outside of the womb. Evidence to support this hypothesis comes from studies investigating the effects of consuming certain diets during gestation on various outcome measures in the offspring. For example, recent research has found that the offspring of animals fed with a high-fat diet during gestation are more likely to weigh more and consume more of a high-fat diet compared to controls [13]. While one hypothesis takes into account an evolutionary perspective and the other a more developmental view, both of these hypotheses may have value for understanding the current issues of obesity and disordered eating.

In regard to possible cultural and environmental influences of obesity, the past several decades have seen five major developments that are thought to have tipped the balance between caloric intake and energy expenditure to an unfavorable disproportion: (1) expanding labor market opportunities for women, (2) increased consumption of food outside of the home, (3) rising costs of healthy foods relative to unhealthy foods, (4) increasing quantities of caloric intake with declining overall food price, and (5) decreased requirements of occupational and environmental physical activity (J [30].). General food accessibility issues and an inability to find healthy food options in certain areas, the so-called food deserts, are also an important factor which disproportionately affects minorities and individuals of a lower socioeconomic status [17]. Other environmental factors implicated in the development of patterns of overeating include advertisements, sights, smells, and sounds, which have all been shown to induce food cravings and can result in overeating [11]. Indeed, eating is more than a physiologic response; it can serve as a social lubricant, facilitating both personal and professional interactions, and is a prominent centerpiece for most individuals at holidays and celebrations (M. S [31]); food also plays a major role in many religions, cultures, and communities [24]. Stress and the difficulties of modern life may also lead to patterns of overeating [29], potentially through the production of the neurohormone corticotropin-releasing factor [50].

These factors highlight the cultural aspect of obesity, but with them come a new set of challenges. During the Coronary Artery Revascularization in Diabetes (CARD) trial, which followed a population of 18–35-year-old patients over 10 years, the average patient showed a weight increase of at least 7 kg regardless of race and sex. This study demonstrated that significant weight gain over the course of adult life is now normative, suggesting a strong cultural component [49]. In order to be classified as a disease, however, a condition must clearly differ from the norms of society. This conundrum has led some to refute claims that obesity should be included in the DSM-V as it may simply be a behavioral disturbance with an adverse medical outcome, not necessarily a psychiatric condition [21]. While not all individuals who are obese may fit the existing criteria for food addiction, it is possible that individuals who do may represent a subcategory of obesity that is characterized in part by significant distress due to their thoughts and behaviors regarding food and/or exhibit compromised functioning as a result of these thoughts and behaviors. As such, these individuals may be recognized as having a psychiatric condition despite being within a weight range that may be considered relatively "normal" based on current trends within society. In fact, over- and/or normal-weight individuals can meet the criteria for food addiction.

Obesity is often described as an imbalance between caloric intake and energy expenditure. This simplified view has led some to suggest that obesity is the fault of the person due to excessive consumption, inadequate activity, or a combina-

tion of the two, resulting in much of the stigma that is associated with this condition [21]. While decreased caloric consumption and increased physical activity can be effective in normalizing weight, these lifestyle modifications have proven very difficult to sustain [61]. The failure of many lifestyle modifications to reduce obesity over the long term suggests that obesity may not be entirely a metabolic disorder, but likely has a neuropsychogenic component [61]. While food addiction certainly does not explain all cases of obesity, the prevalence of people who eat for reasons other than obtaining energy suggests that other factors may play a role in motivating and/or reinforcing feeding behaviors.

With the rapidly increasing number of cases of obesity, it may be time to consider new ways of understanding and approaching this problem. Some hypothesize that obesity, at least in certain cases, is related to dysregulation of the brain's reward system. The hypothalamus is accepted as the primary brain region responsible for managing signals that regulate the intake of food, primarily through hormones such as ghrelin, leptin, and insulin which effect both the hypothalamus and the reward neurocircuitry in such areas as the caudate nucleus, hippocampus, and insula [59]. Food, especially when it is rich in fat and sugars, stimulates brain reward circuitry, in part, through the release of endogenous opioids, cannabinoids, and DA [1, 23]. Since these are some of the same neuropathways and neurotransmitters associated with drug addiction, as mentioned earlier, some have suggested that repeated exposure to certain foods in vulnerable individuals may result in compulsive food consumption, poor control, conditioning to food stimuli, and ultimately excess weight gain [61]. Further evidence of neurochemical similarities between substance addiction and obesity comes from studies showing that like individuals with drug addiction, obese individuals have decreased striatal D2/D3 receptor availability and demonstrate elevated levels of DA metabolism [19, 63]. Such findings suggest dysfunction within the brain reward mechanisms of individuals with obesity.

The addictive behaviors underlying some cases of obesity may be hardwired. There have been reports of a subset of patients who have undergone bariatric weight loss surgery for obesity (and, therefore, are less likely to be able to consume food in excess) later developing other addictive behaviors such as gambling, substance abuse, and impulsive spending [18, 64]. Interestingly, sweet preference has also been shown to correlate with a paternal history of alcoholism. In fact, one study found that having a family history of alcoholism increased the chance that one preferred a stronger sweet taste by five times [42]. Though this association requires further investigation, the implication of these findings is that the tendency toward increased reward sensitivity – which may lead to addiction – could be intrinsic [59].

There is a wide range of treatments for obesity. Stimulant drugs such as methamphetamine or cocaine are known to curb appetite presumably by affecting the reward circuitry, while partial blockade of these same pathways by antipsychotics has been associated with overconsumption, thereby increasing the risk for obesity and metabolic syndrome [61]. Taken together, current evidence suggests that similar neurological pathways are associated with both addiction and obesity. Thus, medications used to treat drug addiction, including cannabinoid antagonists; opioid antagonists, such as naloxone; GABA agonists, such as baclofen; and corticotropin-releasing hormone antagonists, such as CRF-1, have been suggested for the treatment of obesity, as have some of the same behavioral interventions, including cognitive behavioral therapy (CBT), cognitive behavioral therapy with guided self-help (CBT-gsh), dialectical behavioral therapy (DBT), interpersonal therapy (IPT), incentive motivation, and 12-step programs [50, 61, 66].

71.2.3 Binge Eating

Binge eating disorder is now listed in the DSM-V as a stand-alone diagnosis. Binge eating is characterized by eating rapidly, eating more than was intended, eating alone, and feelings of disgust, guilt, or depression secondary to these binges. It has been reported that 3.5% of adult women and 2% of adult men within the US population suffer

from binge eating disorder, making it the most prevalent eating disorder. These numbers are reported to be slightly lower for adolescents (2.3% females, 0.8% males) [55].

Bingeing has long been associated with bulimia nervosa, as binge eating is one of the major diagnostic criteria for this disorder, but it is also associated with obesity [4]. The key difference between binge eating and bulimia nervosa is that binge eating disorder patients do not engage in compensatory behaviors (i.e., vomiting, laxative use, excessive exercise) to expel calories after consumption. Thus, the excess caloric intake is not compensated for, which may result in weight gain. Indeed, one study found that nearly 70% of participants with binge eating disorder were obese and 20% were overweight [33]. A larger, national study found obesity to have a lower prevalence rate among individuals who ever had binge eating disorder. However, this number was still relatively high, with approximately 40% of these individuals considered either obese or severely obese [38].

Many studies have attempted to elucidate the relationship between binge eating and obesity. Longitudinal studies have demonstrated a correlation between binge eating and significant non-developmentally appropriate weight gain in adolescents and young adults [58]. Further, one study demonstrated a correlation between binge eating and both being obese and gaining weight over a 20-year span [37]. Another study also shows that cessation of binge eating is associated with weight loss, while continued binge eating is associated with ongoing weight gain [22]. Studies such as these strongly suggest a connection between uncompensated binge eating and weight gain and suggest that binge eating could ultimately contribute to obesity [21, 56]. It is thus reasonable to suggest that normal-weight individuals with binge eating disorder may be at risk for obesity.

In addition to the association between binge eating and obesity, binge eating has several similarities to addiction. Some of the criteria used to identify disorders characterized by binge eating are remarkably similar to those used to assess substance dependence. These include (1) binge-type intake, defined as consuming a larger amount of food than typically considered normal in a discrete period of time, (2) a sense of lack of control over eating during a binge episode, and (3) marked distress regarding binge eating. In fact, binge eating has been described as including "compulsion, marked change in affect, and long-term harm," and it is noted that "physiologically based satiety tolerance enables escalation of food 'dose'" [52].

The types of foods consumed during binge episodes are typically those that should be consumed in moderation due to their high-fat, high-calorie, and high-sugar content [41]. Consuming foods rich in sugar and fat activates the reward circuitry of the brain, as mentioned earlier. Bingeing on both high-sucrose and high-fat foods has been shown to elicit DA release in the nucleus accumbens in animals [5–7] and together to have supra-additive effects on the reward system [23]. Animal models have also shown that bingeing is associated with downregulation of D2 receptor mRNA and an increase in D3 receptor mRNA in the nucleus accumbens [57]. Interestingly, these dopaminergic changes seen in response to bingeing are the same as those observed in obesity and drug dependency [40, 43]. This has led some to speculate that binge eating of palatable foods may result in neurochemical changes and subsequent addictive-like behaviors ([13]).

Studies such as these have also led some to wonder if the dopaminergic system could provide a target for pharmaceutical intervention of bingeing behaviors. Indeed, one study using an animal model of binge eating found the D2 antagonist, raclopride, reduces binge intake of high-fat foods while having no effect on ad libitum consumption [20]. Similarly, studies suggest that naltrexone, an opioid antagonist, can suppress bingeing behaviors [20]. Further, single-photon emission tomography (SPECT) studies have demonstrated that when compared to obese controls, decreased 5-HT transporter binding was found among obese binge eaters, suggesting that this may be another potential pharmaceutical target [44]. Currently, the stimulant prodrug lisdexamfetamine is the only medication approved for the treatment of BED [12].

Within the brain, the ventral limbic circuit and the orbitofrontal cortex are important in the regu-

lation of feeding behaviors as well as identifying emotional stimuli and facilitating a subsequent response, and atrophy or deregulation within these regions has been noted in persons with bingeing behaviors [46]. This suggests a link between emotions and binge eating. Indeed, one study found that 100% of participants, all of whom were obese women who binge eat, reported that mood contributed to binge behavior, 68% reported depression or sadness, and 55% reported boredom preceding a binge episode [16]. It is not surprising, therefore, that the teaching of affect regulation skills through the use of dialectical behavioral therapy (DBT) has yielded promising results in this population [60].

71.2.4 Screening Individuals for Food Addiction

Given the potential magnitude and severity of food addictions, efforts have been made to develop screening tools for addictive-like eating. Gearhardt et al. [25] created the Yale Food Addiction Scale (YFAS), which consists of a series of questions based on the substance addiction criteria as outlined in the DSM-IV [25]. This tool is designed to identify and better characterize signs and symptoms consistent with food addiction. Respondents use a yes/no format and 5-point Likert scale for questions regarding frequency. In early testing, the YFAS exhibited adequate internal reliability, good convergent validity with other measures of disordered eating, and good discriminant validity relative to related yet dissimilar conditions such as alcohol consumption and impulsivity [26]. A recent study has shown a link between YFAS scores and mood disorders among obese patients with binge eating disorder. The YFAS has also been shown to be a good predictor of the frequency of binge eating episodes in this patient population [27].

As noted by the authors, the YFAS may help clinicians better identify disordered eating habits in their patients as well as allow researchers to better identify potential candidates for future studies. Additional screening tools that might aid in the diagnosis of addiction-like disordered eating include the Eating Disorders Inventory, Eating Disorder Diagnostic Scale, Eating Disorder Examination Questionnaire, Bulimia Test-Revised, Binge Eating Scale, Night Eating Symptoms Scale, and Eating Behaviors Questionnaire [47]. Future studies in this area may facilitate the development of screening tests for addiction to specific food ingredients, such as fat or sugar, which may lead to a better understanding of the types of foods that may be associated with food addiction, as well as the development of more specific approaches to treatment.

71.2.5 Management of Food Addiction

The study of food addiction is relatively new, and specialized treatment approaches have not yet been developed. However, because of overlaps between binge eating, obesity, and food addiction, it is possible that strategies that are effective for treating binge eating and obesity may also prove helpful in the treatment of food addiction. Certain types of psychotherapy, including cognitive behavioral therapy (CBT), cognitive behavioral therapy with guided self-help (CBT-gsh), and interpersonal therapy (IPT), have shown success in the treatment of binge eating disorder [22, 39]. As mentioned earlier, DBT has also been shown to be effective in treating binge eating behavior [60]. Aside from lisdexamfetamine, fluoxetine, desipramine, imipramine, and topiramate have been suggested to be effective in the treatment of binge eating disorder [62], and phentermine, diethylpropion, and orlistat are often provided for obesity [51], as has the combination of naltrexone and bupropion [34], which can also be used for BED combined with depression. Duloxetine has also been shown to help curb hunger and reduce weight gain [2]. For some, binge eating may become an ingrained behavior that serves as a form of self-medication in response to negative emotional states such as depression, anxiety, loneliness, boredom, anger, and interpersonal conflict. This highlights the role of behavior modification, in addition to pharmacological interventions, in the treatment of food addictions [59]. It should be noted that treat-

ment of disordered eating can be a long and arduous process marked by alternating periods of relapse and recovery.

With regard to obesity, some patients turn to invasive procedures such as bariatric surgical treatments including gastric bypass and gastric banding. While these procedures do result in dramatic weight loss, they can be expensive and can have significant risks, including the development of gastric dumping syndrome and increased risk of bone fractures [48]. As a result, much attention today is focused on developing better treatment options. Given the rise of obesity not only in the USA but around the world [65], a number of pharmaceutical companies are looking to develop new treatments for obesity based on the addiction hypothesis [11]. Indeed, a number of new treatments are in both phase II and phase III clinical trials [3]. The majority of these potential treatment options target the neuropathways and neurotransmitters discussed in this chapter, including raclopride, bupropion, and antipsychotics which target dopamine; naltrexone, naloxone, and nalmefene which target the opioid system; baclofen and topiramate which target the GABAergic system; SR141716, AM 251, and rimonabant which target cannabinoid receptors; and several new pharmaceuticals [10, 66]. However, these medications are not without risk; many of these drugs carry significant side effects including increased risk for depression, anxiety, obsessive-compulsive disorder, seizures, suicide, confusion, or memory deficits [11]. Given the risks and side effects associated with these drugs, physicians will need to exercise great care when considering whether to prescribe these treatments and should carefully select their population base prior to prescribing [11].

71.3 Conclusion

As it stands, obesity and binge eating behaviors continue to be a threat to global health [5–7]. As such, more research is needed to better describe and understand the early signs and risk factors for BED and obesity. It is perhaps also time to reevaluate the current food environment from many aspects while taking into consideration both the individual's perspective and society as a whole. Societal measures may, in fact, be required at this time as dysfunctional eating behaviors affect not only the current generation but also its offspring due to the effects that consuming certain highly palatable foods may have on the developing brain in utero.

Given that some of the cultural factors discussed in this chapter are driven by economic factors that lie outside the control of the individual, the topic of obesity cannot simply be relegated to the domain of personal responsibility. Rather, economic incentives that may encourage people to make unhealthy food choices may need to be reevaluated on a larger scale. Indeed, any plan to combat the rise in obesity will need to address the economic, political, social, psychological, and biological factors that contribute to obesity, as well as factors such as taste, accessibility, convenience, cost, and level of promotion [65]. Moreover, society may need to closely reevaluate the current state of food marketing. As mentioned earlier, one study has found that food-addicted persons respond at an even higher level to food cues than their nonaddicted counterparts [28]. This finding suggests that advertising cues may contribute, at least in part, to compulsive eating in at-risk persons. Further, societal changes such as reevaluating where government subsidies are allocated, taxation, publicly enforced well-care programs, and corporate-driven employee well-being programs may also be needed to address the issues of disordered eating and obesity. While these efforts are not expected to cure obesity, binge eating, or food addiction, they may help to reduce their prevalence and aid prevention efforts.

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Part VII

Comorbid Medical Disorders & Responses

Alexander Baldacchino and Paul Haber

72

Medical Disorders and Complications of Alcohol and Other Drugs and Multiple Morbidities: An Introduction

Alexander M. Baldacchino and Paul S. Haber

Content

Keywords

Multimorbidity · Physical complications
Substance misuse

Multimorbidity is characterised by distinct clustering of multiple concurrent health conditions. Multimorbidity is a growing concern worldwide particularly amongst certain 'at-risk groups', such as drug and alcohol users and/or individuals with mental health problems [1, 14]. Some clusters are particularly common and often share a mechanistic basis (concordant conditions). Mechanistically distinct (discordant) morbidities [7, 9] may sometimes be a secondary consequence of ill-health (e.g. depression), whereas adverse reactions to treatment may also underlie some common clusters. Importantly, some clusters show no obvious connection, hinting at currently unknown risk factors or causal linkages.

Multimorbidity shows a non-random geographic distribution, but it is particularly common in rural and semirural areas, in part reflecting the age distribution as well as areas of deprivation. In many countries, the high burden of infectious disease is a major contributor: HIV/AIDS, hepatitis B and TB are highly prevalent, and chronic infections often coexist with other morbidities. Furthermore, epidemiological, demographic and nutritional transitions significantly affect patterns of ill-health [13]. Migration to cities and increased exposure to more affluent diets and lifestyles are shifting risk exposures and contributing to a marked rise in cardiometabolic diseases. Furthermore, many LMICs are facing the simultaneous challenge of widespread undernutrition, particularly in children coexisting with growing rates of obesity later in life, both of which have implications for the development of multimorbidity. As access to treatments in many countries improves, people with chronic medical conditions are living longer with additional morbidities and

A. M. Baldacchino (✉)
Population and Behavioural Science Division (Psychiatry and Addictions), University of St Andrews and NHS Fife, St Andrews, UK
e-mail: amb30@st-andrews.ac.uk

P. S. Haber
University of Sydney and Drug Health Service, Royal Prince Alfred Hospital, Camperdown, NSW, Australia
e-mail: paul.haber@sydney.edu.au

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with health consequences triggered by slowed disease progression and long-term treatment.

Multimorbidity affects all ages but is likely to be experienced differently at different stages of life. While multimorbidity is most common in older people, it is also common in younger age groups and affects substantial numbers of middle-aged people. Life expectancy is continuing to rise globally leading to larger numbers of older people with multiple health conditions. Further, modelling studies suggest that complex multimorbidity in old age will increase significantly over the next 20 years (The [15]). Indeed, it appears that the growing complexity of multimorbidity is contributing to a falling life expectancy in some countries including the UK and the USA.

It has been suggested that there is a need to understand common clusters, risk factors (biological and social) and disease mechanisms at different life stages, to inform prevention and models of care, including continuum of care as individuals transition into and out of care pathways (e.g. from juvenile to adult care) [2, 4]. As is the case with many individual chronic conditions, considerable social patterning is evident for multimorbidity. Young and middle-aged adults living in the most socioeconomically deprived areas have similar rates of multimorbidity to those 10–15 years older in the most affluent areas [1]. A 2017 study indicated the contribution of known risk factors, such as smoking and diet, to socioeconomic inequalities in multimorbidity across the life course [6]. The life-course perspective also emphasises that, as is clear from individual non-communicable diseases, the roots of multimorbidity may lie in much earlier influences.

A focus on multimorbidity across the life course, together with mechanistic studies, could reveal early predictors and biomarkers of multimorbidity and whether the impact of early influences relates solely to their effects on individual conditions or whether they have a more complex relationship with multimorbidity. This understanding could support the use of targeted interventions at different points in the life course, to influence long-term disease trajectories. Again, it will be important to determine the impact of these interventions on multimorbidity as well as individual conditions. One particular concern is multimorbidity that involves both physical and mental health conditions, as existing healthcare structures are not well aligned to deal with this, and outcomes for those with multimorbidity comprised of physical and mental health conditions tend to be worse [11]. Outcomes for mental/physical multimorbidity are particularly poor for those in the most socioeconomically deprived areas [8]. Reasons include poor general health, poor engagement with healthcare, lower rates of treatment uptake and higher rates of treatment dropout. Furthermore, the financial burden of multimorbidity in the healthcare system is higher when there is mental/physical comorbidity [3].

A particularly vulnerable group of the population, a high proportion of whom have multimorbidity, are people who use drugs [10]. The health consequences of drugs are major problems throughout the world with billions of people using legal (tobacco and alcohol) and illegal drugs (amphetamines, cocaine, opiates, hallucinogens and marijuana). Drug use is associated with burdensome social, economic and health consequences, the latter involving almost every physiological/biochemical system. These may include psychiatric, neurocognitive, cardiovascular, metabolic and hepatic complications and infectious diseases. Infectious diseases form the focus of several chapters in this section. An estimated one-third of the global population of 7 billion is living with one or more bacterial or viral infections (United Nations AIDS (UNAIDS) [16]). There are an estimated 500 million people who use illegal drugs regularly [17] in the world, and this population is at increased risk of bloodborne viruses and other infections.

Drug-related deaths (DRD) are a significant and increasing public health concern. Deaths attributed to the use of illegal or prescription drugs in 2016 showed an increase of 106% compared to 2006 in Scotland [12]. From the review of the literature, the increased mortality risk is clear—approximately six times higher for opioid users than for the general population—but the relative contribution of a range of factors is not

proven. The majority of opioid users die from causes other than overdose. Amongst opioid users in England, increased mortality has been shown for all causes using standardised mortality ratios (SMR), e.g. infectious disease (SMR 12.6), respiratory (SMR 9.2) and mental and behavioural (SMR 4.3) conditions. Predicted hospital admissions in Scotland for cardiorespiratory, hepatic and mental health conditions in drug users are anticipated to rise. Recent analysis of all-cause mortality in people prescribed with methadone identified circulatory disease as a leading cause of death [5].

Although there is a myriad of problems related to drug use, it is the medical consequences that are the leading causes of death, and consequently, these are of great medical concern. It is evident that this section on medical consequences of drug abuse is an important component of a comprehensive textbook of addiction medicine that should describe, most if not all, these health effects and their clinical management. In general, the principles of assessment and management of these disorders are no different from people who do not abuse drugs or alcohol, but this section of the textbook describes particular patterns of morbidities and approaches to management that distinguish this population.

This second edition reflects the increasing medical morbidities present to people with substance use. The complications and management of liver-related disorders including viral hepatitis in drug- and alcohol-using populations have been addressed by John Dillon et al. Additionally Dr. Brian Conway focused around co-occurring infections beyond HIV treatment. Neuropsychiatric and neurocognitive complications due to alcohol and drug use have been separated and addressed by Thomas Gilbertson et al. and Antonio Verdejo Garcia et al., respectively, acknowledging the increasing knowledge base that clinical neuroscience in addiction medicine is offering us.

The cardiopulmonary complications of alcohol and other drugs have been addressed by Peter Moore et al. and Stephen McNamara et al. This group has provided an overview on the broad range of cardiopulmonary issues including both the pathophysiological approach and practical approach for clinicians. Acute pain issues have been comprehensively reviewed by Michael Dinh et al. around trauma emergencies and by Steven Gilbert et al. around perioperative issues.

Gastrointestinal, endocrine and renal disorders are commonly seen in the substance-using population and addressed by Paul Haber et al., Anna Quirk and Annemarie Hennessy et al., respectively. Sexual dysfunction is another clinical problem that may be overlooked in clinical practice. This has been addressed by Richard Hallinan. Tim Roehrs et al. describe sleep disorders and present a clinical approach to their management. Finally, we expanded the chronic pain and dependence chapter addressed again by Steven Gilbert et al. and also introduced oral health issues in addictions addressed by Ruth Freeman et al.

In summary, this section provides the necessary knowledge base and core competencies to manage medical conditions that present as either comorbidities associated with drug and alcohol use and often as multiple morbidities. These conditions will need the best of care and interventions. The addiction medicine specialist of tomorrow needs to be well placed to coordinate and/or manage such complex care.

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Cardiovascular Consequences of Addiction

73

Ryan Cotter and Mori J. Krantz

Contents

R. Cotter
Division of Cardiology, University of Colorado, Aurora, CO, USA

M. J. Krantz (✉)
Division of Cardiology, University of Colorado, Aurora, CO, USA

Denver Health Medical Center, Division of Cardiology, Denver, CO, USA
e-mail: Mori.Krantz@dhha.org

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Abstract

Drugs of abuse often have important effects on the cardiovascular system, some of which are life threatening. An understanding of the intersection between addictive and cardiovascular disorders is increasingly relevant to general practitioners, emergency physicians, and psychiatrists. The effects of these drugs vary

depending upon the agent, dose, route of administration, and potential interactions with other medications. Cardiovascular consequences can range from innocuous side effects, such as mild tachycardia and hypertension, to life-threatening ventricular arrhythmias and myocardial infarction. Hemodynamic alterations are common with both active drug abuse and withdrawal and are frequently mediated by the autonomic nervous system.

The relationship between alcohol use and cardiovascular health is complex. Alcohol is one of the leading causes for systemic hypertension and often overlooked. Alcohol is also a common cause for atrial fibrillation and cardiomyopathy. Moderate alcohol use is linked to reduction in myocardial infarction but increased rates of stroke. Sympathomimetic drugs including amphetamines and cocaine result in an expected increase in blood pressure and heart rate. However, they may also cause substantial cardiotoxicity including ventricular arrhythmia, stroke, myocardial infarction (MI), heart failure, and death. Moreover, chronic stimulant drugs are atherogenic. Some of this is mediated by increases in blood pressure and lipids, but may also occur due to proinflammatory effects or increased hypercoagulability. By contrast, some drugs such as opioids lead to small reductions in pulse and blood pressure. Most naturally occurring opioids do not alter cardiac repolarization; however, synthetic opioids, such as methadone, may result in QTc-interval prolongation and torsade de pointes (TdP), a form of life-threatening ventricular arrhythmia. In this chapter, we review the cardiovascular effects of common drugs of abuse.

Keywords

Myocardial infarction · Cardiotoxic · Arrhythmia · Sudden death · Heart failure

73.1 Introduction

Drugs of abuse have a myriad of cardiovascular effects. Depending on the drug, dose, and route of administration, cardiovascular consequences can range from innocuous side effects, such as mild tachycardia and hypertension, to life-threatening ventricular arrhythmias and MI (Table 73.1). Hemodynamic alterations are common with drug use and most often are mediated through interactions with the autonomic nervous system [35]. Sympathomimetic drugs like amphetamines and cocaine increase the release and inhibit the reuptake of peripheral catecholamines stimulating increases in heart rate, systemic vascular resistance, and cardiac contractility, thus resulting in augmentation of cardiac output and blood pressure. In contrast, several drugs are directly cardiodepressant in the acute setting, and many drugs of both types are cardiotoxic causing cardiomyopathy and congestive heart failure with long-term use.

Changes in the balance of myocardial oxygen supply and demand with drug use can lead to myocardial ischemia [35]. For example, cocaine augments oxygen demand in the myocardium by increasing heart rate, afterload, and contractility, while simultaneously decreasing supply by inciting epicardial coronary vasoconstriction. Modulation of lipid profiles, coagulation factors, platelet function, and inflammation further heighten the risk of cardiac ischemic events in patients using these drugs.

Table 73.1 Clinical cardiovascular effects of drugs of abuse

Drug	Cardiovascular effect
Ethanol	Hypertension
	Arrhythmias
	Dilated cardiomyopathy
	Stroke
Cocaine	Tachycardia
	Hypertension
	Accelerated atherosclerosis
	Chest pain
	Angina pectoris
	Myocardial infarction
	Ventricular and atrial arrhythmias
	Left ventricular hypertrophy
	Dilated cardiomyopathy, myocarditis
	Aortic dissection
	Infective endocarditis
	Stroke
	Mesenteric ischemia

Table 73.1 (continued)

Amphetamines	Tachycardia
	Hypertension
	Chest pain
	Myocardial infarction
	Ventricular and atrial arrhythmias
	Sudden cardiac death
	Aortic dissection
	Cardiomyopathy
	Infective endocarditis
	Stroke
	Accelerated atherosclerosis
Opioids	Orthostatic hypotension
	Cardiac arrest
	Torsade de pointes (synthetic opioids)
	Infective endocarditis (with intravenous use)
Nicotine	Accelerated atherosclerosis
	Angina pectoris
	Myocardial infarction
	Stroke
Cannabis	Tachycardia
	Bradycardia
	Hypertension
	Orthostatic hypotension
	Syncope
	Worsens angina pectoris
	Myocardial infarction
	Ischemic stroke
	Arrhythmias
Anabolic steroids	Prothrombotic risk
	Hypertension
	Dyslipidemia
	Myocardial infarction
	Ischemic stroke
	Ventricular hypertrophy

Many recreational drugs are arrhythmogenic in the acute setting or during abstinence/withdrawal. Mechanisms of arrhythmias are complex and likely result from interplay between the direct effects of drugs, electrolyte derangements, sympathetic nervous alterations, and cardiac ischemia. Of particular importance is the interaction of several drugs, especially the synthetic opioids, with a subunit of a voltage-gated potassium channel coded by the human Ether-à-go-go-related gene (hERG) [45]. Inhibition of this subunit causes alterations in repolarization during phase 3 of the action potential, which can lead to acquired prolongation of the rate corrected QT (QTc) interval, augmenting the risk of the ventricular arrhythmia torsade de pointes (TdP), and sudden cardiac death (Fig. 73.1)

Stress cardiomyopathies are also an increasingly recognized entity. In addition to extreme physical or emotional stressors, stress cardiomyopathy can develop from the abuse of sympathomimetic drugs or withdrawal states from depressant drugs (including alcohol and opioids). These patients often present with signs and symptoms of heart failure, elevated troponin, and ST-segment elevation on EKG, often resulting in initial treatment as an acute coronary syndrome. On echocardiography, the classic findings are that of apical "ballooning" with spared myocardial function at the base and no coronary obstruction on angiography.

This overview highlights the variety of short-term and long-term cardiovascular consequences of drugs of abuse, with a particular focus on alcohol, cocaine, and opioids employing a clinical vignette format.

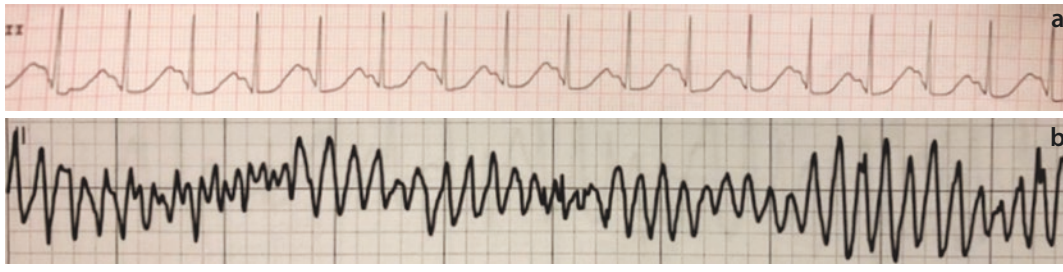

Fig. 73.1 (**a**) Prolonged rate corrected QT interval (QTc). (**b**) Torsade de pointes (TdP), a type of polymorphic ventricular tachycardia

73.2 Main Text

73.2.1 Alcohol

Light-to-moderate alcohol consumption has been associated with a reduced risk of vascular events, but chronic heavy alcohol use is associated with hypertension, atrial fibrillation, stroke, and cardiomyopathy. Adverse cardiovascular effects begin to appear clinically with consumption of two to three standard drinks/day or more and increase thereafter in a dose-dependent fashion, though there may be subclinical evidence of echocardiographic dysfunction with even mild consumption [41, 56]. Alcohol is toxic to cardiomyocytes, in addition to increasing sympathetic tone, activating the renin-angiotensin-aldosterone system, and is associated with endothelial dysfunction [37, 56, 76].

Abstinence often results in rapid improvement in many of cardiovascular consequences and in some cases may the only intervention necessary in the long term to address alcohol-associated cardiovascular risk. However, acute alcohol withdrawal, delirium tremens in particular, can precipitate fatal cardiovascular collapse. Hypertension and tachycardia are classic symptoms of acute alcohol withdrawal, and though they improve within 3–4 days of alcohol cessation, they may precipitate ischemic or hemorrhagic stroke, acute decompensated heart failure, or cardiac ischemia. Fatal arrhythmias may also be precipitated by adrenergic surge, electrolyte deficiencies, and QT-interval prolongation. There is little direct evidence regarding management of cardiovascular complications of acute alcohol withdrawal in the setting of specific cardiac conditions, but propranolol and clonidine are most commonly suggested to treat withdrawal-related autonomic instability as well as aggressive replacement of potassium, magnesium, and phosphate. Intravenous dexmedetomidine, a central alpha-2 agonist, is increasingly used as an adjunct to benzodiazepines in treating withdrawal-associated agitation in the intensive care unit (ICU) setting. This medication may be particularly effective at reducing sympathetic outflow in the withdrawal state, but its use can cause bradycardia or hypotension and should be avoided in patients with pre-existing heart block [92].

Vignette

A 48-year-old man is evaluated in the emergency department for intermittent palpitations and chest pressure over the preceding 48 h. He does not regularly receive medical care and takes no medications. He smokes cigarettes, but uses no other drugs. He reports drinking a 12-pack of beer daily and consumed double his normal amount the week prior to presentation. He has an irregular heart rate of 130 bpm, a blood pressure of 140/90 mmHg, and pedal edema. The clinical diagnosis was alcohol withdrawal complicated by atrial fibrillation and was confirmed by ECG.

73.3 Atrial Fibrillation

Atrial fibrillation (AF) was identified in 1978 as the "Holiday Heart Syndrome" defined as dysrhythmia immediately following binge drinking, classically following a weekend, vacation, or year-end holiday [27]. Since then, moderate-to-heavy drinking has been associated with both new onset AF as well as exacerbation of existing paroxysmal AF, and it is suspected that alcohol is a causative factor in up to two-thirds of patients ≤65 years of age presenting with AF [18] (Fig. 73.2).

Acute AF related to alcohol and/or drug use often reverts to sinus rhythm without requiring electrical cardioversion in young patients [53]. However, if the patient is likely to continue to use alcohol, they will remain at an elevated rate of future episodes of paroxysmal AF that may become persistent. There are no specific recommendations regarding management of AF related to alcohol use. β-blockers have a theoretical advantage over calcium channel blockers for rate control in light of the adrenergic excess thought to contribute to alcohol-related AF. Alcohol and

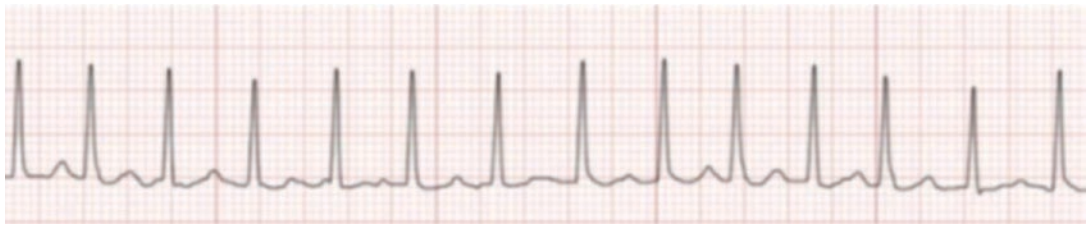

Fig. 73.2 Atrial fibrillation. Note, the rhythm is "irregularly irregular"

drug abuse have been associated with a lower likelihood of treatment with guideline-directed antithrombotic therapy, and it remains important to risk stratify all patients using a validated risk score such as the $CHADS_2$ or CHA_2DS_2-Vasc score when deciding whether to initiate prophylactic antiplatelet or anticoagulation therapy [21]. However, heavy drinkers (>20 drinks per week for men, >13 for women) are at increased thromboembolic risk than lighter drinkers, even when controlling for anticoagulation or CHA_2DS_2-Vasc score [72]. Unlike warfarin, newer direct oral anticoagulants offer the advantage of not requiring routine monitoring and have been associated with lower rates than warfarin of intracerebral hemorrhage and gastrointestinal bleeding (particularly apixaban), both of which occur more frequently in alcoholics than nonalcoholics [62]. Nonetheless, very heavy drinkers are at high risk of fall and bleeding, limiting the safety of systemic anticoagulation.

73.3.1 Hypertension and Vascular Disease

Alcohol is associated with dose-dependent increases in blood pressure both acutely and chronically in men and women [65]. Abstinence has been associated with clinically meaningful reductions in blood pressure comparable with effects of antihypertensive medications [26]. In moderate or heavy drinkers, reduction in alcohol consumption can significantly improve systolic blood pressure, but no improvements were seen in hypertension when light drinkers abstained [88]. Therefore, abstinence or at least reduced consumption remains a primary recommendation for all patients with hypertension who misuse alcohol.

The association between alcohol and cardiovascular mortality is J-shaped, with small to moderate amounts of ethanol producing reductions in vascular events [99]. However, heavy alcohol use is associated with increases in coronary artery disease, ischemic stroke, and cerebral hemorrhage compared with moderate drinkers [59, 89]. The mechanism of this association remains controversial, but is likely due in part to increased serum triglycerides, hypertension, decreased nitric oxide synthesis, and increased inflammation [12]. Binge drinking may cause an acute increase in stroke risk within 1–24 h of abuse [89]. This may be due to reactive thrombocytosis and increased platelet aggregation during alcohol withdrawal, and we speculate that increased adrenergic activity may also play a role. The increased risk of stroke and MI returns toward baseline in former heavy drinkers, and apart from abstinence, there are no risk reduction strategies recommended [87].

73.4 Cardiomyopathy

Although light-to-moderate alcohol consumption has been associated with a lower rate of heart failure than nondrinkers, chronic heavy alcohol use is a well-known cause of left ventricular (LV) systolic dysfunction. Most men who develop alcoholic cardiomyopathy have consumed ≥5 standard drinks per day for ≥5 years [70]. Women appear to be more sensitive to the cardiotoxic effects of alcohol and may develop cardiomyopathy with a smaller comparative exposure [28]. Evidence of cardiotoxicity may be apparent on

echocardiography long before the emergence of symptoms, even in light or moderate drinkers [41]. Direct myocardial damage may be mediated by acetaldehyde, the first metabolite of ethanol. Acetaldehyde levels are particularly elevated in heavy drinkers, in part due to reduced hepatic aldehyde dehydrogenase activity [100]. Chronic activation of the renin angiotensin aldosterone system and sympathetic nervous system and nutritional deficiency (especially thiamine) may also contribute to progression of myocardial dysfunction by potentiating alcohol and acetaldehyde-induced cell death.

Abstinence can result in significant improvement in LV systolic function if achieved early during the progression of myocardial dysfunction. Long-term survival in patients with alcoholic cardiomyopathy who achieve abstinence is the same or better than patients with idiopathic dilated cardiomyopathy, whereas patients who continue to drink have a lower survival [78]. In addition to standard heart failure therapies, additional considerations in the setting of alcoholic cardiomyopathy are nutritional and vitamin supplementation, particularly vitamin B12 and folate.

73.5 Sudden Cardiac Death

Large studies have demonstrated an elevated risk of sudden death associated with heavy drinking, even in patients without pre-existing ischemic or structural heart disease [75]. Sudden death may also occur during periods of abstinence or withdrawal [17]. The QTc interval may be prolonged in up to 63% of cases during alcohol withdrawal and normalizes with remission of withdrawal symptoms. Electrolyte abnormalities, catecholamine excess, impaired vagal control of heart rate, myocardial fibrosis, and sleep apnea may also contribute to a heightened risk of arrhythmia [57].

In addition to correction of electrolyte abnormalities, particularly hypokalemia and hypomagnesemia (which prolong the QTc interval), it is essential to provide cardiac telemetry monitoring during the early stages of withdrawal, particularly in the setting of underlying structural heart disease and severe symptoms including delirium tremens. Furthermore, administration of QTc-prolonging medications such as antipsychotics must be used cautiously, as there appears to be acute, transient prolongation of the QTc interval and increased QT variability during alcohol withdrawal. There is currently no recommendation for prophylactic antiarrhythmic therapy or continuing therapy after alcohol withdrawal has subsided, although β-blockers to treat hypertension and tachycardia are often used.

73.6 Cocaine

Vignette

A 44-year-old man presents to the emergency department with complaints of midsternal chest discomfort of moderate severity, which has been unremitting for the past 3 h and radiates to his shoulders. He denies illicit drug use but became more agitated when this line of questioning was pursued. Blood pressure is 178/90 mmHg, pulse rate is 95 beats per minute, while respiratory rate, temperature, and oxygen saturation are within normal limits. Urine toxicology is positive for cocaine metabolites. Upon sharing these results, the patient confides that he and his girlfriend consumed an "eight-ball" (3.5 grams) of cocaine by intranasal route. His electrocardiogram (ECG) demonstrates ST-segment elevation in leads V2-V5 with peaked T-waves. QRS duration and rate corrected QT (QTc) intervals are prolonged. Chest X-ray and serum chemistries (including cardiac troponin) are unremarkable.

Cocaine incites a wide array of cardiovascular consequences ranging from acute alterations in hemodynamics to myocardial ischemia, ventricular arrhythmias, and dilated cardiomyopathy (Table 73.1). The extensive effects on the cardiovascular system result from its numerous mecha-

nisms of action. Cocaine is a potent sympathomimetic that augments central sympathetic outflow and has the ability to increase peripheral catecholamine concentration. Cocaine also exhibits inhibition of voltage-gated sodium channels and potassium channels and has complex, poorly understood interactions with L-type calcium channels [80].

73.6.1 Hemodynamic Effects

Sympathomimetic activity dominates at low-to-moderate doses resulting in tachycardia, systemic vasoconstriction, and coronary vasospasm. When taken at low doses (~0.35 mg/kg) through the intranasal route, cocaine results in slight elevation of systolic blood pressure. Higher doses (~1.3 mg/kg) will cause an increase in systolic and diastolic blood pressure (~30/15 mm Hg) and elevation of the heart rate (~20 bpm). The onset of these alterations occurs at 2 min and peaks at 5–10 min [81]. Moderate cocaine doses (2–3 mg/kg) have a positive inotropic effect, resulting in an increase in LV contractility and cardiac index [10].

Tachycardia is mediated through β-adrenergic receptor stimulation as β-blockade with propranolol abolishes the increase in heart rate caused by cocaine [47]. Hypertension is partially mediated through α-adrenergic receptors as α-blockade with prazosin experimentally prevents vasoconstriction [23]. However, positive inotropic effects facilitated through β-adrenergic stimulation contribute to hypertension caused by cocaine, as propranolol attenuates the rise in mean arterial pressure by diminishing the cocaine-mediated rise in LV contractility. Combined α- and β-blockade with labetalol eliminates cocaine's chronotropic effect on the heart and significantly blunts the increase in blood pressure [47].

73.6.2 Myocardial Ischemia

Cocaine-related chest pain is typically described as pressure-like in quality and is frequently associated with dyspnea, diaphoresis, nausea, palpitations, and anxiety [68]. The reported incidence of acute MI in patients with cocaine-related chest pain ranges between 0.7% and 6%. There is a 24-fold increased risk of acute MI within the first hour of cocaine use. However, myocardial injury can also occur hours after use, presumably due to cocaine metabolites [68]. Cocaine is estimated to play a role in 25% of MIs in patients between the ages of 18 and 45, and half of patients with cocaine-related MIs have no evidence of atherosclerotic coronary artery disease on angiography [55, 79]. The diagnosis of MI in those with recent cocaine use is difficult. There are no historical factors useful for distinguishing MI from chest pain without myocardial injury in this population. Specific characteristics of pain such as onset, location, quality, and duration are not predictive, nor are histories of chest pain, MI, or risk factors for atherosclerotic coronary artery disease [40]. ECG data is equally challenging: Presenting ECGs are abnormal in approximately 55–85% and up to 43% of patients with cocaine related chest pain meet diagnostic criteria for ST-elevation MI (as defined by >0.1 mV elevation in contiguous leads) [15]. The positive predictive value of ECG for MI in this population is reportedly only 18% with a sensitivity of approximately 36% [40]. Serum troponin assays remain effective in detecting myocardial injury in cocaine users [55].

The sympathomimetic actions of cocaine augment myocardial oxygen consumption by increasing heart rate, blood pressure, and myocardial contractility, while also leading to vasospasm [55]. In addition to α-adrenergic stimulation, cocaine causes vasospasm by increasing the expression of the potent vasoconstrictor endothelin and decreasing levels of nitric oxide [71, 96]. In several studies employing a recreational dose of cocaine (2 mg/ml) intranasally in humans, coronary artery caliber is reduced [8]. In a study of patients with and without coronary artery disease undergoing diagnostic catheterization, coronary diameter decreased more than twice as much in diseased arteries (>50% stenosis) versus normal arteries [31]. The time course of coronary vasospasm does not simply follow peak serum levels of cocaine and

occurs at a greater magnitude at 90 min post-administration versus 30 min when serum levels peaked [11]. The degree of vasospasm is augmented by concurrent cigarette smoking. Aside from vasospasm, habitual cocaine use has been linked to premature coronary artery disease in postmortem studies, which is thought to result from increase vascular permeability to low-density lipoprotein (LDL) cholesterol [55]. Acute cocaine use is also associated with intracoronary thrombus formation, by triggering platelet aggregation [55].

Those with chest pain in the setting of cocaine use should receive IV benzodiazepines promptly, which relieves chest pain and mitigates hemodynamic alterations. Nitroglycerin reverses cocaine-associated coronary vasoconstriction and calcium channel blockers are recommended after benzodiazepines and nitroglycerin have failed. Phentolamine, an α-adrenergic blocker, may also be administered as a second-line agent among hypertensive patients, as it reverses coronary vasoconstriction.

Recent guidelines for unstable angina and non-ST-elevation MI recommend treating patients with cocaine-related acute coronary syndrome like patients with no history of cocaine abuse, unless signs of acute intoxication are present (hypertension, tachycardia, and euphoria). If these signs are present, then the use of benzodiazepines is supported and β-blockers should be used cautiously unless vasodilators (e.g., nitroglycerine) are being co-administered, because unopposed α-adrenergic stimulation can potentially exacerbate coronary vasoconstriction and worsen arterial hypertension [3]. Several retrospective studies have evaluated outcomes in patients with cocaine-related chest pain who were given β-blockers prior to the discovery of their recent cocaine use. It was found that β-blocker therapy was associated with a lower incidence of MI without change in the rate of adverse outcomes or peak levels of troponin [42]. More recent systematic reviews have suggested that use of combined α- /β-blockers such as labetalol or carvedilol are safe and efficacious at mitigating the tachycardia and hypertension of acute intoxication, though this finding will need to be confirmed in larger trials [84].

Due to the risk of coronary thrombus formation, patients should be given aspirin, and those with proven MI should receive unfractionated heparin or low molecular weight heparin if there are no contraindications [68]. Fibrinolytics should be used with caution, as there are reports of devastating complications in cocaine users and the diagnosis of STEMI is challenging in this population due to baseline ECG abnormalities [55, 68]. Percutaneous coronary intervention is the preferred management of intracoronary thrombus [3].

Outcomes are generally better in cocaine-related MI compared to MI not related to cocaine [68]. The incidence of ventricular arrhythmias, congestive heart failure, and death are 4–17%, 5–7%, and < 2% respectively [55]. Improved outcomes are presumably due to the overall younger age of patients experiencing MI while using cocaine. However, those who experience cocaine-related MI are at high risk for recurrent ischemic events as more than half will continue to use cocaine and up to 58% will have recurrence of ischemia [68].

73.6.3 Cardiac Conduction and Arrhythmia

Cocaine can cause a wide range of electrocardiographic alterations [80]. Cocaine acts similar to Vaughan Williams Class I antiarrhythmics by blocking voltage-gated sodium channels (I_{Na}) in the inactive state. Cocaine also blocks the *hERG* coded voltage-gated potassium channel responsible for the rapid delayed rectifier potassium current (I_{Kr}) that allows for repolarization. Together, the inhibition of I_{Na} and I_{Kr} slow the rapid upstroke of the action potential during phase 0 and prolong the action potential duration by delaying phase 3. Electrocardiographically this can result in *both* widening of the QRS complex and prolongation of the QTc interval.

Clinically, cocaine use is associated with a variety of arrhythmias and ECG abnormalities (Table 73.2) [55]. The most common alteration is sinus tachycardia, but an assortment of rhythm disturbances have been temporally related to cocaine use, including non-sustained supraven-

Table 73.2 Arrhythmias and ECG abnormalities associated with cocaine

Arrhythmia	ECG abnormality
Sinus tachycardia	PR interval shortening
Sinus bradycardia	PR prolongation (first degree AV block)
Supraventricular tachycardia	QRS widening:
Atrial fibrillation	Nonspecific intraventricular block
Atrial flutter	Right bundle branch block
Second and third degree AV block	Left bundle branch block
Accelerated idioventricular rhythm	Left anterior fascicular block
Torsade de pointes	QTc-interval prolongation
Ventricular tachycardia	ST-segment elevation/ depression
Ventricular fibrillation	T-wave peaking, flattening, inversion
Asystole	Acquired Brugada pattern
	ST elevation, down-sloping ST-segment and T-wave inversion

tricular tachycardia, atrial fibrillation, and sinus bradycardia [80]. Excluding cocaine-related TdP, prospective studies have not consistently demonstrated an increased risk of ventricular arrhythmias other than frequent premature ventricular complexes. However, the literature contains frequent case reports of monomorphic ventricular tachycardia and ventricular fibrillation in cocaine users. These associations are often confounded by polysubstance use and electrolyte derangements, especially acidosis.

A retrospective report found that QTc-interval prolongation is present in approximately 4% of chronic cocaine abusers, 26% of patients treated for cocaine toxicity in the ED, and 75% of cases of cocaine-related mortality [15]. In addition to its ability to prolong the QT interval, cocaine has been shown to induce early afterdepolarizations, further increasing the risk of the ventricular arrhythmia TdP [48]. In the case report literature, QT prolongation is frequently reported, and associated TdP occurred in almost half of these cases [80].

Cocaine has seemingly contradictory interactions with atrioventricular conduction [80]. Several small observational studies have shown that cocaine use is associated with PR segment shortening, which would suggest that cocaine enhances conduction through the AV node. However, the case report literature is incongruent with these results and contains several cases of PR prolongation with various degrees of AV block. QRS interval widening reportedly occurs in up to 6% of patients using cocaine, which is most commonly due to nonspecific intraventricular conduction delay or right bundle branch block. It is important to note that many of these cases may be confounded by electrolyte derangements and concomitant ingestion of other substances.

There have been cases of acquired Brugada pattern associated with cocaine use [80]. However, electrophysiological testing did not induce sustained ventricular arrhythmias in any of these cases, and it is unknown if cocaine-associated Brugada pattern confers any additional risk of sudden cardiac death.

73.6.4 Other Effects: Cardiomyopathy, Endocarditis, Aortic Dissection, and Stroke

Cocaine can cause LV hypertrophy and can be a myocardial depressant resulting in LV systolic dysfunction [55]. There are reports of dilated cardiomyopathy in long-term cocaine users as well as acute, reversible, profound LV dysfunction after binge use [55]. One study found that LV dysfunction is present in 7% of apparently healthy, asymptomatic cocaine users [9].

In those with congestive heart failure, stimulant use (cocaine and amphetamines) is associated with an increased incidence of hospitalization and reduced ejection fraction [20]. Cocaine cessation leads to improved myocardial function, and cocaine relapse can cause recurrence of decompensated heart failure [93]. The possible mechanisms of cocaine's reduction in systolic function include myocardial ischemia/infarction, repetitive sympathetic stimulation (similar to cardiomyopathy associated with pheochromocytoma), hypersensitivity to adulterants or infectious agents leading to myocarditis, alteration of intracellular calcium concentration, and stimulation of cytokine production resulting in remodeling and myocyte necrosis [55].

As with any substance used by the intravenous route, there is a risk of bacterial endocarditis with IV cocaine use [55]. For unknown reasons, cocaine seems to increase the risk of endocarditis compared to other drugs. Left-sided valves are more frequently involved with cocaine than other IV drugs.

Aortic dissection is well described in the setting of cocaine intoxication [22]. The mechanism of cocaine's association with aortic dissection is thought to involve hypertension and tachycardia with a resulting increase in arterial wall shear stress. Cocaine is associated with decreased aortic elasticity, increased smooth muscle cell apoptosis, and premature atherosclerosis, all of which play a role in increasing the risk for aortic dissection [49].

Cocaine use confers a twofold increase in the risk of ischemic and hemorrhage stroke [93]. Subarachnoid hemorrhage most commonly results from rupture of arterial aneurysms, and intracerebral hemorrhagic strokes are thought to result from large spikes in blood pressure. Cocaine users with hemorrhagic strokes have worse functional outcomes and increased mortality [66]. Overall, cocaine is widely considered among the most cardiotoxic among drugs of abuse.

73.7 Amphetamines

Amphetamines cause an increase in catecholamine concentrations both centrally and peripherally by stimulating their release, blocking their reuptake, and inhibiting their metabolism by monoamine oxidase [30]. This section focuses primarily on three commonly abused amphetamines: amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA).

Amphetamines cause tachycardia, vasoconstriction, and hypertension, similar to the effects of cocaine [14]. The most common clinical presentations of amphetamine users requiring hospitalization are chest pain, tachyarrhythmia, palpitations, and hypertension. There are an abundance of reports of acute MI in amphetamine users [14]. The pathogenesis of coronary ischemia results from an increase in myocardial oxygen demand, chronotropy, wall stress, and afterload, with a simultaneous reduction in coronary blood flow secondary to vasoconstriction [14].

Amphetamines are also associated with sudden cardiac death due to malignant ventricular arrhythmias [14]. Methamphetamine has been shown to prolong the QTc interval in humans, increasing the risk of TdP. The mechanism is not well understood, but may relate to inhibition of transient outward potassium current, inward rectifying potassium current, and via the L-type calcium channel [60].

Aortic dissection has been strongly associated with methamphetamine intoxication in case reports [46]. In fact, one autopsy series found that after hypertension, methamphetamine use was the most common risk factor for fatal acute aortic dissection [94].

Like cocaine, amphetamines are linked to cardiomyopathy in the acute and chronic setting. In some cases the cardiomyopathy may reverse with abstinence. Additionally, Takotsubo cardiomyopathy has been described in the setting of acute amphetamine use [14]. As with other cardiomyopathies, the cornerstone of therapy is neurohormonal blockade. Similar to acute cocaine intoxication, β-blockers should be considered carefully in acute amphetamine intoxication. The available evidence would suggest that combined α- /β-blockers such as labetalol and carvedilol are safe and effective at treating the associated tachycardia and hypertension [82].

73.8 Amphetamine-Like Drugs

Synthetic "designer drugs" have gained increased popularity in recent years. These include "bath salts," [7] which typically contain 3,4-methylenedioxy-N-methylcathinone (methylone), 4-methylmethcathinone (mephedrone), and 3,4-methylenedioxypyrovalerone (MDPV), as well as alpha-pyrrolidinovalerophenone ("Flakka"). These drugs are synthetic cathinones; cathinone is found naturally in khat (*Catha edulis*) and exhibits amphetamine-like properties

[16, 19]. In addition to significant behavioral disturbances, the use of these drugs has been associated with sudden death, endocarditis, MI, and cardiomyopathy [7, 16, 19]. While no trials currently exist as to the optimal treatment of cardiovascular complications of cathinone derivatives, they should be approached similar to acute cocaine or amphetamine intoxication [85].

73.9 Opioids

Cardiovascular effects of opioids tend to be relatively mild, with no direct effect of most opioids on cardiac rhythm or myocardial contractility. However, orthostatic hypotension may occur, presumably secondary to histamine release and vasodilation of peripheral arteriolar vessels. In patients with acute coronary syndromes, opioids are often used intravenously for relief of chest discomfort. Intravenous morphine leads to mild venodilatation, which decreases preload and myocardial oxygen consumption in the setting of LV systolic dysfunction and pulmonary edema. Intravenous opioids also result in a small decrease in pulse and blood pressure in the acute coronary syndrome patient. Opioids may also improve myocardial energetics at the cellular level and have been associated with enhancement of "ischemic preconditioning." This phenomenon entails repetitive episodes of noncritical ischemia, which may provide myocardial protection to patients chronically treated with opioids, where a lower burden of coronary artery disease was noted relative to expected global risk (Framingham) score [64]. The authors found a lower burden of coronary artery disease among opioid users and postulated that this may relate to ischemic preconditioning.

By contrast to the potential protective effects of opioids regarding atherosclerotic risk, evidence suggests that synthetic opioids, such as methadone, may block the delayed rectifier potassium ion current known as I_{Kr}, which is encoded by the *hERG* gene, leading to TdP, a form of polymorphic ventricular tachycardia that occurs in the obligatory setting of QTc-interval prolongation. The pathobiologic sequence of events leading to sudden cardiac death in susceptible individuals receiving methadone is depicted in Figure 73.3. Blockade of the hERG potassium channel increases the action potential duration, which delays repolarization. This manifests as QT prolongation. If a premature ventricular complex occurs (early after depolarization or EAD), this triggers TdP, which may degenerate into ventricular fibrillation (VF) and death.

Vignette

A 34-year-old law school student presents to your psychiatry office with fevers, malaise, and rigors for 10 days. He has a 7-year history of intermittent recreational opioid

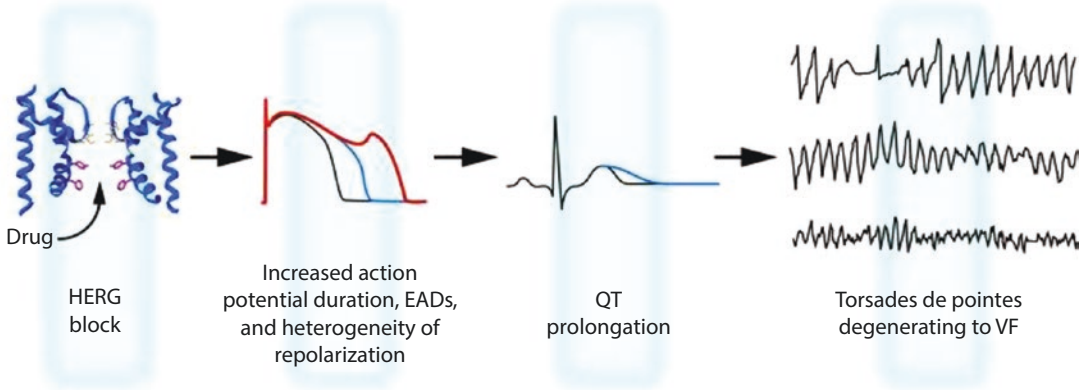

Fig. 73.3 Mechanism of drug induced TdP. From Roden and Viswanathan [101]

abuse. Over the past 6 months, he reports escalation in prescription opioid use including oxycodone and hydrocodone cough syrup with dextromethorphan. When he is unable to use opioids, he develops withdrawal symptoms and 2 weeks ago he admits to a period of heroin use. His last opioid consumption was 2 h ago. The patient is in no acute distress. Examination is notable for a temperature of 38.5 °C; blood pressure is 135/70 mmHg, and pulse is 112 bpm. Cardiovascular exam is notable for a grade III systolic murmur. He reluctantly rolled up his sleeves, revealing the presence of healed track marks and a small abscess in the left antecubital fossa.

73.9.1 Heroin

The effects of heroin on the cardiovascular system are not extensive, which may in part reflect its close derivation from the natural opium poppy. Heroin abuse is associated with acute pulmonary edema, but this is generally non-cardiogenic in origin. The typical hemodynamic findings include normal pulmonary-capillary wedge pressure and a normal or increased cardiac output suggesting the absence of direct myocardial toxicity [6]. Although moderately elevated pulmonary artery pressures have been described, this is most likely due to direct pulmonary toxicity in the setting of injected impurities or in overdose reflective of hypoxemia leading to subsequent increased pulmonary-capillary leakage akin to respiratory distress syndrome.

The most feared cardiovascular complication of intravenous heroin abuse is the development of infective endocarditis, often due to virulent pathogens such as *Staphylococcus aureus*. Heroin may also result in embolic stroke due to systemic embolization of valvular vegetations to the brain. Infective endocarditis of the right-sided heart valves (tricuspid and pulmonic) should always alert the clinician to the possibility of surreptitious intravenous drug abuse. Cases of potential endocarditis should be confirmed immediately by blood cultures and transthoracic echocardiography, which is often diagnostic particularly for right-sided valvular vegetation. If there is a high clinical suspicion, transesophageal echocardiography is increasingly utilized as it offers enhanced visualization, particularly of left-sided valvular structure [5].

Vignette (continued)
The patient is effectively treated for tricuspid valve endocarditis with 6 weeks of intravenous antibiotics with resolution of symptoms. He returns to school but eventually begins to relapse and abuse heroin. He asks for assistance and it's decided to induce him onto methadone maintenance therapy. He is initiated on 30 mg/day and he is up-titrated to 90 mg daily at which point he feels well and discontinues illicit opioids entirely. One month later he is at the opioid treatment center and develops the sudden onset of tonic-clonic seizures and loss of consciousness. He regains awareness and you refer him for neurologic evaluation. Computed tomography of the brain and electroencephalography are normal. Subsequently, magnetic resonance imaging is performed without focal lesion. He is started on low-dose antiepileptic therapy but one month later is involved in a motor vehicle accident after passing out while driving.

73.9.2 Methadone and Synthetic Opioids Used in Addiction Treatment

The most feared cardiovascular effect of methadone and synthetic opioids QTc prolongation and subsequent ventricular arrhythmia. The arrhythmic risk is primarily derived from the effects of these drugs on cardiac repolarization, which is the phase in the cardiac cycle where myocytes "reset" and is clinically characterized by the QTc interval on the surface ECG. The cardiac repolar-

ization changes associated with synthetic opioids were characterized in human cells stably transfected with the hERG gene which encodes the I_{Kr} current [45]. The ratio of the concentration of drug that blocks 50% of I_{Kr} channels (IC50%) was divided by the expected maximal plasma concentration (Cmax) in man for the individual drugs yielding the IC50/Cmax. This ratio predicts the likely occurrence of QTc prolongation, with higher numbers suggesting the greatest margin of safety. The IC50/Cmax observed with codeine and morphine (and by extension diacetylmorphine or heroin) was >400. These "naturally occurring" opioids therefore are not associated with QTc prolongation and TdP. By contrast, the synthetic opioids fentanyl, meperidine, and buprenorphine exhibited modest blockade with IC50/Cmax ranging from approximately 50 to 200. Notably, the most potent I_{Kr} blockade was observed with methadone and levacetylmethadol (LAAM), with ratios of 2.7 and 2.2, respectively. This creates a challenging paradox: while synthetic opioids clearly reduce the harm of injection drug use including the risk of hepatitis, HIV, and endocarditis, they also have a cardiac safety liability in susceptible individuals.

Methadone and buprenorphine are the only FDA-approved therapeutic choices for opioid-dependent patients. In 2002, a case series of TdP associated with high-dose oral methadone was first described [51]. In the case presented within the clinical vignette, it is likely that the patient's grand-mal seizures and syncope were manifestations of TdP. TdP is a self-terminating arrhythmia in most cases, though it may degenerate into ventricular fibrillation and lead to sudden cardiac death. A case of methadone-induced arrhythmia masquerading as epilepsy has been previously described [50]. This highlights the fact that ventricular arrhythmia may result in marked reduction of cardiac output and cerebral hypoxemia and subsequent seizures. Thus, seizures are not always due to epilepsy and should alert clinicians to the possibility of life-threatening arrhythmia.

Ventricular arrhythmia and cardiac arrest are now the most frequent FDA-reported class of methadone-associated adverse events, and reports of QTc prolongation and TdP have increased sharply [44]. Because methadone causes QTc-interval prolongation and TdP, a consensus guideline suggesting QTc-interval screening was developed [52]. The guideline emphasized five recommendations for physicians prescribing methadone (Table 73.3). Because the arrhythmia risk associated with methadone is a direct consequence of its effect on cardiac repolarization, the recommendations are applicable to patients either receiving current treatment with methadone or being considered for initiation of methadone treatment for addiction or pain management. Methadone is now considered an essential medication by the World Health Organization, and its utilization is expected to rise, highlighting the need to enhance its cardiac safety.

Table 73.3 Consensus recommendations for QTc-interval screening in methadone treatment [52]

Recommendation 1 (Disclosure)	Clinicians should inform patients of arrhythmia risk when they prescribe methadone
Recommendation 2 (Clinical history)	Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope
Recommendation 3 (Screening)	Obtain a pretreatment ECG for all patients to measure the QTc interval and then a follow-up ECG within 30 days and annually. Additional ECG is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures
Recommendation 4 (Risk stratification)	If QTc interval is >450 ms but <500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing methadone or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy
Recommendation 5 (Drug interactions)	Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone

73.9.3 Nicotine

Cigarette smoking is the leading risk factor for developing cardiovascular disease, increasing risk of coronary artery disease by up 80–100% [58]. Secondhand smoke exposure is also harmful, potentially increasing risk of coronary artery disease by up to 30% [95]. The biologic effects of secondhand smoke have been well characterized and mirror those of direct tobacco exposure. In particular, coronary arterial plaque destabilization is triggered by nicotine in secondhand smoke; this stimulates the matrix metalloproteinase enzyme that degrades the fibrous cap in coronary plaques [13]. Secondhand smoke is also associated with impaired coronary endothelial function and increased aortic stiffness [63].

Nicotine acts in part by stimulating release of norepinephrine from sympathetic nerves and by release of epinephrine from the adrenal glands, which produce increases in heart rate and blood pressure shortly after exposure. Although the precise role of nicotine relative to other components of cigarette smoke is unclear, cigarette smoking is also associated with vasomotor dysfunction mediated by reduced availability of nitric oxide, systemic inflammation that increases adherence of leukocytes to endothelial cells, increases in serum low-density lipoprotein and triglycerides with decreases in high-density lipoprotein, platelet dysfunction, and alteration of thrombotic factors [2]. Consequently, cigarette smoking is associated with increased rates of all-cause and cardiovascular mortality, first MI, recurrent infarction or revascularization in patients with coronary artery disease, sudden death, and stroke [36, 86].

Cessation of smoking is associated with rapid decreases in cardiovascular events including MI, stroke, and sudden death, with rates returning to near that of nonsmokers within 3–4 years in many cases [34]. Although the increased risk of cardiovascular events associated with smoking appears to increase with age, the benefits of cessation are independent of age. Despite the clear risks of smoking and benefits of smoking cessation, smoking rates remain relatively stable, and the rate at which physicians in the USA advise patients to stop smoking has actually decreased over time [54]. Intensive support including structured behavioral modification counseling and pharmacotherapy with either nicotine replacement therapy and/or bupropion appears superior to one-time counseling in patients hospitalized for coronary disease or heart failure, although even a brief statement to outpatients of the risks associated with smoking can result in increases in smoking cessation [61]. Despite the stimulating nature of nicotine, large studies have failed to show an increased risk of cardiovascular events or death following initiation of nicotine replacement therapy in the setting of cardiovascular disease. There are very few drug-drug interactions between nicotine replacement therapy and cardiovascular medications. Bupropion appears safe to use in patients hospitalized for acute MI, but may not be as effective as in chronic, stable outpatients [24]. The use of varenicline in patients with cardiovascular disease has been controversial, but recent data indicate that varenicline use is both safe and efficacious even in the immediate post-MI setting [25]. As patients are most likely to quit immediately after having an MI, the use of prescription cessation medications in these patients may present a unique opportunity to augment their efficacy [74].

73.10 Cannabis

Cannabis (marijuana) is generally thought to be relatively benign by the community despite growing evidence that implicates it in several serious cardiovascular complications including MI and ischemic stroke. Cannabis is most commonly smoked and rapidly absorbed through the lungs with physiologic changes appearing shortly after use [35]. When consumed through the enteral route, absorption is slower and less predictable. The adverse cardiovascular effects of marijuana are thought to be mediated by the CB1 receptor, which is activated by tetrahydrocannabinol (THC) – the main psychoactive constituent of marijuana [73].

THC causes a biphasic autonomic response. The sympathetic nervous system is activated at

low-to-moderate doses, and the parasympathetic nervous system predominates at higher doses [35]. This results in tachycardia and augmented cardiac output at lower doses and hypotension and bradycardia at high doses. Even at low doses, cannabis can cause both hypertension and hypotension. Blood pressure alterations during cannabis use are often positional; blood pressure increases while in the seated or supine position and drops while standing. Hypotension can also occur during the act of smoking due to rapid changes in autonomic nervous system output, and orthostatic hypotension with resulting syncope is not an uncommon occurrence. Autonomic changes are generally well tolerated in healthy individuals, and cannabis-induced hypotension usually resolves spontaneously or responds to intravenous fluid boluses [35].

Cannabis use increases myocardial oxygen demand by increasing heart rate, wall stress, and sometimes blood pressure. Additionally, when smoked, it decreases oxygen supply through carboxyhemoglobin formation. Cannabis use has been shown to decrease the threshold for symptomatic angina pectoris [4]. Furthermore, in a systematic review of over half a million patients, cannabis users are at higher risk of acute MI shortly after using marijuana and continued use after MI was associated with an increased risk of death during the follow-up period [83].

In addition to cardiac ischemia, evidence is emerging that implicates cannabis use with other acute vascular emergencies, including aortic dissection, vasculitis, and ischemic stroke [67, 91, 97]. In a 2013 study, there were 59 reported cases of stroke associated with cannabis use [97]. All but one were ischemic in origin and the patients were often young. Cannabis use has been particularly strongly associated with two specific etiologies of ischemic stroke: reversible cerebral vasoconstriction syndrome (RCVS) and multifocal intracranial stenosis (MIS). In a prospective study evaluating cannabis' role in ischemic stroke, a single center enrolled every patient under 45 years of age that presented with ischemic stroke [98]. It was found that cannabis use was highly associated with ischemic strokes caused by multifocal intracranial stenosis. Caution must be taken with attributing these events solely to cannabis, as patients also smoked tobacco regularly and half of these patients had binged on alcohol shortly before their ischemic events. However, further study has demonstrated a 17% increased risk of ischemic stroke in cannabis users, even when controlling for comorbidities and abuse of other substances [90].

A number of arrhythmias have also been temporally related to cannabis use such as sinus bradycardia, atrial fibrillation, atrial flutter, premature ventricular contractions (PVCs), and second degree AV block [29, 77]. The onset of arrhythmias can begin within a few minutes of cannabis use, peaks at about 30 min, and can last as long as 90 min [43]. The majority of these arrhythmias revert spontaneously to sinus rhythm. There are two cases of cannabis-induced Brugada pattern, neither of which were associated ventricular arrhythmias [77].

Synthetic cannabinoids have gained increasing popularity in recent years; street names include "K2," "Spice," and "Black Mamba." The active compounds are often many times more potent than THC in activating CB1 receptors with some compounds reportedly 170 times more active than THC. There are numerous case reports of adverse cardiovascular effects associated with their use. The expected cardiovascular morbidity and mortality is likely higher with synthetic cannabinoids than cultivated cannabis, though the variation in active ingredients and lack of regulation make systematic study difficult [73].

Interestingly, there has been some research which suggests that certain cannabinoids may have cardioprotective effects. Cannabidiol (CBD), a non-psychoactive component of marijuana, has gained popularity with a wide range of reputed effects and uses including treatment of chronic pain. CBD has demonstrated anti-inflammatory properties which may result in plaque stabilization and has also been demonstrated in animal models to protect against doxorubicin-mediated cardiomyopathy [38, 73]. Further research is required to further evaluate the clinical efficacy of these cardiovascular effects in humans.

73.11 Anabolic Steroids

Anabolic steroids are associated with direct myocardial effects such as LV hypertrophy and myocardial fibrosis and indirect effects, including dyslipidemia, hypertension, arrhythmia, and MI [39]. It is likely that chronic exposure to these agents can result in significant alterations in the cardiovascular system, beyond the expected increase in salt and water retention leading to elevations in blood pressure in susceptible patients.

The most feared complication of anabolic steroids is acute MI. In addition to increasing thrombotic risk, there is further concern that anabolic steroids may accelerate the overall atherosclerotic process with ongoing abuse. A framework for understanding this risk has been put forward [69]. Four mechanisms are suggested:

1. Atherosclerosis-dyslipidemia model given marked reductions up to 70% in high-density lipoprotein (HDL) cholesterol, which is responsible for reverse cholesterol transport and > 20% increases in the atherogenic low-density lipoprotein (LDL) cholesterol.
2. Vasospasm model given alterations in the vascular nitric oxide system.
3. Thrombosis model involving alterations in platelet and clotting function including increases in plasminogen activator activity.
4. Direct myocardial injury model including impaired myocardial relaxation and diastolic dysfunction.

Another factor that enhances the risk of MI is polycythemia associated with anabolic steroids, which increases blood viscosity and thrombosis. As such, a complete blood count should be obtained in patients using anabolic steroids who present with ischemic complications. Beyond the risk of MI, these agents are associated with stroke as well as fatal arrhythmias [32, 33].

Surreptitious anabolic steroid use should be considered in young athletes with hypertension, very low serum HDL and elevated LDL cholesterol levels, or LV hypertrophy by ECG. The actual prevalence of significant coronary artery disease among anabolic steroid users is not known, and cardiovascular risk reduction should conform to standard age-appropriate guidelines until additional data is available. Blood pressure and lipid abnormalities will generally resolve after 6–12 months of abstinence, but there is evidence that pathologic LV hypertrophy may persist for years after discontinuation although this persistence may be due to sustained or ongoing strength training [1]. There is no clear evidence for pharmacologic treatment of LV hypertrophy, although dilated cardiomyopathy as a result prolonged steroid use and/or ischemic events should be treated in accordance with heart failure guidelines.

Key Points

Drugs of abuse have a variety of effects on the cardiovascular system. Alcohol may have beneficial effects in light-to-moderate drinkers, but heavy or binge drinkers are at risk for hypertension, heart failure, arrhythmia, and stroke. Sympathomimetic drugs, including cocaine and amphetamines, accelerate atherosclerosis, predispose to acute coronary events and arrhythmias, and lead to cardiomyocyte toxicity which can result in heart failure. Naturally occurring opioids may have a protective effect against developing ischemic heart disease and do not have clinically significant electrophysiologic properties; however, synthetic opioids such as methadone can lead to significant QTc prolongation and torsade de pointes. THC use has a number of adverse cardiac effects including arrhythmias and ischemia; CBD may be potentially cardioprotective but more research is necessary. Anabolic steroids have a number of negative effects including pathologic hypertrophy, accelerated atherosclerosis, increased risk of MI, and arrhythmia.

- Drugs of abuse s acute and chronic cardiovascular effects; given the prevalence of abuse, clinicians are surely to encounter these throughout their careers.
- Abstinence is the best remedy, but patients should also be treated according to established guidelines.

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Respiratory Problems and Substance Misuse

74

B. Nanayakkara and S. McNamara

Contents

Abstract

Respiratory problems account for a significant proportion of the organ-related morbidity associated with substance misuse. Pulmonary injury may occur as a result of direct drug-related toxicity or through an indirect effect, and the spectrum of pulmonary complications from drug abuse is wide. The treating clinician must maintain a high degree of vigilance in considering whether illicit drugs could potentially be contributory – or even the causative factor – in any patient presenting with respiratory symptoms with or without associated chest X-ray and chest imaging changes. This chapter considers the common patterns of illicit drug–related pulmonary complications. After initially discussing the non-specific respiratory complications that are common to a range of different substances of abuse, a focused description of the range of respiratory pathologies that can occur in relation to specific drugs is provided.

B. Nanayakkara · S. McNamara (✉)
Department of Respiratory & Sleep Medicine, Royal Prince Alfred Hospital, Camperdown, NSW, Australia
e-mail: stephen.mcnamara1@health.nsw.gov.au

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Respiratory disease · Drug-related pulmonary toxicity · Pneumonia · Septic embolism · Pleuroparenchymal disease · Pulmonary vascular disease

74.1 Introduction

Drugs of abuse represent a worldwide health problem. These substances can cause both acute and chronic organ toxicity, with the potential for life-threatening consequences. Pulmonary involvement accounts for a significant proportion of organ-related morbidity. This is not surprising as the lung receives the entirety of the cardiac output, and is also the site at which gas exchange takes place. Pulmonary injury may occur as a result of direct drug-related toxicity, or through an indirect effect, such as inhalational thermal burns to the airway, or septic pulmonary embolisation. Therefore, the spectrum of pulmonary complications from drug abuse is wide (see Table 74.1). Furthermore, given the widespread prevalence of drug abuse, the treating clinician must exercise a high index of suspicion that illicit drugs could potentially be a contributory factor, if not a causative factor, in the patient presenting with a non-specific pulmonary infiltrate or other respiratory symptoms.

In this chapter the more common patterns of illicit drug-related pulmonary complications are discussed. Initially, the non-specific respiratory complications that are common to several different drugs are described, followed by a more focussed description of pulmonary insults related to specific drugs and commonly misused substances.

74.2 Non-specific Pulmonary Complications

74.2.1 Infective Complications: Pneumonia, Lung Abscess, Septic Embolisation, and Mycobacterium Tuberculosis

Infective complications, such as aspiration pneumonia and septic pulmonary emboli, are amongst the most prevalent of pulmonary complications in patients suffering from a substance abuse disorder. Any drug that can lead to an impaired level of consciousness and suppression of the gag and cough reflex can predispose an individual to aspiration and the development of pneumonia. Furthermore, concurrent smoking can impair local lung defences such as the mucociliary escalator, whilst bacteremia from injecting drug use can lead to hematogenous spread of infection to the lung. It is not surprising, therefore, that injecting drug users have a 10-fold higher risk of developing community-acquired pneumonia in comparison to the general population [1]. Left

Table 74.1 Spectrum of adverse pulmonary manifestations most commonly seen in specific substances of abuse

	Substance				
Pulmonary manifestation	Alcohol	Marijuana	Opioids	Amphetamines & Amphetamine-like substances	Cocaine
Pneumonia	+	+/–	+	+	+
Septic emboli	0	0	+	+	+
Airway injuries	0	+	+	+/–	+
Pneumothorax & pneumomediastinum	0	+	+	+	+
Acute lung injury	+	+/–	+	+	+
Non-cardiogenic pulmonary oedema	+/–	0	++	+	+
Foreign particle granulomatosis	0	+/–	+	+	+
Eosinophilic lung disease	0	+/–	+/–	0	+
Other parenchymal disease	0	+/–	0	0	+
Pulmonary vascular disease	0	0	+/–	+	+

untreated, suppurative complications such as lung abscess and empyema may also develop. The etiology and clinical presentation of pneumonia is similar to that of non-drug users [2]. Radiologically, aspiration pneumonia characteristically affects the dependent segments of the lungs – the posterior segments of the upper lobe and the apical segments of the lower lobes [3]. Treatment of pneumonia, pulmonary abscess and empyema should not differ from management outlined in current evidence-based guidelines.

If pneumonia does not respond to standard treatment, a high index of suspicion must be maintained regarding the possibility of fungal pneumonia. Several cases of pulmonary candidiasis have been reported in individuals who inject heroin [4]. Pulmonary tuberculosis (TB) should also be considered in the differential diagnosis in this patient group, as rates of latent tuberculosis infection are higher amongst the intravenous drug using community, with some patient cohorts being reported to have a prevalence of 59% [5]. This association is also true for alcohol use disorders. It is hypothesised that this increased susceptibility relates not only to socioeconomic factors more prevalent this group but also the detrimental impact of ethanol on the immune system [6].

Septic embolisation occurs through hematogenous seeding of micro-organisms, either from an infected vein thrombosis at the site of injection or from tricuspid valve endocarditis. Clinical presentations vary, but patients usually report fever, dyspnea, chest pain and cough, including haemoptysis. Chest CT scans may show multiple peripheral nodules with or without cavitation, focal or wedge-shaped infiltrates due to pulmonary infarction and pleural effusions [7] (Fig. 74.1). *Staphylococcus aureus* is the most

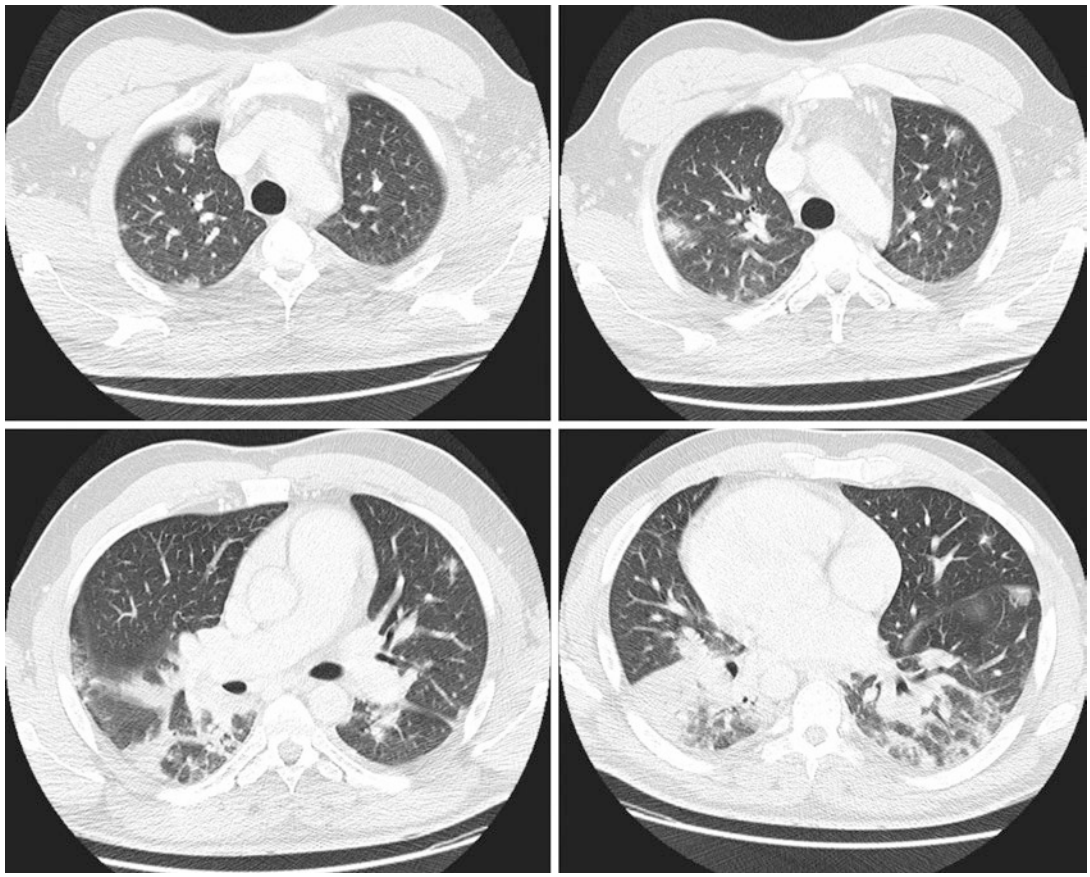

Fig. 74.1 Cross-sectional computed tomography (CT) scan views showing multiple ground glass septic emboli in a 38-year-old male patient with tricuspid valve endocarditis from intravenous heroin use

commonly isolated micro-organism from blood [8]. Transthoracic echocardiography is often sufficient to visualise tricuspid valve vegetation due to the proximity of this valve to the ultrasound transducer, largely negating the need to proceed to trans-esophageal echocardiography [9].

Occasionally, micro-organisms can be transmitted from contaminated media, such as the water used in an inhalational device. There is a case report of severe necrotising pneumonia due to *Pseudomonas aeruginosa* in a marijuana user. *Pseudomonas*, in this case, was isolated from sputum, pleural fluid and subject's water pipe [10].

74.2.2 Non-infective Complications

Magnesium silicate (talc), silicon dioxide (sand), glass beads, microcrystalline cellulose and corn starch are often used to increase the volume and weight of illicit drugs intended for oral use. Intravenous injection of these drugs, such as methylphenidate and methadone tablets, can lead to the deposition of foreign particles within the lungs. This initially leads to the development of an arteritis with rapid influx of neutrophils around the foreign body [11]. Following this, talc particles migrate through the vessel wall into the interstitium where they induce a granulomatous reaction [12]. This leads to discrete, small nodules – foreign body granulomas – that typically have a random distribution on chest CT images. These nodules may coalesce and lead to the development of significant interstitial lung disease including progressive massive fibrosis and, occasionally, diffuse interstitial fibrosis [13]. Emphysema has also been reported in patients who chronically inject crushed methylphenidate tablets [14]. In these patients, the distribution of the emphysematous changes is typically basal predominant and disproportionate to the degree of change that would be expected following tobacco exposure alone. The mechanism by which emphysema develops is thought to be secondary to small vessel occlusion causing alveolar wall necrosis [15]. Chronic pulmonary hypertension may also occur as a complication of pulmonary talcosis [16]. Whilst most patients present with non-specific pulmonary symptoms, occasionally individuals may present with acute hypoxemic respiratory failure [17].

74.3 Pulmonary Complications of Specific Substances

74.3.1 Alcohol

There are two main ways in which ethyl alcohol affects the lungs: through an increase in the risk of pneumonia and through acute lung injury. In 1985, Perlino and Rimland published a case series of patients with alcohol use disorders suffering from pneumococcal pneumonia associated with leukopenia, in whom the mortality rate was more than 80% [18]. Patients with a chronic alcohol use disorder who have pneumonia also suffer from a heightened risk of developing acute respiratory distress syndrome (ARDS), with a relative risk for this condition of 3.7 compared to non-alcoholic patients [19]. It has been hypothesised that disruption to the epithelial barrier and reduced antioxidant levels leads to the increased susceptibility to acute lung injury in these patients [20]. There has also been a case report of negative pressure acute pulmonary oedema that has developed in a young male who presented stuporous following acute alcohol intoxication. It is hypothesised that the development of pulmonary oedema in such cases relates to increased hydrostatic pulmonary capillary pressure from an increased venous return, which in turn is generated by the excessively negative intrathoracic pressures that occur during inspiration against a closed glottis [21].

74.3.2 Cannabis

Cannabis contains the active ingredient tetrahydrocannabinaol (THC) and is derived from the flowers, dried leaves and extracts of the hemp plant *Cannabis sativa*. Due to its high lipophilic-

ity, cannabis is mainly inhaled, but can be ingested, and very rarely injected.

Interestingly, in healthy habitual cannabis smokers, there is a decrease in airway resistance and increase in airway conductance occurring within minutes of inhalation, suggesting an acute bronchodilatory effect. This effect, which peaks between 15 and 20 minutes after exposure and lasts for approximately 60 minutes, has been directly attributed to the presence of THC [22]. Care must be exercised in interpreting this result as potentially therapeutic. Large doses (5–20 mg) of aerosolised THC have been shown to induce acute bronchoconstriction [23], in comparison to smaller doses (0.2 mg) that show bronchodilation [24]. Despite the bronchodilation effect, cannabis smokers suffer from similar respiratory symptoms to that of tobacco smokers, including chronic cough, recurrent bronchitis and wheeze. However, there may be an added burden of these symptoms if the individual smokes both substances [25]. A large epidemiological survey of US adults did not show an association between cannabis use (expressed in joint-years) with decline in forced expiratory volume in one second (FEV_1). Rather, the investigators reported that cannabis use was associated with an increase in forced vital capacity (FVC), an effect that is difficult to explain but has been postulated as being related to the effects of respiratory muscle training from breath holding during cannabis smoking [26].

There has been an association between apical bullous disease, spontaneous pneumothoraces and habitual cannabis smoking. However, these have only been reported in case series. The association is hypothesised to be a result of the increased depth of inhalation and occasional Valsalva maneuvre that many marijuana smokers employ when smoking, rather than from the toxic effects of marijuana itself [27] (Fig. 74.2).

Interstitial lung disease is a rare manifestation of marijuana smoking and has also only been reported in case series. These have included case reports of eosinophilic pneumonia and pulmonary alveolar proteinosis. Two cases of an acute pneumonitis have been described in patients smoking marijuana laced with other substances, such as formaldehyde and phencyclidine [28]. There is controversy surrounding the link between marijuana smoke and lung cancer. At present, no quality evidence exists to establish a causal link [29]. There has been a case report of pulmonary talcosis in a 29-year-old who inhaled marijuana adulterated with mineral substances [30].

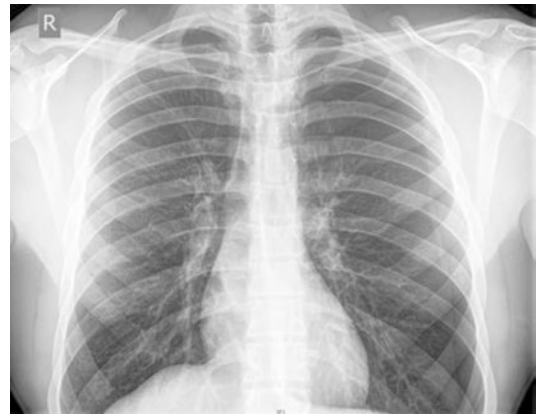

Fig. 74.2 Frontal radiograph showing a left-sided pneumothorax in a 22-year-old male who reported the sudden onset of left-sided pleuritic chest pain whilst smoking marijuana from a water-pipe ("bong") device

74.3.3 Miscellaneous Inhaled Substances

Amyl and butyl nitrites are inhaled substances used for their aphrodisiac properties, including relaxation of rectal smooth muscle tone and prolongation of penile erection. This effect is mediated through the production of nitric oxide via an oxidation-reduction reaction of nitrogen dioxide with haemoglobin. This generates methemoglobin, and significant abuse can lead to severe methemoglobinemia. The clinical phenotype is characterised by the presence of slate-grey skin with cyanosis and normal arterial oxygen tension but reduced arterial oxygen saturation, as the standard oximeter cannot distinguish between deoxygenated haemoglobin or methemoglobin. Blood is characteristically chocolate brown in colour [31].

Whilst toluene sniffing, or glue sniffing, was rare prior to 1960s, it has now become the most commonly abused volatile substance. Because toluene is an excellent solvent for substances such as paint, lacquers, thinners, coatings and glues, it is widely available. The desired effects in individuals sniffing toluene include a sense of euphoria, excitation, delusions and distorted perception. Pulmonary consequences from this form of substance misuse include pneumothorax [32] and panacinar emphysema [33]. A case of Goodpasture syndrome bearing a close temporal relationship with glue sniffing has also been described in a 17-year-old girl [34].

Pulmonary effects from inhaling other volatile hydrocarbons include pneumonitis [35], diffuse alveolar haemorrhage [36] and airway angioedema [37].

74.3.4 Opioids

Opium, derived from the opium poppy plant *Papaver somniferum,* contains over 20 alkaloids including morphine and codeine [38]. Semi-synthetic opioids, such as heroin and hydromorphone, are derived from morphine as a precursor. Purely synthetic opioids are not derived from an opiate but still bind to the opioid receptor. These include fentanyl and methadone [39].

74.3.4.1 Airway Complications

As a result of chronic injection, a heroin user's veins become sclerosed. Many individual users will subsequently attempt high-risk sites of injection, including the approach described as a "pocket shot", which involves directly injecting into the veins of the supraclavicular fossa. One case of bilateral lung pneumothoraces has been reported due to two failed "pocket shots" in an individual [40]. Cervical injection of heroin has also been shown to cause vocal cord paralysis. In a case series of nine such patients, five required tracheostomies due to resultant vocal cord paralysis causing acute airway obstruction [41]. Nasal septum perforation has also been described in a case series of patients who inhaled crushed hydrocodone-paracetamol [42]. Acute bronchospasm may also occur; this is thought to be mediated by direct histamine release from mast cells [43].

74.3.4.2 Respiratory Drive and Respiratory Failure

The most immediate life-threatening acute toxicity of opioid administration is respiratory depression. This occurs due to both a reduction in central chemoreceptor sensitivity to hypercapnea and a heart block-like effect on the respiratory centre pattern generating neurons in the pre-Botzinger complex [44]. This central action of opioids also increases the risk of sleep-disordered breathing by increasing central apneic events during sleep [45].

Life-threatening truncal and laryngeal rigidity has also been reported after the administration of synthetic opioids such as fentanyl, with one case requiring intubation and administration of muscle relaxants [46].

74.3.4.3 Pleuroparenchymal Disease

Non-cardiogenic pulmonary oedema is a well-known complication of acute opioid overdose occurring after either inhalation or injection and has an estimated prevalence of 3% in the heroin overdose population seen in hospital [47]. Presentation with respiratory distress and a pulmonary infiltrate usually occurs within 4 hours, and, with supportive care, symptoms usually resolve within 24–48 hours [47]. The mechanism by which pulmonary oedema develops in this circumstance is debated, with various pathophysiologies proposed, including direct hypoxia-related epithelial damage, a direct toxic effect of opioids on lung parenchyma, the effects of excess negative intrathoracic pressure against an occluded upper airway, as well as the development of increased pulmonary capillary permeability [38]. Naloxone administration is a plausible contributor, and it is hypothesized that in opioid users, naloxone administration triggers a substantial catecholamine release with resultant acute cardiac dysfunction [48]. Management of non-cardiogenic pulmonary oedema in this

circumstance is supportive, most critically ensuring adequate oxygenation. Rare cases of acute eosinophilic pneumonia have been reported following inhalation of heroin, with complete remission occurring following treatment with corticosteroids [49].

74.3.4.4 Pulmonary Vascular Disease

Opioid abuse is not classically associated with the development of pulmonary hypertension. Traclet and colleagues performed a single centre registry analysis of 222 consecutive patients with Group 1 pulmonary arterial hypertension, amongst whom 10 patients had been exposed to heroin. Whilst there was no difference in baseline clinical characteristics between heroin and non-heroin-exposed groups, the patients who abused heroin were diagnosed with pulmonary hypertension 10 years earlier than the non-exposed group, raising a possible connection between heroin use and the development of pulmonary hypertension [50]

74.3.5 Amphetamines and Amphetamine-Like Substances

Amphetamines and amphetamine-like substances, including methamphetamine, methylphenidate and methyl-enedioxy-methamphetamine (MDMA) are sympathomimetic non-catecholamine compounds. Their mechanism of action is multifactorial. By blocking catecholamine re-uptake, inhibiting enzymatic degradation, and facilitating catecholamine release from the pre-synaptic terminals, amphetamines and amphetamine-like substances increase catecholamine concentrations at the synaptic cleft [51].

74.3.5.1 Airway Complications

Methamphetamine users frequently exhibit severe dental disease, predisposing them to respiratory tract infection. "Meth mouth" is characterised by severe dental caries, rotting and crumbling teeth and relates to a combination of factors including poor oral hygiene, increased oral cavity acidity, frequent craving for refined carbohydrates, bruxism, xerostomia and gastro-esophageal reflux disease [52].

74.3.5.2 Pleuroparenchymal Complications

Cases of pneumomediastinum have been reported following aggressive inhalation of crystal methamphetamine ("crystal ice") related to the barotrauma of negative pressure inhalation and subsequent Valsalva maneuvre, prior to exhaling against a pursed lip [53]. Case reports of MDMA pneumothorax and pneumomediastinum have also been reported. The mechanism is thought to be related to excessive physical exertion with wide swings in intrathoracic pressure, rather than direct drug-related effects [54].

Non-cardiogenic pulmonary oedema has been reported in case studies and should be considered in the differential diagnosis in patients taking MDMA and amphetamines who present with dyspnoea, hypoxia and a pulmonary infiltrate [55, 56]. Methamphetamine abuse may also mimic a systemic vasculitis, with one case report of a 27-year-old female presenting with a pulmonary-renal syndrome, in whom a chest computed tomography (CT) scan showed multifocal patchy ground glass opacities and brain imaging revealed changes suggestive of vasculitis [57]

74.3.5.3 Pulmonary Vascular Disease

There is a well-known association between methamphetamine use and pulmonary arterial hypertension. In comparison to a matched cohort of patients with idiopathic pulmonary arterial hypertension, patients with methamphetamine-associated pulmonary hypertension show a more severe disease phenotype characterised by worse 5-year and 10-year event-free survival [58].

74.3.6 Cocaine

Cocaine, an alkaloid derivative synthesised from the leaves of the *Erythroxylum coca* species, is a central nervous system stimulant and anaesthetic

[59]. It is often self-administered by nasal insufflation of the hydrochloride salt or by inhaling vapour from heating of the freebase form. The hydrochloride salt is water soluble, thus also allowing it to be injected. Cocaine is also lipophilic, enabling it to also be absorbed via the nasal mucosa [60]. Frequently, cocaine is adulterated with substances to dilute the active ingredient, often to increase the profit margin per unit sale of the product. One of the most frequently detected adulterants is levamisole, an antihelminthic drug [61].

The mechanism of action of cocaine is complex. The predominant mechanism, occurring both peripherally and centrally, is a blockade in the re-uptake of catecholamines. This causes an increase in the concentration of catecholamines in the synaptic cleft, leading to increased adrenoreceptor and dopamine receptor stimulation. Serotonin re-uptake is also inhibited centrally via its competitive inhibitory effect on the serotonin reuptake transporter [62]

74.3.6.1 Pulmonary Symptoms

Pulmonary symptoms from cocaine misuse are common, non-specific and often camouflaged because of the concurrent co-ingestion or inhalation of other substances such as tobacco and marijuana in the period prior to presentation. Symptoms can include wheeze, cough, haemoptysis, black sputum (melanoptysis), chest pain and dyspnea [63]. In a study of 192 cocaine smokers in Los Angeles, the prevalence of acute cardiorespiratory symptoms upon exposure to cocaine was high. Within 1–12 hours of inhalation, 43.7% of respondents noticed cough with black sputum, 38.5% reported chest pain, whilst 5.7% experienced haemoptysis [64].

74.3.6.2 Airway Complications

A variety of upper airway complications can occur in cocaine users. These include alterations in sensory perception of smell, epistaxis, mucosal irritation, persistent sniffing and sinus-related problems [65]. Velopharyngeal dysfunction, triggering nasal regurgitation of oral contents, hypernasal speech and alteration of speech intelligibility, has recently been reported in a case series of four patients snorting cocaine [66]. Severe disfiguring midline nasal destruction is also reported, including total nasal septal bony and cartilaginous vascular necrosis, saddle nose deformity and osteolytic sinusitis with involvement of the optic nerve [67]. This is thought to be secondary to the direct vasoconstrictor efects of cocaine on the nasal mucosa causing localised ischemia [68]. However, an autoimmune mechanism has also been postulated, given the disproportionately high rate of positive anti-neutrophil cytoplasmic antibody (ANCA) directed against human neutrophil elastase detected in patients with cocaine-induced midline destructive lesions [69]. Indeed, biopsy of these lesions often reveal pathological granulomatous changes indistinguishable from systemic vasculitis/granulomatosis with polyangiitis [70, 71].

Clinicians must also be wary of the potential for acute airway obstruction in cocaine users. Uvulitis and uvular angioedema have been reported in cocaine users [72]. Vocal cord paralysis from neck injections of cocaine have also been reported [41], as well as stridor related to oedema of the arytenoids, epiglottis and vocal cords in smokers of free-base cocaine [73]. Bilateral saccular cysts causing acute airway obstruction have been described in a cocaine user, necessitating an emergent tracheostomy [74].

There is also a plausible link between asthma severity and cocaine abuse. Asthma exacerbations, including episodes of severe bronchospasm requiring endotracheal intubation and mechanical ventilation, are more severe and more frequent in patients admitting to the prior use of cocaine (or identified as having recently used cocaine via identification with urine cocaine metabolites) [75–77].

74.3.6.3 Pleuroparenchymal Complications

Barotrauma causing pneumothoraces, pneumopericardium, pneumomediastinum and pneumoperitoneum have been noted to occur in users smoking cocaine. The mechanism probably arises from aggressive inhalation against a small

pipe, often followed by a Valsalva maneuver after inhalation – with or without violent coughing episodes – causing barotrauma [78]. The common practice of partners smoking cocaine forcefully exhaling into one another's mouths is another proposed mechanism by which this complication might occur. Pleural effusions have also been described but are rare [79]. The pleural effusion may appear macroscopically purulent and therefore masquerade as an empyema. However, on careful characterisation, the fluid contains abundance of eosinophils and markers of eosinophilic inflammation such as interleukin-5 [80].

Cocaine-induced acute interstitial pulmonary oedema is a well-known phenomenon. Cardiogenic oedema may occur because of acute myocardial infarction and left ventricular dysfunction [81]. Non-cardiogenic oedema, manifesting as diffuse pulmonary infiltrates with normal capillary wedge pressures, is a common manifestation of cocaine induced pulmonary toxicity. Mechanisms are likely related to direct cellular, epithelial and endothelial injury [82].

The frequency of cocaine induced interstitial and alveolar disease is worryingly high. In an autopsy series of patients with toxicology studies suggesting cocaine use, the prevalence of interstitial pneumonitis and fibrosis was as high as 38%. Furthermore, the rates of acute and chronic pulmonary haemorrhage were 58% and 40%, respectively [83].

"Crack lung" is a well-known entity. The term "crack" arises from the characteristic crackling sound that cocaine makes when it is heated and "crack lung" refers to the acute pulmonary syndrome that develops within 48 hours of inhalation after smoking "crack" cocaine or freebase cocaine. "Crack lung" is characterised by diffuse pulmonary infiltrates, fever, hypoxemia and sometimes haemoptysis. On biopsy, there is evidence of diffuse alveolar damage with hyaline membranes, pulmonary haemorrhage and eosinophilic inflammation, sometimes with the accumulation of immunoglobin E (IgE) deposition in lymphocytes and alveolar macrophages [84]. Pulmonary eosinophilia associated with cocaine use is also well described. This may manifest as an acute syndrome characterized by pulmonary infiltrates, bronchoconstriction and hypoxemia. Assessment of washings obtained from bronchoalveolar lavage in such patients can reveal an eosinophilia, whilst transbronchial biopsies can reveal a dense eosinophilic infiltrate [85].

There is an association between levamisole-containing cocaine and the development of ANCA-associated vasculitis [86]. The p-ANCA antibody is usually detected, although titres to myeloperoxidase (MPO) may be low. Atypical p-ANCA antibodies – such as lactoferrin, cathepsin G or human neutrophil elastase – may also be present [87].

74.3.6.4 Pulmonary Vascular Disease

The association between inhalational cocaine and the development of pulmonary hypertension is not strong [88]. Histopathological findings include pulmonary artery vascular abnormalities such as medial hypertrophy [89]. Vasoconstriction from cocaine can lead to pulmonary perfusion abnormalities, which on a ventilation-perfusion scan can be misinterpreted as "high probability" for pulmonary embolus [90]. Pulmonary infarction can also occur [91]. Pulmonary hypertension itself may be caused by the adulterant levamisole, which is converted to aminorex (a potent anorexigen associated with idiopathic pulmonary hypertension) [92].

74.3.7 Cigarettes

The harmful effects of cigarette smoke on the lungs are unparalleled by any other addictive substance. Pathologically, smoking combustible cigarettes leads to loss of cilia, mucus gland and goblet cell hyperplasia, inflammation, squamous metaplasia, mucus plugging, destruction of alveoli and reduction in pulmonary capillary density [93]. A complete discussion on pathophysiology and disease manifestations is beyond the scope of this review; however, we will focus on the most important aspects of pulmonary injury.

74.3.7.1 Respiratory Infections

The risk of acquiring a respiratory tract infection, including viruses, typical bacteria and

mycobacteria, is much higher in cigarette smokers than non-smokers [94]. For example, the risk of invasive pneumococcal disease in immunocompetent adults was highest in current smokers (odds ratio [OR] 4.1, 95% confidence interval [CI] 2.4–7.3) in comparison to non-smokers, with the risk only declining to that in non-smokers after 10 years smoking cessation [95]. Additionally, the risk of community-acquired pneumonia is almost twice as high in smokers compared to non-smokers [96].

74.3.7.2 Airways

The most well-known association between cigarette smoking and the lungs is its causal relationship with airways disease. Cough is a frequent symptom [97], irrespective of the presence or absence of chronic bronchitis, and is probably triggered by chronic cigarette smoke induced upregulation of the cough reflex [98], occasionally leading to cough syncope [93]. There is a clear and undisputed link between cigarette exposure and the development and progression of chronic obstructive pulmonary disease [99, 100]. Smoking cessation can reduce the rate of decline in FEV1 back to the level of non-smokers, but the loss of lung function cannot be regained [101]. Furthermore, smokers without spirometric obstruction (FEV_1/FVC >0.7) may also suffer with chronic respiratory symptoms, exacerbations and airway remodelling [102]. Whether current treatment strategies for COPD are applicable to these patients is currently under review. Carbon monoxide from cigarette smoke can also add to the burden of exercise intolerance as it binds avidly to haemoglobin reducing the oxygen carrying capacity of blood as well as peripheral oxygen release [103, 104]. There is a link between cigarette smoking and the development of asthma, with a large British national study suggesting that regular smoking was associated with a 4.4-fold increased risk of asthma [105], a result corroborated by a large Finnish study [106].

74.3.7.3 Pleuroparenchymal Complications

Less well known is the strong association between smoking and interstitial lung diseases (ILD). Robust associations are seen with respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), Langerhans cell histiocytosis (LCHx) and desquamative interstitial pneumonitis (DIP). These three entities are commonly referred to as smoking related ILD [107]. If fibrosis is not established, smoking cessation may lead to resolution of interstitial changes and physiological abnormalities. However, immunosuppression with corticosteroids may be required for patients with significant impairment [108]. Smoking is also a well-known risk factor for idiopathic pulmonary fibrosis [109] and rheumatoid arthritis associated ILD [110]. A rare but important entity temporally associated with cigarette use is acute eosinophilic pneumonia, presenting with an acute interstitial infiltrate characterised by bilateral ground glass opacities [111]. Despite its name, peripheral blood eosinophilia may not be present, and bronchoalveolar lavage eosinophilia is needed to confirm the diagnosis [111]. Treatment includes supportive ventilatory strategies with prompt initiation of high-dose corticosteroids [112].

74.3.7.4 Malignancy

There is a strong association between lung cancer and cigarette smoking through the carcinogenic effect of cigarettes on the human genome [112, 113]. Interestingly, with the rates of smoking declining and an increase in the use of filtered cigarettes, there has been a corresponding increase in peripherally based adenocarcinomas in place of squamous cell carcinomas [114]. Patients should be counselled on smoking cessation as this has been a clearly established strategy to reduce the risk of developing lung cancer. Indeed, those who were abstinent from smoking cigarettes for more than 15 years had an 80–90% reduction in risk of lung cancer in comparison to current smokers [115].

74.3.7.5 Electronic Cigarettes (E-Cigarettes)

E-cigarettes have been marketed as a battery powered device that is less toxic than conventional cigarettes [116]. However, there has been an alarming increase in the number of reported cases of vaping-associated pulmonary injury. A recent publication in the New England Journal of

Medicine identified 53 cases of severe vaping-associated pulmonary injury, characteristed by respiratory, gastrointestinal and constitutional symptoms with bilateral pulmonary infiltrates revealed on pulmonary imaging [117]. The majority of these patients were young, not regular smokers who reported use of tetrahydrocannabinol products in their e-cigarette devices [117]. This epidemic may be attributed to poor regulation of the materials used in e-cigarettes

74.4 Conclusion

Pulmonary complications of illicit substance abuse are common amongst patients who suffer from a substance abuse disorder. The toxic effect of illicit substances may be direct and impact almost any part of the respiratory tract, from the nasopharynx through to the pleura. The effects may also be indirect, such as occurs with aspiration pneumonia and septic embolisation. Furthermore, patterns of injury may be specific to the route of drug administration, such as foreign particle granulomatosis in injecting drug users, or inhalational thermal injury to the airways.

Given the wide spectrum of polysubstance abuse, it is often difficult to attribute specific patterns of pulmonary toxicity to an individual drug in an individual patient. Clinicians should therefore be alert to and aware of the wide spectrum of pulmonary manifestations that may befall patients who use illicit substances and formulate a broad differential diagnosis when assessing this patient cohort. Apart from naloxone for opioid-induced respiratory depression, there is usually no specific management strategy, and treatment is dependent upon the specific pulmonary insult that has occurred and the provision of appropriate supportive care.

Key Points

- Respiratory complications are amongst the most common medical complications of drugs of abuse. Tobacco causes the greatest burden of disease.
- Infectious complications, whilst not specific to a certain drug class, are common and can progress to suppurative conditions such as empyema and pulmonary abscess. This is a result of decreased airway clearance mechanisms in conjuction with altered level of consciousness.
- The pattern of diffuse pulmonary infiltrates is relatively common. It may result from an interstitial infectious pneumonia, pulmonary talcosis (particularlarly if the infiltrate is nodular), septic embolisation, cardiogenic and non-cardiogenic pulmonary oedema, acute hypersensitivity pneumonitis, pulmonary vasculitis and pulmonary haemorrhage.
- Knowledge of the offending drug may help with the differential diagnosis. However, because the pattern of pulmonary involvement is common amongst a number of drug classes, the extrapolation of offending drug from the pattern of injury can often be difficult.
- Additive compounds may have an important effect on toxicity, for example, levamisole leading to an ANCA-associated vasculitis in cocaine users and pulmonary talcosis with massive progressive fibrosis from the intravenous injection of talc containing tablets.

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Oral Health and Addiction: Consequences of Substance Use

75

Garima Arora and Ruth Freeman

Contents

Abstract

This chapter is a review of the effects of drugs and substance use upon oral health. It provides the latest WHO and FDI definition of oral health together with a brief description of the main oral diseases, i.e., dental caries and periodontal disease. It describes the effects of substance use and their physiological actions on teeth, oral mucosa and other oral diseases. Finally, it presents the dental treatment and oral health management for people with a history of substance use. The overall aim of the chapter is to present the effects of substance on oral health and therefore to illustrate the need for practitioners working in the addiction field to include an oral assessment and referral for dental treatment as part of their overall treatment strategy.

Keywords

Oral health · Substance abuse · Drug abuse · Addiction

G. Arora
Dental Health Services Research Unit, University of Dundee, Dundee, UK
e-mail: g.arora@dundee.ac.uk

R. Freeman (✉)
Dental Health Services Research Unit, University of Dundee, NHS Tayside, Dundee, UK
e-mail: r.e.freeman@dundee.ac.uk

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75.1 Introduction

Oral health is considered as one of the non-communicable disease and contributes to the global burden of disease [37]. While dental caries and periodontal disease represent a considerable portion of disease burden, oral-health-related quality of life is now considered to play an important part when considering the totality of oral health. Therefore, the World Health Organization (WHO), in 2003, defined oral health in terms of physical and psycho-social well-being; however, by 2016, oral health was redefined by the International Dental Association (FDI). FDI described oral health not simply in terms of physical disease but also in terms of oral-health-related quality of life and function. Moreover, the FDI definition included the role of environment and circumstances as a major determinant of oral health. Therefore, social determinants of health were recognised as playing a significant role in the distribution, prevalence and severity of oral diseases. It is apparent that lifestyle factors, including substance use, affected people's oral health status.

Box 75.1 WHO [85] FDI [24] Definitions of Oral Health

WHO [85]: 'a state of being free from chronic mouth and facial pain, oral and throat cancer, oral infection and sores, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders that limit an individual's capacity in biting, chewing, smiling, speaking, and psychosocial wellbeing'.

FDI [24]: 'Oral health is multifaceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow, and convey a range of emotions through facial expressions with confidence and without pain, discomfort, and disease of the craniofacial complex. Further attributes of oral health:

- It is a fundamental component of health and physical and mental well-being. It exists along a continuum influenced by the values and attitudes of people and communities.
- It reflects the physiological, social, and psychological attributes that are essential to the quality of life.
- It is influenced by the person's changing experiences, perceptions, expectations, and ability to adapt to circumstances'.

75.1.1 Dental and Oral Diseases

There are two main oral diseases which make up the greatest global burden of disease [37]. These are dental caries and periodontal disease. Other oral disease associated with mucosal disorders include oral cancers, HIV, oro-dental trauma, cleft lip and palate and noma [87].

Dental caries is caused by the action of free sugars upon the tooth surface. Free sugars contained in foods and drinks are converted into acids by *S. mutans* in the plaque. The acid attack, which lasts about 30 minutes after the ingestion of free sugars, causes a loss of calcium together with demineralisation which results in tooth decay or dental caries. While the acid attack and the effect upon the tooth surface is affected by the buffering effects of saliva and tooth morphology, it is the total daily calorific intake which is primarily responsible for tooth decay [86]. WHO [86] recommends that the consumption of free sugars should be limited to 5% (10 kg/person/year) of the total calorific intake to prevent dental caries. Therefore, the prevention of dental caries is firstly to reduce free sugar consumption to 5% of the total calorific intake and secondly to brush teeth to introduce and distribute fluoride toothpaste (1450 pmm) across the teeth to strengthen the tooth enamel against carious attack.

Periodontal disease and specifically gingivitis are associated with poor plaque control. Gingivitis presents as bleeding and swollen gums. Acute and chronic periodontitis are associated with destructive bone loss that supports the tooth. However, since the natural history of periodontal disease remains unknown, there is not necessar-

ily a natural progression from gingivitis to periodontitis. Chronic periodontitis and the loss of attachment of the gum to the tooth can lead to (i) a pocket formation between tooth and gum, (ii) cause bad breath, (iii) increase tooth mobility and (iv) in some cases eventual tooth loss [52]. Recognised aetiological factors in chronic periodontitis are tobacco smoking and to a lesser degree alcohol consumption [72].

Oral cancer as defined by the WHO includes the cancers of lip and all subsites of the oral cavity, and oropharynx [87] caused predominantly by tobacco smoking and alcohol consumption.

These tooth and mucosa-related dental diseases can be caused directly from the consumption of addictive substances or arise indirectly as a consequence. Currently, alcohol, tobacco and drugs are readily available. The apparently easy access to substances makes it crucial for the health care providers to be aware of the oral manifestations and respond in the best interest of any patient with a history of alcohol and drug use.

75.2 The Oral Health Effects of Substance Misuse

The oral health effects of the most commonly used drugs, and the implications to the dental treatment of a drug user, approach to dental treatment and management are presented in Tables 75.1, 75.2, and 75.3.

Table 75.1 Depressants and oral health

Substance	Physiological effect	Oral manifestations			Dental treatment and management
Depressant		Tooth	Mucosa	Other	
Alcohol	Inhibits saliva secretion, increases mucosal permeability, gastric reflux	Dental caries, tooth erosion associated with reflux and vomiting, periodontal disease	Oropharyngeal cancer, oral pigmentation, glossitis associated with Vitamin B1 and B6 deficiencies periodontal disease	Halitosis, xerostomia and bilateral enlargement of parotid glands (sialadenosis)	Haematological investigation before oral surgery Check for alcohol consumption before prescribing medication Arrange referral for alcohol counselling
Opiates Morphine Heroin Oxycodone Tramadol Methadone Buprenorphine	Increased consumption of free sugar, reduced saliva flow, immune suppression	Rampant caries	Periodontal disease, mucosal infections, e.g., candidiasis, dysplasia	Xerostomia, severe bruxism, taste impairment	Extreme dental anxiety associated with local anaesthetic injections, reduced responsiveness to local anaesthesia; increased pain tolerance: possibility of infective endocarditis Prevention includes dietary advice, fluoride mouthwashes (after methadone), varnish applications and improved toothbrushing with fluoride toothpaste; sugar-free gums, artificial saliva
Cannabis	Anticonvulsant, immune-suppressive properties	Dental caries	Gingivitis, destructive bone loss, oral cancer, candidal infections, leukoedema	Xerostomia, nicotinic stomatitis, uvulitis lesion	Dietary advice, use of fluoride toothpaste Patients to discontinue marijuana use 1 week prior to the dental treatment Local anaesthetic agent with adrenaline should not be used

Table 75.2 Stimulants and oral health

Substance	Physiological effect	Oral manifestations			Dental treatment and management
Stimulant		Tooth	Mucosa	Other	
Cocaine Crack cocaine	Decrease in salivary flow and pH, necrosis of nasal septum and surrounding tissue vasoconstriction	Greater prevalence of dental caries, attrition, glossy appearance of tooth surfaces, rapid tarnishing of gold crowns	Gingival lesions at the site of drug application, destructive periodontitis Crack cocaine increased prevalence of oral mucosal lesions, e.g., ulceration	Oro-nasal perforation, severe bruxism, orofacial pain, xerostomia, numbness	Local anaesthetic agent with adrenaline should not be used treatment postponed for 6–24 hours if cocaine use is assumed following a period of abstinence surgical closure of palatal defect or removable maxillary obturator
Amphetamines Methamphetamine	Reduction in salivary secretion hyper-metabolism causing increased sugar craving, increased motor activity, mild dysphoria	'Meth mouth': Rampant dental caries, erosion, attrition		Xerostomia, severe bruxism	Local anaesthetic without vasoconstrictor should be used for dental treatment Prevention includes fluoride mouthwashes, varnish applications and improved toothbrushing with fluoride toothpaste, sugar-free gums, artificial saliva
MDMA / Ecstasy	Muscle rigidity raising body temperature, dehydration, high consumption of sugary fizzy acidic drinks, dry mouth and low saliva buffering capacity	Enamel erosion, dental caries, attrition	Mouth ulcers	Xerostomia, severe bruxism, clenching and grinding, facial and TMJ pain, altered speech, tingling of lips	Sugar-free chewing gum, fluoride mouthwash, high-fluoride toothpaste Caution must be taken in administering a local anaesthetic agent containing epinephrine

Table 75.3 Other substances and oral health

Substance	Physiological effect	Oral manifestations			Dental treatment and management
Other		Tooth	Mucosa	Other	
Tobacco *(Nicotine)* Stimulant and depressant					
Smoked tobacco and reverse smoking	Oral microflora, immunity, periodontal inflammation, resorption of alveolar bone, impaired salivary function	Discoloration of teeth Discoloration of dental fillings and dentures, tooth abrasion, dental caries	Oral cancer, precancer: epithelial dysplasia, leukoplakia, erythroplakia Black hairy tongue, candidal infection, smokers' melanosis and palate Periodontal disease	Altered taste and smell, Halitosis, delayed wound healing, some evidence of increased prevalence of cleft lip and palate in infants	Brief intervention on smoking cessation (ask, advice, assist), referral to smoking cessation services, NRT Give clear post-operative instructions to prevent complications after surgical procedure
Smokeless tobacco	In addition to above: abrasive in nature	In addition to above: root caries, cervical abrasion	In addition to above: gingival recession		
Gabapentin (anticonvulsant)		Dental caries as a consequence of dry mouth and reduced saliva	Gingivitis	Xerostomia, dry throat	Prevention includes dietary advice, fluoride mouthwashes, varnish applications and improved toothbrushing with fluoride toothpaste; sugar free gums, artificial saliva

75.2.1 Depressants and Oral Health: Alcohol (Table 75.1)

75.2.1.1 Tooth-Related

Alcohol consumption has shown to affect oral health. Although the severity of tooth-related disease depends on the levels of alcohol consumption, higher levels of decayed tooth surfaces have been reported in those with a history of high alcohol use [36]. In addition to higher number of decayed teeth, as a consequence, people who consumed 24 g of alcohol per day were shown to have higher number of missing teeth when compared to social drinkers (subjects consuming ≤8 g of ethanol per day) [23]. Some findings, however, contradict the above evidence, indicating a preventive role for alcohol. For instance, in the UK, some beers contain fluoride that prevents tooth decay while others point to the inhibitory effect on cariogenic flora [22]. Since alcohol consumption is related to reduced salivary flow and dry mouth, dental caries in alcohol users is often attributed to salivary factors and poor dental health behaviours.

Enamel erosion or tooth wear is another complication of chronic alcohol consumption, typically affecting the palatal surfaces of the upper front teeth. Most alcoholic beverages have acidic pH or are consumed with acidic mixers such as carbonated drinks or fruit juices. Due to higher concentration of titratable acids, white wines are more corrosive than red wines for teeth [56]. The presence of dental erosion is related to duration of alcoholism and gastro-oesophageal reflux and vomiting [51].

Evidence suggesting the role of alcohol in staining the tooth is limited, red wine being the only alcoholic drink linked to tooth staining. Binge drinkers or those consuming high levels of alcohol are significantly more at risk of dental trauma.

75.2.1.2 Mucosa-Related

A systematic review from 2009 provided evidence to suggest that alcohol consumption could be considered as a risk factor for periodontitis [3]. A recent meta-analysis reported a dose-response relationship between alcohol consumption and periodontitis risk with risk of periodontitis increasing by 0.4% for each 1 g/day increment in alcohol consumption [81].

Chronic periodontitis is thought to have a systemic host mediated element associated with impairment of white cell and T-cell functioning. Since a link between alcohol consumption and periodontal disease has been proposed, and Tezal et al. [72] support this proposition having identified an important relationship between the number of drinks per week and destruction of the periodontal ligament supporting the tooth in the bone (clinical attachment loss).

Alcohol as a causative factor in oropharyngeal cancer is well established. While there is no clear explanation on how alcohol exerts its carcinogenic effect, possible explanations are, (i) 'genotoxic effect of acetaldehyde', (ii) 'role as a solvent for tobacco carcinogens', (iii) 'production of reactive oxygen and nitrogen species' and (iv) 'changes in folate metabolism' [13]. More recent research suggests that drinking more than 4 drinks per day increase the risk of oropharyngeal cancer by 5 times [50]. In their meta-analysis, Turati et al. [78] reported a dose-response relationship between alcohol consumption and oral cancer. They [78] stated that there was an increased risk of 1.32 among social drinkers and 2.54 among heavy drinkers (>4 drinks/day) of oral cancer. Moreover, they noted that smoking had a synergistic effect increasing the risk among smokers to 2.92 (social drinkers) and 6.32 (heavy drinkers), respectively.

75.2.1.3 Other

Presence of bad breath is associated with alcohol [62]. Halitosis is related to reduced saliva and sometimes xerostomia, which is associated with sialadenosis and reduced functioning of the parotid glands. This is particularly noticeable in those with alcohol cirrhosis of the liver. Glossitis and angular stomatitis are linked to Vitamin B1 and B6 deficiency observed in those with alcoholism.

75.2.2 Depressants and Oral Health: Opioids (Table 75.1)

Opioids commonly abused included in this review include morphine, heroin (diamorphine) and prescribed medications such as methadone, oxycodone, tramadol, etc. (Table 75.1).

75.2.2.1 Tooth-Related

People who use opiates have high prevalence of obvious dental caries experience with surface level data (tooth surfaces) revealing caries distribution predominantly on 'the smooth and cervical surfaces' [46]. This has been attributed to a complex, dynamic relationship between multiple factors. Therefore, irrespective of the economic status, it is the heightened craving for sweet carbohydrates [74], together with the neglect of personal care that has been observed in opioid users [1] which is thought to contribute to dental caries. The role of sugar-containing methadone prescribed to people on maintenance programme has been highlight as central in the causation of dental caries. This was first reported in 1978 [18] and has been supported by numerous researchers ever since. The effect of opioids and methadone are known to dry the mouth and reduce the buffering effect of the saliva upon the acid produced during the consumption of sugars resulting in tooth decay. However, Tripathee et al.'s [77] systematic review examining the link between sugar-containing methadone and dental caries showed no strong evidence to support a link and pointed to the role of other factors such as reduced salivary function.

75.2.2.2 Mucosal-Related

The increased experience of gingivitis and periodontal disease noted in those using morphine and heroin is associated with lack of toothbrushing and plaque removal [74]. Morphine in particular is known to inhibit the phagocytosis of *Candida albicans* and when this is coupled with xerostomia predisposes users to thrush [70].

75.2.3 Depressants and Oral Health: Cannabis (Table 75.1)

75.2.3.1 Tooth-Related

The role of saliva in buffering effects and preventing the acid attack on the teeth has been described. A study by Schulz-Katterbach et al. [65] aimed to clarify the role of reduced salivary function in dental caries among regular younger cannabis users. Regular cannabis users had more decayed tooth surfaces (smooth surfaces of anterior and molar teeth), stated that they brushed their teeth less, visited the dentist less and consumed greater amounts of sugar-containing beverages compared to non-cannabis users. It has been proposed, therefore, that the increased caries experience is due to the joint effects of reduced salivary buffering capacity and immediate desire to consume sweet foods and drinks after cannabis consumption.

75.2.3.2 Mucosal-Related

Cannabis has also been found to have a detrimental effect on the oral soft tissues, possibly due to a number of factors including the higher temperature at which cannabis burns compared with tobacco causing irritation to the oral mucosa together with the carcinogenic effect of tetrahydrocannabinol (THC).

Layman [38] and colleagues [6] were the first researchers to conclude an association between smoking cannabis and gingival enlargement. More recently a case report presented marijuana-associated gingival enlargement or swollen gums in men [54]. Since, phenytoin and cannabidiol (CBD) have common anticonvulsant properties [71], it has been suggested that the gingival enlargement observed in marijuana users could be caused by the same mechanisms to that of phenytoin [66].

Increased prevalence of leukoedema and density of *Candida albicans* has been reported in cannabis users [20, 80]. Leukoedema is thought to be a result of cellular damage due to local irritation of smoking cannabis, whereas it is the immunosuppressive effects of THC that are proposed to permit candida proliferation. Nicotinic stomatitis (smokers' palate) has been reported in marijuana smokers [20, 54]. Uvulitis has also been extensively reported in cannabis smokers whether acute or chronic [54].

Theoretically, a role of THC as a risk factor of oral cancer has been proposed; however, the evidence remains ambiguous. It is thought that the increased amount of carcinogenic hydrocarbons, such as benzo-alpha-pyrene, that is higher in marijuana tar compared to tobacco tar and that marijuana smoking involves inhaling three times more tar compared to tobacco smoking [33] increases the risk of head and neck cancer. Moreover, it has been suggested that it is through a dose-response relationship

between frequency and duration of cannabis smoking [91] that gives rise to an increased risk of oral cancer. In contrast, Rosenblatt et al. [63] and Lyewellyn et al. [39] found little evidence for an association between cannabis use and oral cancer.

75.2.3.3 Other

The experience of dry mouth immediately after cannabis use has been reported by nearly 70% of the people in Darling et al.'s study [20]. However, accuracy of the duration of having a dry mouth was not established by Darling [20].

75.2.4 Stimulants and Oral Health: Cocaine (Table 75.2)

Snorting and smoking cocaine are the main methods of use. In order to smoke cocaine, it must be converted into a smoke-able form and so sodium bicarbonate is added. Heating this produces a cracking sounding giving it the name 'crack'. A third form of use is rubbing of cocaine into gums or oral mucosa. Much of the oral health effects may be explained by the method of administration.

75.2.4.1 Tooth-Related

Bruxism, worn teeth [49] and tooth abrasion [27] have been observed in cocaine users. The resulting clenching and grinding of the teeth causes painful facial muscles and temporomandibular joints [27]. Cocaine hydrochloride can decrease salivary pH causing loss of calcium from the enamel, giving the smooth and occlusal surfaces of the teeth a smooth and glossy appearance [11]. Cocaine hydrochloride also causes tarnishing of gold crowns [17]. More recently, Cury et al.'s [19] work showed that crack cocaine or cocaine users had four times increased risk of dental caries.

75.2.4.2 Mucosa-Related

Gingival lesions at the site of cocaine application have been reported in a case report by Gandara-Rey et al. [28]. Of the four cases described, the patients used cocaine to relieve pain due to cluster headaches. Intraorally it was observed that they had erythematous lesions at the site of application, i.e., the alveolar gingiva and buccal mucosa. For a patient with history of 4 years of cocaine use, the patient had a necrotic lesion leading to bone exposure. These lesions have been attributable to the vasoconstrictive mechanisms of cocaine's pharmacodynamics.

Administration of local anaesthesia after recent cocaine use may induce an acute increase in blood pressure. Therefore, local anaesthetic without epinephrine should be used if cocaine use is suspected and dental treatment should be postponed for 6–24 hours to allow for its elimination [90].

75.2.4.3 Other

Other orofacial effects of cocaine addiction include perforation of nasal septum and palate. Nasal septum perforation is a complication observed in nearly by 5% of cocaine snorters [40]. This is explained by the vasoconstrictive action of cocaine, causing local ischemia resulting in the necrosis of the nasal septum and its surrounding tissues. Chemical irritation by contaminants in 'cut' cocaine further aggravates tissue necrosis. The use of pens or pencils to remove excessive cocaine from the nose increases the risk of nasal perforation [69]. Finally, snorting cocaine decreases the nasal defence against infection by damaging the 'nasal mucociliary transport system'. Therefore, reduction in nasal support results in a broad flat nose known as 'saddle nose deformity' [40]. Palatal perforations are follow-on from nasal perforation. These lesions are mostly seen on the hard palate. Sizes vary from a diameter of a pinhole to 15 mm. Perforation of the hard palate results in speech impairment and difficulties in eating or drinking due to nasal regurgitation.

75.2.5 Stimulants and Oral Health: Amphetamines and Related Compounds

Amphetamines are classified as CNS stimulants. They give a sense of well-being, combat sleepiness, suppress appetite and are relatively easy and

cheap to obtain and purchase [26, 57]. The drugs described in this section are (i) methamphetamine (MA) (known as 'Meth' or 'Speed') and (ii) 3,4-methylenedioxymethamphetamine (MDMA) (known as 'Ecstasy', 'XTC' or 'Adam'). MA and MDMA can be taken orally, by snorting, smoking or injecting, as they are readily water and alcohol soluble. MA hydrochloride is produced in clear chunky crystals called 'ice' that can be smoked and gives it names called 'Crystal Meth, Crystal Glass and Ice'. MDMA tablet is used orally but its powder can be snorted, inhaled or injected. Consumption of MDMA with alcohol, cannabis and cocaine has also been reported [76] and so the effects of amphetamines may be due to synergistic effects of alcohol, cannabis and cocaine upon the oral tissues.

75.2.5.1 Methamphetamine

Tooth-Related

Abuse of MA is associated with several negative effects on oral health. MA abusers generally present with rampant dental caries that clinically resembles early childhood caries. This form of presentation is known as 'Meth Mouth' [4]. Teeth are described by users as 'blackened, stained, rotting, crumbling or falling apart' [4]. The dental caries pattern in chronic Meth users involves 'buccal smooth surfaces of posterior teeth and interproximal surfaces of anterior teeth' [67]. Caries progression in MA users is described as slow and goes through periods of arrest instead of progressing rampantly [58]; however, eventually process progresses to involve the entire tooth [30]. This pattern of intermittent caries activity differentiates the carious lesions in MA users from the caries seen in cocaine and other narcotic drug users. Numerous studies have identified increased incidence of caries among MA users compared to non-MA users [45, 60, 61]. A combination of factors have been documented to cause 'Meth Mouth' suggesting it may be related to xerostomia (dry mouth), long periods of poor oral hygiene, frequent ingestion of sugar and fizzy drinks and acidic nature of MA [30, 32, 41].

Mucosa-Related

Strong evidence of oral health neglect has also been reported in MA users along with higher levels of gingival bleeding and periodontal disease among crystal meth users [60, 61].

Other

The role of MA in causing xerostomia is unclear; however, some explanations have been provided by Shaner et al. [67] associated with vasoconstriction and reduction in salivary flow and dehydration due to hyperactivity. Rommel et al. [60, 61] reported that 72% of MA users compared to non-MA users had dry mouth. With regard to clinical findings, their results suggested poorer saliva production and lower salivary pH values among MA users.

Tooth wear in MA users has also been associated as an outcome of increased bruxism [30]. Following the hyperactive phase after Meth use, users can begin 'tweaking' during the drug's wear off phase. This feeling is characterised by restless anxiety, irritability, fatigue and dysphoria, and it is during this phase they have a tendency to grinding and clenching of teeth and jaws resulting in temporomandibular joint pain [60, 61, 68].

75.2.5.2 MDMA (3,4-Methylenedioxy-Methamphetamine)

Tooth-Related

Ecstasy use has been reported to cause tooth erosion and dental caries as a result of its xerostomic effects. Dry mouth, for instance, was reported by 93–99% of Ecstasy abusers compared to non-Ecstasy users [41, 42, 55]. MDMA induces neuromuscular stimulation causing muscle rigidity and breakdown of muscle fibres leading to a raised body temperature. As this drug is popular among people who attend 'rave' parties, in combination with vigorous dancing in hot and crowded clubs, it could lead to an excess water intake [15]. Further complication of the drug is, therefore, that it stimulates the secretion of antidiuretic hormone, which is normally responsible for

regulating and balancing the amount of water in the body. Therefore, to prevent hyponatraemia, consumption of isotonic drinks is recommended; however, to relive dry mouth and dehydration, Ecstasy users consume fizzy sugary drinks, which ultimately leads to dental caries and tooth wear [42].

Mucosa-Related

In a questionnaire-based interview conducted by Verheyden et al. [79] on 466 regular MDMA users, symptoms of mouth ulcers were reported by 2.3% 24 hours later and 8.2% 24–48 hours later after use. Tropical application of the drug can also have profound effects on the oral mucosa. Brazier et al. [16] reported 'a swelling of the maxillary vestibule in relation to upper front teeth with some tooth mobility and pain on percussion' following use of MDMA. At the 2-day follow-up, once the swelling had resolved, mucosal fenestration with exposure of the underlying alveolar bone was observed. This clinical presentation was associated with placing Ecstasy tablet on the site of the lesion. In a second case report by Ahmed et al. [2], 'an 18-year-old patient presented with extensive perioral and intraoral swelling, consisting of substantial oedema of the upper and lower labial mucosa, bilateral buccal mucosa, dorsum of the tongue, and the bilateral tonsillar region. Grossly the appearance was of a greyish-white cast with a coarsely wrinkled surface after consumption of one Ecstasy tablet with unknown quantity of alcohol about two hours prior'.

Other

Jaw clenching (bruxism) and grinding of teeth have been frequently reported among Ecstasy users [41, 42, 55, 79]. There have been reports of painful jaw muscles [41], jaw clenching up to 24–8 hours after MDMA consumption [79], and tooth wear [42, 47].

MDMA interacts with medication prescribed to manage temporomandibular joint pain such as tricyclic antidepressants. Caution should be taken while administering local anaesthetic containing epinephrine.

75.2.6 Other Drugs and Oral Health: Tobacco (Nicotine)

Tobacco is smoked as cigarettes, cigars, bidis, kreteks, pipe or hookah. The use of e-cigarettes is one of the fastest-growing method of smoking. Socioeconomic, geographic and cultural factors strongly influence the type of smoking. Reverse smoking, mostly seen in India and South America, is a form in which the burning end of the cigarette or cigar is held inside the mouth. Smokeless tobacco is also used by many and is consumed either by sniffing (dry snuff) or chewing. Tobacco that is chewed comes in the form of loose leaf in pouches, plug or twist form which is placed in the mouth, cheek or lip and is either sucked or chewed. Tobacco pastes or powders are consumed in a similar way and applied to the gums or teeth. Twenty-eight carcinogens have currently been identified in smokeless tobacco [35]. Nicotine is an addictive chemical present in all tobacco products which is absorbed through the oral mucosa with a higher absorption occurring from products with a higher pH [10]. Nicotine has a wide range of negative effects on oral health. Therefore, the negative impact of tobacco consumption relates to both smoked and smokeless forms of consumption and will be discussed separately in this section.

75.2.6.1 Tobacco Smoking

Tooth-Related

There is limited evidence to support the role of tobacco smoking in caries causation. A systematic review published in 2013 [7] could identify just four studies to support an association between tobacco smoking and dental caries. It concluded by highlighting that the study quality was poor, hence questioning the substantiation for such an association. Saliva acts as a protective factor for dental caries and usually younger age groups have naturally higher salivary flow rate; therefore old age can be considered a confounder while identifying such as association. Further, lifestyle and socio-economic factors have been associated with caries experience. Therefore, the evidence supporting the actual role of tobacco smoking is

still lacking. Pipe smoking, on the other hand, can lead to tooth abrasion at the site of pipe placement.

Mucosal-Related

Tobacco smoking is the primary risk factor for oral and oropharyngeal cancer. Numerous studies describe tobacco-associated risk of oral cancer to be dose dependent, with the risk increasing significantly with increasing frequency and duration. A meta-analysis on 12 studies estimated cancer risk in the USA, Uruguay, Sweden, Italy, China, India, Taiwan and Korea reported the pooled cancer estimate to be 3.43 times higher in smokers compared to non-smokers [29]. Wyss et al. [88], in their work, used the pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium (comprising 13,935 cases and 18,691 controls in 19 studies from 1981 to 2007). They [88] identified that cigarette smokers aged 45 years and above had higher risk of oral cancer compared to cigarette smokers under 45 years of age. They also found an independent increased risk of head and neck cancer with cigar (OR = 3.49) and pipe smoking (OR = 3.71). There is further evidence suggesting that there is a three times increased risk of oral cancer among bidi smokers compared with cigarette smokers [53]. Work by Montazeri et al. [43] has linked pipe smoking with oral cancer and precancerous lesions. The role of tobacco in causing cancer is due to the mutagenic actions causing chromosomal damage, impairing the cell's regulatory processes. The two primary carcinogens present in tobacco smoke are 'benzo (a)-pyrine' and 'nitrosamines' (TSNA). Despite tobacco smoke being a major risk factor for oral cancer, relatively lower proportions of those exposed develop malignancy. This is thought to be due to individual variation with regard to the ability of their enzyme systems to metabolise and deactivate the tobacco carcinogens.

Oral leukoplakia and erythroplakia are the two known precancerous lesions which are likely to transform into oropharyngeal cancer over time. Presence of oral epithelial dysplasia is the hallmark for cancer development [83] and appears mostly in exclusive tobacco consumptions and exclusive alcohol consumption. Other non-cancerous effects of tobacco smoking on mucosa include candidal infections, smokers' melanosis and smoker's palate [82].

Smoking has a major negative impact on periodontal health. A systematic review involving 70 cross-sectional, 14 case-control and 20 cohort studies indicated a strong association between smoking and periodontal disease [8]. Numerous mechanisms have been postulated to explain tobacco smoking-related periodontal pathogenesis: (i) smoking may cause a disruption in the composition of microflora due to a decrease in the oxygen levels in the periodontal pockets, (ii) disruption in cell-mediated and humoral-mediated immunity of the host, (iii) alteration of periodontal inflammatory responses and (iv) increased secretion of bone resorbing factors. Furthermore, tobacco smoking and its association with tooth loss have also been documented extensively in cross-sectional [48] as well as longitudinal studies [21].

Warnakulasuriya et al. [82] in their work summarise additional studies to explore this association corroborating the above findings. They [82] point to studies outside of the Europe and the USA where the evidence to support the association between smoking and periodontal disease is poor.

Other

Warnakulasuriya et al. [82] in their work report other causes of tobacco smoking such as black/brown discoloration of teeth and dental restorations and dentures, alteration of taste and smell, black hairy tongue (coated tongue), smoker's breath and impaired and delayed wound healing after tooth extractions or any other surgical procedure. Although there is limited evidence, current literature suggests dental implant failure is more common among smokers than non-smokers. In a recent systematic review and meta-analysis, maternal passive smoking exposure was found to be associated with a 1.5-fold increase in the risk of non-syndromic orofacial clefts which is similar to that reported for active smoking previously [64]. Therefore, evidence of an association between maternal passive and active cigarette smoking and risk of oral cleft exists.

75.2.6.2 Smokeless Tobacco

Tooth-Related

Smokeless tobacco has been identified to be associated with cervical abrasion and root caries [59] along with an increased prevalence of decayed tooth surfaces including root surfaces [75]. Increased susceptibility to root caries results from gingival recession caused by smokeless tobacco and its high sugar content.

Mucosa-Related

Similar to tobacco smoking, smokeless tobacco has also been attributed to oral carcinogenesis. At present, the oral use of smokeless tobacco is practised in Africa, North America, Southeast Asia, Europe and the Middle East [35]. A systematic review on South East Asian countries [9] identified 11 publications on chewing tobacco and oral cancer, where the pooled odds ratio was 4.3 (3.1–5.8) after adjusting for alcohol and smoking. In the same study, chewing paan/betel quid with tobacco significantly increased the odds of oral cancer (adjusted for alcohol and/or smoking OR = 6.3). The study also identified a dose-response relationship. Two meta-analyses on American and European populations have documented the effects of smokeless tobacco and oral cancer. Weitkunat et al. [84] in their meta-analysis identified 38 studies for all types of smokeless tobacco of which six studies provided information on oral cancer relative risks specifically among never smokers. The pooled data from these studies were suggestive of an association between oral cancer and smokeless tobacco. In a second meta-analysis on population in the USA and Nordic countries, Boffetta et al. [14] stated that the relative risk for oral cancer was 1.8 (95% CI = 1.1–2.9; $p < 0.01$). More recently, Wyss et al. [89] in their study using pooled US data showed that snuff was strongly associated with cancer of the oral cavity among never cigarette smokers (OR = 3.01, 95% CI 1.63–5.55) than tobacco chewing (OR = 1.81, 95% CI 1.04–3.17). Berthiller et al. [9] argue that there may be differences in the type of smokeless tobacco used in South East Asia compared to North America and Europe, further highlighting the differences in the effect sizes and the effect of geography on the relationship between oral cancer and smokeless tobacco.

Leukoplakia or snuff-induced lesions present as white plaques with a wrinkled surface are the premalignant lesions usually seen at the site of tobacco placement [73].

Some studies have shown an association between smokeless tobacco consumption and increased incidence of gingival recession [44] whereas others have not [34]. Studies conducted among Asian populations have shown that smokeless tobacco users tend to have higher scores and risk for periodontal disease [5]. Similar finding was reported by a study based on National Health and Nutrition Examination Survey III data conduced in the US [25]. The pattern of periodontal destruction which has been reported suggests that mandibular tooth loss and gingival recession is observed at sites adjacent to mucosal lesions [44]. The mechanism of periodontal destruction cause by smokeless tobacco is similar to that for tobacco smoking.

75.2.7 Other Drugs and Oral Health: Gabapentin

Gabapentin and pregabalin have been reclassified as a Class C controlled substance in the UK [31], and is it known to have potential effects on oral health. This is primarily as a consequence of its anticholinergic effects upon salivation resulting in dry mouth. Therefore, dental caries is an unwanted outcome of the use of both gabapentin and pregabalin [12] (Table 75.3).

75.3 Conclusion

This chapter has presented the effects of substance use, including tobacco, alcohol and drugs upon on oral health. These effects range from dental caries, periodontal disease to oral cancer. These tooth and mucosa-related dental diseases are caused directly from the consumption of substances or arise indirectly as a consequence. The apparently easy access to substances and their

use makes it crucial for health care providers to be aware of the oral manifestations and respond in the best interest of any patient with a history of alcohol and drug use. We call for the inclusion of oral health as part of the common risk factor approach as an integral part of the care for people with a history of drug and alcohol use.

75.4 Clinical Relevance

This chapter points to the need for multidisciplinary working between medical and dental practitioners involved in the care of people with a history of substance use. Dental practitioners who see patients on a regular basis are in a position to notice and identify early signs of substance use in the dentition and oral cavity. Complaints about xerostomia or specific white patches in the mouth should alert dentists to be concerned of their patients' health status. Addiction medicine specialists, treating people with a history of alcohol and drug use, need to be mindful of the effect of these substances upon the oral tissues and the role of dentist in this regard. Addiction medicine specialists should be encouraged to complete an oral health assessment of their patients as part of a multidisciplinary team (MDT) approach and to have referral pathways for dental management. This is of central importance, since improved oral health, being able to smile, speak to others, eat and kiss, has a significant effect upon quality of life – reducing stigma and increasing confidence and self-esteem for those with a history of substance use. Therefore it is imperative that health care providers work in unison to provide holistic care for those with and recovering from substance use, to quote a survivor of substance use, 'The effects are transformative'.

Key Points

- Substance use, including tobacco, alcohol and drugs, has a severe detrimental effect upon oral health.
- People with a history of alcohol and drug use have a greater experience of xerostomia, dental caries, periodontal disease and oral cancer.
- People with a history of alcohol and drug use have greater unmet treatment need due to avoidance of dental treatment, dental anxiety and increased pain threshold associated in particular with opiate use. Health care providers should be aware of the oral manifestations and respond in the best interest of any patient with a history of alcohol and drug use.
- Preventive dental treatment must be provided especially for those with xerostomia in the form of high fluoride concentration toothpaste of 2500 ppm or 5000 ppm.
- Clinicians should be aware of the potential of drug interactions before providing local anaesthesia with ephedrine for dental treatment.
- On initial examination, treatment should be provided to assist the patient to be pain free; further treatment should be tailored to patient need and their current substance use status.

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Gastrointestinal Disorders Related to Alcohol and Other Drug Use

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Guang Chen and Paul S. Haber

Contents

Abstract

Acute and chronic gastrointestinal (GI) problems are common in the setting of alcohol, tobacco, and prescription and recreational drug use. Excessive alcohol use is associated with injury to all parts of the gastrointestinal tract. Alcohol-related liver disease, alcohol-related pancreatitis, and gastrointestinal cancer are important causes of morbidity and mortality related to excessive alcohol use. Tobacco use is associated with gastroesophageal reflux, peptic ulceration, gastrointestinal cancer, and Crohn's disease but appears to protect against ulcerative colitis. Opioids have important effects on gastrointestinal secretion and motility. Narcotic bowel syndrome may develop in the setting of escalating doses of opioid analgesia. Cannabis use is associated with both relief of nausea and vomiting associated with chemotherapy and adverse gastrointestinal effects. Cannabinoid hyperemesis syndrome should be considered in the setting of heavy cannabis use and recurrent vomiting. The body packing syndrome is sporadically encountered at hospitals near international transport hubs and can be challenging when encountered.

G. Chen
Drug Health, Western Sydney Local Health District, Westmead, NSW, Australia

P. S. Haber (✉)
Drug Health Services, Sydney Local Health District, The University of Sydney Central Clinical School, Sydney, NSW, Australia
e-mail: paul.haber@sydney.edu.au

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76.1 Introduction

This chapter describes gastrointestinal (GI) effects of gastrointestinal disorders secondary to the effects of alcohol, tobacco, prescription, and recreational drugs. Excessive alcohol use is associated with injury to all parts of the gastrointestinal tract. Several detailed reviews have been published [22]. The gastric mucosa also contributes to the oxidation of alcohol. Within the gastrointestinal tract, liver disease and pancreatitis are important causes of morbidity and mortality related to excessive alcohol use. Symptoms of intestinal dysfunction are common among patients with alcohol dependence and include diarrhea and malabsorption. Tobacco use is associated with gastroesophageal reflux, peptic ulceration, gastrointestinal malignancy, and Crohn's disease but appears to protect against ulcerative colitis. Opiates have important effects on gastrointestinal secretion and motility. Other drugs such as cannabis and cocaine uncommonly affect the gastrointestinal tract. The body packing syndrome is sporadically encountered at hospitals near international transport hubs and can be challenging when encountered.

76.2 Alcohol

The relative risk of alcohol-related GI toxicity appears to differ between affected tissues and between benign and neoplastic disorders. Similarly the pattern and type of beverage have not been consistently shown to predispose to any specific GI effects of alcohol.

76.2.1 Parotid Glands and Oral Cavity

Painless symmetrical enlargement of the parotid glands (termed sialosis or sialadenosis) is common in patients with alcohol-related liver injury [120]. Abelson et al. [1] found 61% of patients with alcohol-related cirrhosis had enlarged parotid glands. Sialosis is characterized by the triad of acinar cell hypertrophy, myoepithelial degeneration, and neural degeneration. The effect of alcohol use on salivary function in humans is controversial with reports of increased, unaltered [134], and decreased salivary flow [120]. Moreover, patients with alcohol use disorder may suffer from inflammation of the tongue (glossitis) and the mouth (stomatitis). It is unclear, however, whether these changes result from poor nutrition or reflect a direct effect of alcohol on the mucosa.

76.2.2 Esophagus

Both acute and chronic alcohol consumption are associated with symptomatic gastroesophageal reflux disease (GERD). Reflux episodes were increased by 60 g of ethanol given with a meal to healthy subjects without alcohol dependence (Kaufman and Kaye 1979). These episodes were measured by measurement of esophageal pH for 3 h after a standard meal and most were asymptomatic. A number of mechanisms have been identified that may contribute to these effects of alcohol [44]. Direct application of 30% ethanol, but not lower concentrations, causes injury to the esophageal mucosa. An acute dose of alcohol reduces lower esophageal sphincter pressure (LESP) [74] and reduced maximal LESP stimulated by a meal [103]. Chronic excessive alcohol use is also associated with manometric abnormalities relevant to GERD that recover after a month of abstinence [83, 134].

Upper gastrointestinal bleeding (UGIB) is more frequent in patients with alcohol use disorder, especially those with cirrhosis. In a 2007 UK audit of 6,750 patients with acute UGIB, 9% had known cirrhosis and 26% a history of alcohol excess [69]. Mallory–Weiss syndrome is characterized by massive bleeding caused by tears in the mucosa at the cardio-esophageal junction after vomiting. The syndrome accounts for 5–15% of all cases of bleeding in the upper GI tract. Mallory–Weiss syndrome prevalence varies; it is uncommon in China [179]. In one series, almost

50% of these patients were associated with repeated retching and vomiting following excessive acute alcohol consumption [89].

76.2.3 Stomach

76.2.3.1 Alcoholic Gastritis

The clinical term "alcoholic gastritis" is nonspecific and is often used to refer to a broad range of upper gastrointestinal symptoms experienced by patients who drink alcohol excessively. It has been surprisingly controversial despite considerable study [44, 86]. The term gastritis is used to denote inflammation associated with mucosal injury. Epithelial cell damage and regeneration without associated inflammation are referred to as "gastropathy" [36]. It is often difficult to establish with certainty that a particular agent, such as alcohol, has caused gastropathy. Exposure of the gastric mucosa to 20% alcohol induces gastric mucosal injury. Lower concentrations are not toxic, whereas higher concentrations lead to extensive hemorrhagic injury [86].

76.2.3.2 Dyspepsia and Ulcer

In patients admitted for treatment of alcohol dependence, gastric hemorrhagic and erosive lesions and ulcers were commonly seen [129]. Interestingly, Brown et al. [20] found that gastritis was not more common in patients with cirrhosis than healthy controls. Gastritis in patients with alcohol use disorder is strongly associated with H. pylori infection, with histological and symptomatic relief after eradication of the organism, but no improvement with abstinence from alcohol [158]. The presence of alcohol dehydrogenase (ADH) activity in H. pylori organisms may tend to protect the alcohol drinking host from infection as exposure to alcohol leads to the generation of acetaldehyde that may be bactericidal. Alcohol use disorder is associated with reduced medication compliance and delayed healing [123], but the healing of established ulcers is not retarded by moderate alcohol consumption [11].

The available evidence does not convincingly support the conclusion that alcoholic beverages cause chronic chemical gastropathy [26]. Moreover, there does not appear to be a link between chronic atrophic gastritis and alcohol consumption [2]. Other causes may be account for gastritis-like symptoms. Fatty liver may cause upper abdominal discomfort and nausea. It has been proposed that alcohol may directly induce vomiting by central stimulation of the chemoreceptor trigger zone in the area postrema of the floor of the fourth ventricle in the absence of peripheral disease [131]. In addition, bacterial overgrowth has been reported to be more common in patients who drink alcohol excessively and may also contribute to upper abdominal symptoms and diarrhea [68].

76.2.3.3 Alcohol-Related Pancreatitis

Approximately 10% of patients with chronic alcohol use disorder develop attacks of clinically acute pancreatitis. Conversely, alcohol is responsible for approximately 30% of cases of acute pancreatitis in the USA [174]. In a large cohort study from the USA, alcohol was estimated to account half of the cases of chronic pancreatitis, and the incidence has increased in the past 20 years [172] similar to the UK [79].

Definitions

The term acute pancreatitis refers to an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems. Chronic pancreatitis is characterized by chronic inflammation, glandular atrophy, and fibrosis. Clinically, it manifests pain with exocrine or endocrine insufficiency. The revised Atlanta classification of acute pancreatitis identified two phases of the disease: early and late. Severity is classified as mild, moderate, or severe. Mild acute pancreatitis, the most common form, has no organ failure and local or systemic complications and usually resolves in the first week. Moderately severe acute pancreatitis is defined by the presence of transient organ failure, local complications, or exacerbation of comorbid disease. Severe acute pancreatitis is defined by persistent organ failure, that is, organ failure >48 h. Local complications are peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst, and

walled-off necrosis (sterile or infected). Morbidity and mortality is high in this group [8].

Etiology

The most common associations of acute pancreatitis in Western societies are gallstones and heavy alcohol use which together account for approximately 75% cases. Yadav et al. [172] found that while alcohol was the most common etiology in men (59%), it was a less common etiology in women (28%). Nonetheless, only a minority of heavy drinkers develop clinically evident pancreatic disease.

The association between alcohol and pancreatitis appears to be dose-related. Pancreatitis typically occurs in subjects who have consumed greater than 100 g alcohol per day for at least 5–10 years and rarely if ever follows an isolated large alcoholic binge. The risk of pancreatitis may be increased in developing countries raising the hypothesis that impurities within country-made alcoholic products may cause pancreatic injury [9]. Once the disease is established, episodic heavy drinking often precipitates relapses. Relapses have been described after only 1 day of recurrent drinking. Pancreatitis is common among patients with HIV particularly in association with heavy alcohol use [38, 165]. Many patients with acute alcoholic pancreatitis progress to chronic pancreatitis, with continued alcohol abuse being a key prognostic factor [5].

Other than gallstones, relatively common causes for pancreatitis that should be considered include hypercalcemia of any cause and severe hypertriglyceridemia. Hypertriglyceridemia (greater than 10 mmol/l (approximately 1,000 mg/dl) with lipemic serum) of any cause is associated with recurrent attacks of pancreatitis [56]. Although alcohol abuse is a known cause of hypertriglyceridemia, the majority of cases of alcoholic pancreatitis are not associated with marked hyperlipidemia [62]. Other causes include pancreatic trauma, duct pathology, and a number of drugs. In most series, about 10% of cases are idiopathic.

Predisposing Factors

Numerous investigators have attempted to account for this individual susceptibility by studying associations between alcoholic pancreatitis and potential risk factors. These studies have been previously reviewed [63] and have focused on the amount, type, and pattern of alcohol consumption, genetic markers, diet [166], hypertriglyceridemia [62], tobacco consumption [64], and pancreatic ischemia. Numerous genetic markers have been studied, but there is insufficient evidence to consider that any of the above factors are well established. Two important genetic mutations are linked to pancreatitis, but not the alcoholic form. Gain-of-function mutations in the serine protease 1 gene (PRSS1) on chromosome 7q35, which encodes cationic trypsinogen, result in an autosomal dominantly inherited form of hereditary pancreatitis. Mutations in the cystic fibrosis gene (CFTR) have been associated with an autosomal recessive form of pancreatitis [121]. In alcoholic pancreatitis, a mutation of the gene coding for pancreatic secretory trypsin inhibitor (SPINK1) has been described in 5.8% of patients compared with 1% of alcoholic controls [169]. Mutations in chymotrypsin C (CTRC) have also been identified in pancreatitis [127]. These two studies support the concept that genetic factors influence susceptibility to pancreatitis, but given that only 6% and 3% of the subjects carried these mutations, respectively, individual susceptibility to this disease remains largely unexplained.

Pathogenesis

Two important factors leading to tissue injury in pancreatitis are autodigestion and oxidant stress. Several lines of evidence indicate that activated digestive enzymes play an important role in pancreatitis [61]. Oxidant stress is characterized by the production of reactive oxygen species that are atoms or molecules containing oxygen with an unpaired electron in the outer shell (free radicals). Free radicals are highly reactive and bind to lipids, proteins, and nucleic acids leading to cellular injury [50].

Several mechanisms have been proposed to explain why alcohol-related pancreatitis occurs only after many years of alcohol abuse and not after a single binge in humans. These include the role of progressive pancreatic fibrosis related to activation of pancreatic stellate cells by acetaldehyde and oxidative stress [60] and the potential for endotoxin to precipitate pancreatitis in the

alcohol-exposed gland [162]. Plasma lipopolysaccharide levels have been shown to be significantly higher in drinkers (either after chronic alcohol intake or a single binge) compared to nondrinkers and in patients with alcoholic liver disease compared to those with liver disease of other etiologies [15].

Diagnosis

A confident diagnosis of pancreatitis can often be made on the basis of an attack of severe abdominal pain and tenderness with elevation of the serum amylase and or lipase more than three times the upper limit of normal and with imaging studies suggestive of inflammation in and around the pancreas.

Newer tests that may be more specific for acute pancreatitis include trypsinogen activation peptide and trypsinogen-2 but are not widely available [175]. Gallstones should be excluded by ultrasound examination. In cases with a negative ultrasound, serum alkaline phosphatase or transaminase levels raised at least twofold suggest associated gallstones which may be detected by repeat ultrasonography or endoscopic retrograde cholangiopancreatography (ERCP) [55, 160]. Magnetic resonance cholangiography [143] and endoscopic ultrasound are increasingly supplanting ERCP for diagnosis of gallstones in this setting. Dilated common bile duct has been recently described in patients on methadone and with opioid dependence in the absence of gallstones [130].

Assessment of Severity

Several clinical findings, including thirst, poor urine output, progressive tachycardia, tachypnea, hypoxemia, agitation, confusion, a rising hematocrit level, and a lack of improvement in symptoms within the first 48 h, are warning signs of impending severe disease. Admission to an intensive care unit should be considered. Enzyme levels do not correlate well with disease severity. A number of clinical and laboratory scoring systems have been developed to identify patients at risk of complications so that they may be treated more intensively at an earlier stage.

Contrast-enhanced CT scan is now widely performed to detect pancreatic necrosis and complications of severe pancreatitis such as fluid collections, pseudocysts, and abscesses [85]. Caution in the unrestricted use of contrast-enhanced CT scans appears warranted. CT scanning without contrast can detect most diagnostic features of pancreatitis and is often performed. MRI is an option that may spare radiation exposure.

Treatment

Overall, about 20% of patients with acute pancreatitis have a severe course, of these 10–30% will die, despite improvements in intensive care treatment [106]. Severe cases, particularly those associated with respiratory or renal failure, require treatment in an intensive care unit.

Initially, patients are treated with bed rest, analgesics, intravenous fluids, and fasting. Intravenous opiates may be required, usually in the form of a patient-controlled analgesia pump. Fentanyl is being increasingly used due to its better safety profile, especially in renal impairment. Meperidine (pethidine) has traditionally been favored over morphine has a short half-life and repeated doses can lead to accumulation of the metabolite normeperidine that causes neuromuscular irritation and, rarely, seizures. Ebbehøj et al. [40] showed the use of indomethacin suppositories (50 mg twice daily) reduced opioid requirements in 30 patients with acute pancreatitis without risk of gastrointestinal bleeding. There is currently no difference in the risk of pancreatitis complications or clinically serious adverse events between opioids and other analgesia options [10].

Fluid resuscitation should be goal directed including monitoring heart rate, mean arterial pressure, serum urea concentration, and urine output [32]. Aggressive fluid resuscitation is associated with respiratory complications and abdominal compartment syndrome. Ringers lactate may be superior than normal saline [33, 170].

Early feeding is beneficial in acute pancreatitis and may reduce the risk of developing infected pancreatic and peripancreatic necrosis [167]. Delayed feeding (generally defined as >24 h) is associated with higher rates of infected peripancreatic necrosis, multiple organ failure, and necrotizing pancreatitis [7, 41, 182]. Success of early feeding has been demonstrated with low fat, normal fat, and soft or solid consistency, and

thus it is not necessary to start patients with acute pancreatitis on a clear liquid diet before advancement to a solid diet [77, 107]. Patients who cannot tolerate an oral diet may require enteral tube placement for nutritional support, which is preferred over total parenteral nutrition (TPN) [58, 82].

In patients with mild acute pancreatitis, there appears to be no role for prophylactic antibiotics in the absence of cholangitis or other extrapancreatic infections [78].

A number of antioxidant therapies have been evaluated for both acute and chronic pancreatitis given the role of oxidative stress in the pathogenesis of these diseases and encouraging results from early small trials. However, a well-conducted recent trial in acute pancreatitis found no benefit [138]. Protease inhibitors may limit the damage done by activated digestive enzymes, but it is not possible to commence treatment early enough in the attack of pancreatitis to be effective. Peritoneal lavage might improve the outcome by removing toxic inflammatory products from the peritoneum, but the results of controlled studies have been conflicting [104, 144].

ERCP with endoscopic sphincterotomy has been shown to reduce the morbidity of patients with unremitting severe gallstone pancreatitis in two randomized controlled studies [43, 110]. In general, ERCP should be performed within 72 h in those with a high suspicion of persistent bile duct stones (i.e., visible common bile duct stone on noninvasive imaging, persistently dilated common bile duct, jaundice, or rising liver chemistries) but plays no role in alcohol-related pancreatitis.

Surgery is uncommonly required, the main indication being necrotizing pancreatitis [105]. Observational data support delaying surgical debridement of necrotic tissue for at least two weeks if possible while the patient's medical condition is optimized and viable pancreatic tissue becomes evident. This approach appears to improve survival and maximize organ preservation. Pancreatic abscess carries a very high mortality and is an absolute indication for drainage by open surgery or percutaneous techniques. Multiple procedures may be required. Small pseudocysts may resolve spontaneously, but large or symptomatic ones usually require drainage via endoscopic, percutaneous, or operative techniques [101].

Chronic Pancreatitis (CP)

Recurrent episodes of acute pancreatitis, clinical or subclinical, may lead to chronic pancreatitis. Chronic excessive consumption of alcohol is the most common cause and accounts for approximately 75% of cases in Western societies. Interestingly idiopathic pancreatitis is the most common type in India (tropical pancreatitis) and China, accounting for approximately 70% of all cases of CP [53].

Clinical Features

The main clinical problem is usually pain and this may be very challenging. Like that of acute pancreatitis, the pain of chronic pancreatitis is typically diffusely located in the upper abdomen and may radiate to the back when severe. Pain tends to increase with meals and decreases appetite and food consumption and often results in weight loss. A minority present without pain. The other manifestations are endocrine (diabetes mellitus) and exocrine failure (steatorrhea). Weight loss is common but typically is mild. Vitamin deficiency is generally subclinical. Investigations may reveal malabsorption of fat-soluble vitamins and osteopenia. Other complications include pseudocyst formation, bile duct or duodenal obstruction, pancreatic ascites or pleural effusion, splenic vein thrombosis, pseudoaneurysms, and pancreatic cancer.

Treatment

Complete abstinence from alcohol is essential to minimize progression of the disease. Reassurance that the disorder is benign with a tendency to slowly remit is helpful. Nonnarcotic analgesia may suffice, but opioids are often required and should not be unreasonably withheld. A Danish randomized double-blind clinical trial of 64 patients found that pregabalin compared with placebo was a more effective analgesic after 3 weeks of treatment (36% vs. 24%; mean difference) [112]. Celiac plexus neurolysis improves

pain in about 60% of chronic pancreatitis patients. Recent advances in endoscopic ultrasound (EUS) technology and technique have resulted in the development of celiac ganglia neurolysis (CGN). EUS CGN is more effective than traditional celiac plexus neurolysis [176]. Pancreatic enzyme supplements have been evaluated for the treatment of pain, but the evidence is mixed. A trial of 1 month is sufficient to determine whether this works in practice. An emerging treatment option for resistant cases of pain is total pancreatectomy with islet autotransplantation (IAT) which has shown favorable outcomes with regard to pain reduction. Concurrent IAT enabled 46% of patients to be independent of insulin supplementation at 5 years [19].

There is mixed evidence concerning antioxidant therapy in chronic pancreatitis. One study using a combination preparation that contained selenium, beta-carotene, vitamin C, vitamin E, and l-methionine found reduced pain and improve quality of life [84]. Antioxidants were considered useful in a subset of patients with idiopathic and obstructive but not alcohol-related chronic pancreatitis in a non-randomized study [23]. Recent randomized trials yielded conflicting results, but antioxidant therapy was disappointing in alcohol-related pancreatitis [13, 18, 139].

The relationship between pancreatic duct obstruction and pain is not clear, but relief of obstruction is frequently clinically associated with relief of pain. Endoscopic approaches to dilate pancreatic duct strictures and remove calculi have been developed, and surgery is typically reserved for refractory cases. Extracorporeal shock wave lithotripsy (ESWL) creates millimetric fragmentation of pancreatic stones, which has improved the results of endoscopic therapy and may have additional indications in the treatment of patients with chronic pancreatitis. Whipple procedures or modified Whipple procedures are the most commonly performed procedure. The Puestow procedure (lateral pancreaticojejunostomy) involves decompression of a dilated pancreatic duct and side-to-side anastomosis onto a Roux-en-Y loop of jejunum. Two small randomized trials comparing endoscopic and surgical drainage of dilated pancreatic duct in chronic pancreatitis showed that surgery was associated with better long-term analgesia and quality of life [24, 35].

Exocrine failure is treated by dietary modification, vitamin therapy, and pancreatic enzyme replacement. Reduction of dietary fat intake reduces steatorrhea. Pancreatic enzymes are required with each meal and snack. The newer enteric-coated microsphere preparations are more potent and are preferred as they release enzymes only in the duodenum, reducing inactivation of lipase by gastric acid. Lipase inactivation is also due to failure of pancreatic bicarbonate secretion, and proton pump inhibitors may increase effectiveness of treatment. Normalization of fecal fat levels does not typically occur. Diabetes associated with chronic pancreatitis is known as Type 3c (pancreatogenic) diabetes mellitus. It is treated with dietary modification, treatment of malabsorption, and specific therapy. Some patients respond to oral hypoglycemic agents, but most require insulin. The diabetes is "brittle" in that the patient is susceptible to hypoglycemia due to loss of both insulin and glucagon secretion. Long-term surviving patients with this form of diabetes are prone to diabetic complications and should be monitored accordingly [67]. Patients with substantial steatorrhea may require fat-soluble vitamins. The 25-hydroxylated form of vitamin D (calcifediol) is more polar than vitamin D2 or D3 and is therefore more easily absorbed in patients with fat malabsorption. The serum calcium should be monitored for the first few weeks of therapy with this naturally occurring analogue since it is more potent than vitamin D2 or D3 and can more easily produce hypercalcemia.

76.2.3.4 Small Intestine

Diarrhea is common among those who drink alcohol excessively, both acutely and chronically. Multiple factors contribute to this problem including altered motility, permeability, and nutritional disorders. Small intestinal mucosal injury can occur after acute or chronic administration of alcohol. Alcohol is directly toxic to the mucosa. Perfusion of the hamster jejunum with 4.8% ethanol caused separation of the tip of the

villus epithelium forming blebs [12]. Gut microbiome research has recently shown that alcohol may lead to quantitative and qualitative dysbiotic changes leading to inflammation and hyperpermeability [42].

Mucosal blood flow is acutely increased with increased endothelial permeability [12]. Acute administration of alcohol leads to increased gut permeability resulting both in abnormal absorption of luminal content (such as endotoxin, which contributes to the pathogenesis of alcohol-related liver disease; see previous chapter) and abnormal leakage of mucosal contents (such as albumin). Ethanol also inhibits absorption of actively transported sugars, dipeptides, and amino acids. Many defects in absorption have been reported in patients with alcohol use disorder, including water [90, 91], carbohydrate, lipid, vitamins (notably thiamine, folate), and minerals (calcium, iron, zinc, and selenium) [12]. Folate deficiency, common among patients with alcohol use disorder, causes intestinal injury leading to malabsorption and diarrhea and further loss of folate. Ethanol may exacerbate lactase deficiency [117].

76.2.3.5 Colon

Portal hypertension may manifest uncommonly with hemorrhoids and rarely with colonic varices. Colonic varices appear as filling defects on barium enema and may occur in any part of the colon, most commonly in the rectum [44]. Alcohol has also been reported to cause non-ulcerative inflammatory changes in human colonic epithelium [21]. Inappropriate alcohol enema has been reported to cause a chemical colitis [71], and this may result from a toxic effect similar to the direct toxicity of alcohol on the gastric mucosa.

76.2.3.6 Alcohol and Gastrointestinal Cancer

Alcohol use is a recognized risk factor for several gastrointestinal neoplasms, including tumors of the tongue, mouth, pharynx, larynx, esophagus, stomach, pancreas, colon, and liver [48, 97, 125]. The effect of alcohol on cancer risk appears to be dose related. A recent comprehensive Australian overview of the literature reports that relatively modest average daily consumption, 25 g per day, within the guidelines for men in many countries including the USA, is associated with increased risk of gastrointestinal cancer. For example, consumption of 25 g per day was associated with a relative risk of 1.76 for oropharyngeal cancer and 1.52 for esophageal cancer, approximately 1.05 for colon and rectum and 1.17 for liver [96]. Cancer risk rose from zero alcohol consumption with no safe level, suggesting that the less alcohol consumed, the lower the risk of cancer.

The pathophysiology of ethanol-associated gastrointestinal malignancy is varied. Current understanding suggests that alcohol and its metabolites (in particular acetaldehyde) affect the generation of reactive oxygen species (ROS), transforming growth factor-b signaling pathways, the immune system, and cell death and apoptosis and have direct toxic effects, among them the ability to produce aberrant methylation of DNA, with an impairment of its self-repair capacity [59]. Ethanol-induced induction of CYP2E1 increases carcinogen activation, potentiates oxidant stress, diminishes DNA repair, suppresses immune responses, and increases nutritional depletion such as folate deficiency [108]. For example, alcohol-fed rats given N-nitrosomethylbenzylamine developed more esophageal tumors than non-alcohol-fed rats [109]. In addition, nonalcoholic components of alcoholic beverages may in turn add to carcinogenesis. Interestingly, racial differences appear to affect the risk of carcinogenesis. In Asia, a large proportion of individuals carry a mutation of acetaldehyde dehydrogenase (ALDH) 2 which has very low activity leading to an accumulation of acetaldehyde after alcohol consumption. Homozygotes of the ALDH2 mutation develop severe side effects with small amounts of alcohol and hence reduce their drinking and are protected against alcohol-related disorders. In Japan, heterozygosity is prevalent in patients with alcohol use disorder and is significantly associated with oropharyngolaryngeal (OR 11.14), esophageal (OR 12.50), and esophageal cancer concomitant with oropharyngolaryngeal and/or stomach cancer (OR 54.20) [180].

Oropharynx and Esophagus

Alcohol use is associated with an increased incidence of esophageal (and oropharyngeal) cancer,

especially in those who also smoke. A Chinese population-based case–control study of esophageal cancer with 902 cases and 1,552 controls showed the combined effect of heavy smoking and drinking among men was pronounced: OR was 12.0 for those who smoked more than 1 pack per day and drank more than 750 g of ethanol per week [51]. Blot et al. [14] reported a 5.8-fold increased risk among those who drink alcohol, a 7.4-fold increased risk among smokers, and a 38-fold increased risk among those who both drank and smoked. The risk of oral, oropharyngeal, and esophageal cancer is further increased in South American countries where there is a high prevalence of concurrent alcohol, tobacco, and mate use [171]. A recent large meta-analysis of 20 case–control and four cohort studies including a total of 5,500 cases concluded that there was no association between alcohol drinking and esophageal adenocarcinoma risk, even at higher levels of consumption [151, 152]. Moderate and high alcohol intake was associated with risk of esophageal SCC (ESCC). Light alcohol intake appears to be associated to ESCC mainly in studies in Asia, which suggests a possible role of genetic susceptibility factors [75]. The type and quantity of alcoholic beverages consumed may affect the risk of esophageal SCC. Spirits may have a higher risk than wine or beer; however, the cumulative amount of alcohol rather than the type is probably more important [157].

Stomach

The association between gastric cancer and alcohol consumption appears to be modest. Tramacere et al.'s [151, 152] meta-analysis of 34,557 patients provided definitive evidence of a lack of association between moderate alcohol drinking and gastric cancer risk. There was, however, a positive association with heavy alcohol drinking (RR 1.14 (95% CI 1.08–1.21) above 50 g/day). Gastric noncardia adenocarcinomas were more common than gastric cardia cancers. This is supported by the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study which also showed beer but not wine or spirits to be positively associated with gastric cancer [37]. Genetic susceptibility also appears to be important, especially in Asian populations. A Korean study showed ALDH2 polymorphisms were found to modify the susceptibility to the development of gastric cancer associated with alcohol intake, especially ALDH2 *1/*2 genotype [132].

Colonic

A large pooled analysis found that those who consumed 30–45 g per day of alcohol had no increased risk (RR) of colorectal cancer whereas this risk was increased those who consumed more than 45 g per day (RR 1.41 (CI 1.16–1.72)). The relative risks in men and women appeared similar, and the association was seen for cancers of all portions of the colon and rectum [28]. This data is reflected in the Netherlands Cohort Study [46], where risk appeared to increase from proximal colon (RR 1.29) through distal colon (RR 2.07, 95% CI: 1.03–4.18) and rectosigmoid cancer (1.69, 95% CI: 1.08–2.64) [16].

Pancreatic

The role of alcohol in pancreatic cancer pathogenesis appears to be uncertain. Retrospective analysis of the Swedish Inpatient Register suggested that excess risk for pancreatic cancer among patients with alcohol use disorder is small and could conceivably be attributed to confounding by smoking [177]. High lifetime ethanol intake from spirits/liquor tends to be associated with a higher risk, but no associations were observed for wine and beer consumption [52, 126].

76.2.4 Prescription Medications

76.2.4.1 Opioids

It has long been recognized that opioids affect gastrointestinal motility. A US survey of 98 patients with chronic non-cancer pain treated with opioids revealed constipation prevalence was 46.9%, nausea 27%, vomiting 9%, and gastroesophageal reflux disease 33%. Chronic abdominal pain was reported by 58.2% and 6.4% fulfilled the criteria of narcotic bowel syndrome (NBS; Fig. 76.1). It is attributed to the effects of

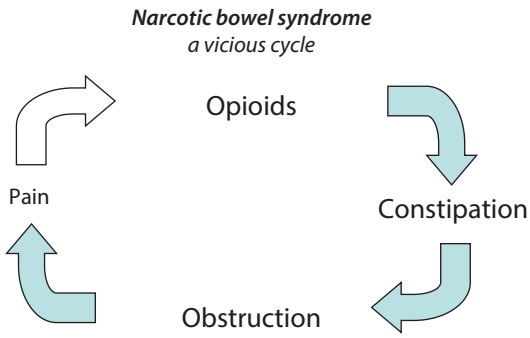

Fig. 76.1 Narcotic bowel syndrome

opioid drugs on bowel function and opioid-induced hyperalgesia [57]. Prevalence of constipation increased with duration of treatment. Health-related quality of life was low in patients with chronic abdominal pain [156]. Opioids act on gut function via all three receptor classes in the brain, spinal cord, and enteric nervous systems. Low doses act at enteric nervous system sites and higher doses also act within the CNS. These effects usually are manifest as constipation, but bloating, early satiety, and pain are possible. Occasionally, patients develop ileus or a syndrome characterized by a relatively high level of abdominal pain.

Opioids induce bowel dysfunction through several expected effects: blockade of propulsive peristalsis, inhibition of the secretion of intestinal fluids, and an increase in intestinal fluid absorption. Opioids decrease the activity of both excitatory and inhibitory neurons in the myenteric plexus. In addition, they increase smooth-muscle tone and inhibit the coordinated peristalsis required for propulsion, leading to disordered, nonpropulsive contractile activity, which contributes to nausea and vomiting as well as constipation. Longer gastrointestinal transit time causes excessive water and electrolyte reabsorption from feces, and decreased biliary and pancreatic secretion further dehydrates stool [34].

Concurrent use of other constipating drugs (e.g., tricyclic antidepressants), dehydration, advancing age, immobility, metabolic abnormalities (e.g., hypercalcemia), chemotherapy (particularly treatment with the vinca alkaloids), and tumor-related bowel obstruction may also contribute. Not all opioid formulations are equally constipating. A systematic review concluded that there is less constipation with transdermal fentanyl than with oral sustained-release morphine [146]. Combination formulation of oxycodone and naloxone may reduce opioid-related GI side effect [87].

Among methadone maintenance patients, constipation is common and tends to be worse early in treatment [93, 173] but persists long-term [65]. The high prevalence of persisting constipation suggests that tolerance to the gut effects of opioids occurs to only a limited extent. In one study, 58% of subjects in methadone maintenance experienced some degree of constipation and 10% had severe problems [181]. Fecal impaction, and even stercoral perforation, has been described [66] and usually responds to increased fluid intake and fiber supplementation to correct for poor dietary intake. Laxatives are not often required but osmotic agents such as lactulose are the laxatives of choice.

Two peripherally acting opioid-receptor antagonists are available for the management of severe opioid-induced constipation: methylnaltrexone and alvimopan. They do not cross the blood–brain barrier and have no antianalgesic effect. Methylnaltrexone was approved by the US FDA in 2008 as a subcutaneous injection for the treatment of opioid-induced constipation in patients with terminal illness requiring palliative care [149].

Randomized trials report some effectiveness for oral alvimopan in the treatment of opioid-induced constipation in patients with chronic pain [115].

76.2.4.2 Laxative Misuse

Surreptitious laxative misuse is among the more common causes for unexplained chronic diarrhea. It represents an intriguing form of substance misuse but is rare and is typically observed in patients without other substance misuse issues. These patients present to family physicians and gastroenterologists. Some are associated with bulimia. Others tend to be older women and the disorder can be viewed as a form of Munchausen's syndrome. The diagnosis rests on identification of laxatives by stool alkalinization, osmolality studies, or a bag search in the hospital [46].

76.2.4.3 Misuse of Anticholinergics

In high doses, anticholinergic drugs alter mood and are occasionally misused, particularly when prescribed to relieve extrapyramidal symptoms in the mentally ill [25] and among those with limited access to other drugs of abuse. Amitriptyline and other tricyclic antidepressant drugs are commonly misused by patients on opioid maintenance treatment [116]. Clonidine and/or buscopan prescribed for opioid withdrawal may also be misused. Patients develop marked constipation and abdominal pain as well as dry mouth and blurred vision.

76.2.5 Tobacco

Tobacco use is associated with a number or benign and malignant disorders of the gastrointestinal tract.

76.2.5.1 Gastroesophageal Reflux

Smoking has been linked to exacerbations of reflux symptoms, and cessation of smoking is one of the lifestyle changes traditionally recommended in the treatment of reflux [114]. Nicotine has been shown to reduce lower esophageal sphincter pressure and promote gastroesophageal reflux in response to straining during coughing and deep breathing [81]. At a practical level, smoking cessation is difficult to achieve and has not been shown to induce remission of reflux or healing of esophagitis. Snus is a form of smokeless tobacco commonly used in Scandinavia. A Swedish study found snus significantly alters the histology of the distal esophagus but does not impact on gastrointestinal symptoms or peptic ulcer disease [6].

Peptic Ulceration

Tobacco smoking increases the risk of both gastric and duodenal ulcers as compared with nonexposed people [113]. Smoking increases risk of ulcer according to the number of cigarettes smoked. Heavy smoking is associated with delayed ulcer healing and the risk of recurrence is increased [88, 140]. Smoking increases the risk of complications from peptic ulcer [119] and mortality [92, 128]. The mechanism by which smoking exacerbates peptic ulcer disease remains unclear.

Pancreatic Disease

Evidence from a number of countries provides a clear link between smoking and pancreatic cancer. Several studies have consistently found a moderately increased risk (about threefold) of pancreatic cancer among smokers [30, 145]. There have been inconsistent findings concerning the relationship between smoking and pancreatitis [30]. A case–control study compared tobacco use in a group with alcohol-related pancreatitis and a control group who drank at least as much alcohol yet did not develop pancreatitis and found no association with smoking [64]. A French study of 108 patients concluded that tobacco intake accelerates the course of alcohol-related chronic pancreatitis in a dose-dependent fashion with a threshold at 20 pack-years [122]. Overall, it would seem appropriate to recommend patients with alcohol-related pancreatitis to quit smoking, in addition to other risks of smoking.

76.2.5.2 Inflammatory Bowel Disease

A curious relationship exists between smoking and inflammatory bowel disease. A meta-analysis of 22 studies showed an association between current smoking and Crohn's disease (OR, 1.76; 95% confidence interval [CI], 1.40–2.22) and former smoking and ulcerative colitis (OR, 1.79; 95% CI, 1.37–2.34). Current smoking had a protective effect on the development of UC when compared with controls (OR, 0.58; 95% CI, 0.45–0.75) [99]. Smoking status is also strongly associated with microscopic collagenous and lymphocytic colitis. The risk is higher in current smokers and is not significantly affected by gender or alcohol consumption [178]. Smokers are more than twice as likely to develop Crohn's disease as nonsmokers [136]. Smoking may also increase the risk of recurrence of Crohn's disease. At least one study suggested that patients who stop smoking for more than 1 year can decrease the risk of flares [31]. Tobacco smoke appears to interfere with epithelial integrity and

immune responses to pathogenic bacteria, but research in this area is ongoing [161].

Patients with ulcerative colitis who begin smoking after the diagnosis of their disease present a significant reduction in the number of recurrences [47], and hospitalization and surgical procedure occur most frequently in heavy smokers who quit smoking before the onset of ulcerative colitis [17]. This suggests nicotine may have a therapeutic potential for this disease. Nicotine influences immune cellular function, increases mucin production, relaxes colonic smooth muscle, increases endogenous glucocorticoids, and influences rectal blood flow and intestinal permeability [148]. Less toxic approaches to this form of therapy have been sought and include topical colonic administration of nicotine. These approaches remain experimental at this time [98].

76.2.5.3 Gastrointestinal Malignancy

Smoking has been strongly linked to cancers of the upper gastrointestinal tract and pancreas as discussed above. The link between smoking and stomach cancer is weaker but is present in most studies [111, 155]. A Swedish population-based prospective cohort of 17,118 twins with up to 30 years of follow-up showed long-term heavy smoking was associated with a statistically significant threefold increased risk of colorectal cancer compared with never smoking (relative risk 3.1, 95% CI 1.4–7.1). Examining colorectal cancer subsites separately, a nonsignificant 60% increased risk of colon cancer was observed only for heavy smokers and a statistically significant fivefold increased risk was observed for rectal cancer [147]. The risk is related to total number of cigarettes smoked and the duration of smoking. Pipe and cigar smoking have a higher risk compared with cigarette smokers [49]. Interestingly, a recent meta-analysis of smokeless tobacco (snus or snuff) available in Scandinavia has shown to be not associated with cancers of the oropharynx, esophagus, stomach, and pancreas once the effects of smoking are removed [94]. Tobacco smoke contains multiple mutagenic and carcinogenic compounds including nicotine, nitrosamines, and polycyclic hydrocarbons. Mouse and cell models reveal a direct promoting action of nicotine on the growth of gastric tumor and neovascularization through sequential activation of the ERK/COX-2/VEGF signaling pathway [133]. The effects of tobacco and alcohol appear to be synergistic. Smoking increases the acetaldehyde burden following alcohol, and alcohol enhances the activation of various procarcinogens via cytochrome P450 induction.

E-Cigarettes

Electronic cigarettes or vaping has increased in popularity over the last few years, especially in the USA [95]. Adolescents tend to use more e-cigarettes compared to older adults [27]. Users of e-cigarettes tend to have more oral symptoms and broken teeth [29].

76.2.6 Body Packing

People smuggling illicit drugs may ingest large amounts of cocaine, heroin, or other drugs aiming to retrieve the packages after reaching their destination [153, 154]. This is referred to body packing, cocaine packing, or body stuffing syndrome [100]. Multiple packages made from latex condoms, wax, or plastic bags are either swallowed or placed retrogradely into rectum or vagina. The incidence of this practice is unknown. Most cases present in police custody raising ethical and potentially funding challenges of managing an involuntary patient. Some people may be coerced to smuggle drugs. Cases involving children and pregnant women have been described [153, 154]. Hospitals close to international airports may encounter these cases and should consider developing a management policy for this challenging problem. An early report describes 10 cases diagnosed only after death in which as many 147 packages were found [164]. Lethal drug absorption through rubber condoms may occur without rupture. The body packer may present with life-threatening symptoms of intoxication, including seizures and cardiorespiratory

collapse, as well as mechanical obstruction from the ingested drug packets. The distal ileum was the most common site of obstruction, whereas rupture tended to occur in the upper gastrointestinal tract [39]. The largest series comprises 61 cases from Milan, Italy, of which only two cases required laparotomy, one each for obstruction and nonfatal drug toxicity [3].

Plain X-ray is the method of choice to detect drug-filled packets within the gastrointestinal tract of body packers [70]. Dilute contrast has been reported to assist identification of the packages [54]. In some cases, CT is required, with potential concerns regarding radiation exposure if repeated examinations are needed. Extensive dose reduction makes low-dose CT a valuable alternative imaging modality for the examination of suspected body packers and might replace conventional abdominal radiographs as the first-line imaging modality [102].

Clinical monitoring comprises frequent clinical and neurological assessment and abdominal examination daily to the detected complications of acute drug intoxication or bowel obstruction or perforation. The patient should be kept in hospital until all drug packages have cleared due to the risk of life-threatening overdose if any rupture. Traub et al. [153, 154] presented a detailed review and clinical approach to management. A light solid diet with free liquids may be given. Oily or polyethylene glycol laxatives can be given repeatedly to accelerate passage of packages [73]. Symptomatic cases may require early surgery [135]. The risk of careful endoscopic removal from the esophagus is probably exaggerated, and in any case, the risk of endoscopic removal is almost certainly less than that of any other surgical approach to the esophagus. The rigid esophagoscope appears to have an advantage over the flexible instrument because of the wide lumen which will accommodate most average-sized pellets. Intact pellets in stomach and small bowel may be retrieved endoscopically or are evacuated through a single gastrotomy and/or enterotomy. Non-obstructing pellets in the colon pose an interesting dilemma. Removal through a colostomy will expose the patient to the risk of sepsis. The risk of rupture of pellets already in the colon must be very low as there are no noxious enzymes here and the pellets are subject to less turbulence within formed stool than they would be in the small intestine [39].

Methamphetamine body stuffers have similar demographics to those of body stuffers of other stimulants but tended to ingest fewer baggies with larger masses and had a higher percentage of severe outcomes (29%) than previously reported with other stimulants. Increases in presenting pulse rate and temperature (pulse rate 120 beats/min or 38.0 °C) are common in patients who will develop end-organ damage [163].

76.2.7 Psychostimulants

Gastrointestinal disorders are uncommon in patients with stimulant use. Juxtapyloric perforation has been described after the smoking of crack cocaine in 50 (95% male) consecutive patients [45]. Cocaine abuse can cause mesenteric ischemia and gangrene, which result in small and large bowel perforation as well as intraperitoneal hemorrhage [150]. This is thought to be related to cocaine-induced arterial vasospasm or vasoconstriction leading to intestinal ischemia with mucosal and transmural necrosis as well as mesenteric vascular thrombosis. The use of preoperative angiography is vital in detecting occlusive lesions that are amenable to revascularization [72]. The usual management of small or large bowel gangrene or perforation is by resection and primary anastomosis.

76.2.8 Cannabis

Cannabinoid receptors are widely expressed throughout both the upper and lower GI tract and are also expressed on hepatic stellate cells. Consequently, cannabinoids may influence a range of GI functions in health and disease [118]. Cannabinoids have been implicated in the patho-

physiology of satiety, nausea/emesis, gastrointestinal secretion, gastrointestinal motility, gastrointestinal sensation, as well as inflammation [76].

Nausea and vomiting are side effects of many chemotherapeutics and reduce the quality of life of patients with diabetes, cancer, and acquired immune deficiency syndrome. Cannabis and other cannabinoids appear to be effective antiemetics. The antiemetic effect has been demonstrated in an animal model and is related to the expression of CB1 receptors in the dorsal vagal nucleus [159]. Cannabinoids are also involved in inhibition of gastric emptying and gastric acid secretion.

The endocannabinoid system provides a potential therapeutic target for cannabis and cannabinoids and animal models have shown benefit in decreasing inflammation. A recent Cochrane review failed to show the benefit of cannabis for the treatment of Crohn's disease [80]

Cannabis use has been linked to recurrent intractable hyperemesis with associated dehydration and electrolyte abnormality [4, 137, 142]. Cannabinoid hyperemesis is often relieved by frequent hot showers [141]. The mechanism is not understood. Standard antiemetics are often ineffective. Benzodiazepines and antipsychotics have been shown to be effective in some cases [124, 168]. Capsaicin cream (typically 0.025–0.075% applied to the abdomen or back) is increasingly used in the emergency department setting, but there are no controlled trials. Side effects include heat and burning at the application site.

Key Points

- Excessive alcohol use is associated with injury to all parts of the gastrointestinal tract particularly the pancreas.
- Alcohol increases the risk of gastrointestinal cancer particularly in smokers.
- Tobacco use also leads to gastroesophageal reflux, peptic ulceration, gastrointestinal cancer, and Crohn's disease.
- Opioids have important effects on gastrointestinal secretion and motility.
- Narcotic bowel syndrome reflects a vicious cycle of pain and increasing doses.
- Cannabinoid hyperemesis syndrome is becoming more common and should be considered in cannabis users with recurrent vomiting.

Clinical Relevance

The gastrointestinal consequences of alcohol and drug use are very common but often neglected. For example, the link between even regular moderate alcohol use and colorectal cancer supports international guidelines to limit alcohol use even in the absence of an alcohol use disorder. Pancreatitis is becoming more common and is a serious, often life-threatening, disorder with the potential for debilitating chronic pain and other complications. Narcotic bowel syndrome is also growing in prevalence and is a significant clinical challenge to manage. Cannabis hyperemesis, once questioned or considered rare, is commonly seen in the emergency department, particularly in regions where cannabis use has risen as a result of regulatory changes. Diagnosis of the cause of these gastrointestinal disturbances allows for better management of their symptoms and, by linking these to the underlying substance use disorder, sets the foundation for comprehensive treatment and prevention of recurrences.

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Liver Disorders Related to Alcohol and Other Drug Use

77

Hannah M. Dix, Emma M. Robinson, and John F. Dillon

Contents

Abstract

The addiction specialist will encounter many patients with liver disease, most commonly either as a consequence of excess alcohol consumption or as a result of hepatitis C infection acquired through injection drug use. Less commonly this is due to hepatitis B infection and drug-induced liver injury due to idiosyncratic reactions to drugs of abuse. This chapter will outline the epidemiology and pathogenesis of

H. M. Dix
Gastroenterology Department, NHS Tayside, Dundee, UK

E. M. Robinson · J. F. Dillon (✉)
Gut Group, Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, UK
e-mail: j.f.dillon@dundee.ac.uk

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these individual conditions; it will then describe the investigation of liver disease and finally describe the management of chronic liver failure. The ideal pathway of care for patients with an addiction and chronic liver disease is a multidisciplinary team-based approach. The addiction specialist will help support adherence to therapy and provide prognosis for the addiction when decisions are being made about highly invasive therapies such as liver transplantation.

77.1 Introduction

77.1.1 Epidemiology of Substance-Related Liver Disease

Alcohol is the most prevalent misused substance worldwide with alcohol misuse disorders more common in men than women. Age-standardised prevalence is reducing, to a larger extent in women than in men, and there is geographical variation worldwide with alcohol misuse more common in high-income countries, compared to low-income countries. Religious beliefs, prohibiting alcohol consumption also accounts for geographical variation. Eastern Europe has the greatest age-standardised prevalence of alcohol misuse disorders with 4245.6/100,000 people, and Northern Africa and the Middle East have the lowest prevalence of 593/100,000 people [1]. Excessive alcohol use is a risk factor in over 200 diseases and injuries with the largest number of deaths related to cardiovascular diseases, traumatic injuries, gastrointestinal disease and cancer [2]. Globally, 3.3 million deaths and 139 million disability adjusted life years are attributable to excess alcohol annually [3].

The second most prevalent misused substance is opioid medication, including both prescribed medication and illicit substances such as heroin with an age-standardised prevalence 353·0 cases per 100 000 people and incidence of 26·8 million cases worldwide. Prevalence, like alcohol misuse, is higher in men than women with age-standardised prevalence reducing to a larger extent in women than in men. Geographical variation is also seen in drug misuse with the highest age-standardised prevalence in Australasia. Intravenous drug use leading to chronic hepatitis C infection (HCV), cirrhosis and hepatocellular carcinoma contributes substantially to the disease burden of drug misuse, and chronic hepatitis B (HBV) has a lesser but still significant impact [1]. Depending on the availability of needle exchange facilities and opiate substitution therapy, HCV prevalence among current and former PWID varies between 40% and 80%.

77.2 Pathophysiology of Substance Related Liver Disease

77.2.1 Alcohol-Related Liver Disease

The pathophysiology of alcohol-related liver disease is not completely understood but thought to be a combination of behavioural and environmental factors in a genetically susceptible host [4].

In low-level alcohol consumption, alcohol dehydrogenase acts within the cytosol of hepatocytes to convert ethanol to acetaldehyde, a hepatotoxic metabolite. In heavy alcohol consumption of more than 40 g of alcohol per day, cytochrome P450 2E1 (CYP2E1) in the mitochondria of hepatocytes is induced 10- to 20-fold to convert alcohol to acetaldehyde and other reactive oxidative species. This can occur after just 1 week of heavy alcohol consumption and leads to higher levels of toxic metabolite and hepatocyte damage [5].

The spectrum of alcoholic liver disease begins with steatosis, defined as fatty infiltration of the liver. Steatosis is seen in 90% of patients with heavy alcohol consumption, but only 30% develop more severe disease, in the form of alcoholic hepatitis, hepatic fibrosis, cirrhosis and hepatocellular carcinoma, indicating other factors are required to cause significant liver injury. Recognised factors include female gender, obesity, daily heavy drinking with young age of onset and some genetic differences [6] (Fig. 77.1).

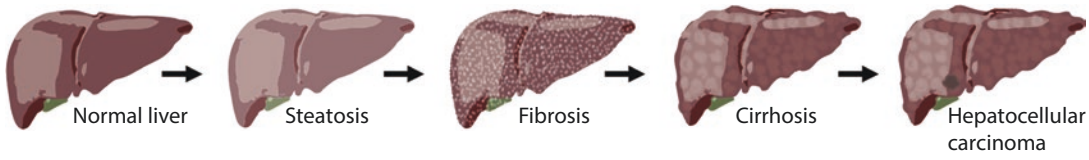

Fig. 77.1 Progression of liver disease

Accumulation of fat (triglycerides, phospholipids, and cholesterol esters) within hepatocytes occurs via three mechanisms. Hepatotoxic acetaldehyde causes reduced oxidation of fatty acids and increased lipogenesis within the hepatocyte. Outwith the hepatocyte, alcohol consumption reduces small bowel absorption of fatty acids, therefore stimulating compensatory mobilisation of fatty acids from adipose tissue and increased uptake by the liver [7]. Chronic alcohol consumption inhibits autophagy within hepatocytes, an important mechanism in the removal of fat from hepatocytes [6].

Sustained liver injury and steatosis associated with chronic heavy alcohol consumption results in fibrosis of the liver. In an attempt to heal damage, hepatic stellate cells are activated to myofibroblasts causing fibrogenesis and increased deposition of extra-cellular matrix (ECM) proteins, including collagen [8]. These cells also inhibit ECM breakdown by expressing tissue inhibitors of metalloproteinase (TIMPs). Removing the cause of liver injury (alcohol cessation) can lead to apoptosis of the hepatic stellate cells and loss of inhibition of ECM breakdown, reversing fibrosis in the liver [9].

Chronic liver injury and progressive fibrosis leads to cirrhosis. This is defined as an accumulation of ECM proteins to such an extent as to distort the liver architecture. Regenerative hepatic nodules and surrounding fibrous septa are seen, distorting hepatic vasculature, leading to portal hypertension and reduced functioning hepatocyte mass causing impaired liver function [10].

77.2.2 Drug-Related Liver Disease

Viral hepatitis C and B infections cause a similar spectrum of liver disease seen in alcohol misuse. Steatosis is less prominent except in HCV genotype 3. Acute infection with hepatitis C virus can be asymptomatic or lead to an acute hepatitis. Twenty to thirty percent of acute infections are cleared spontaneously, but the remaining 70–80% have viral persistence and progress to steatosis, fibrosis and cirrhosis. Once at the stage of advanced fibrosis or cirrhosis, 3–5% per annum develop hepatocellular carcinoma. Viral proteins are involved in the pathogenesis of all stages of liver disease. They interact with hepatic lipid metabolism causing accumulation of lipid within the liver, leading to steatosis. Viral proteins interfere with host DNA repair leading to accumulation of gene mutations, fibrosis, cirrhosis and oncogenic activation. When coexistent with the direct viral protein inhibition of tumour suppressors, hepatocellular carcinoma can develop [11].

Acute HBV infection in PWIDs is normally cleared in 90% of people, with most having a subclinical infection. Of those who develop chronic HBV infection, 40% progress to steatosis, fibrosis, cirrhosis and hepatocellular carcinoma with similar pathogenesis to HCV. There are higher rates of hepatocellular carcinoma associated with HBV than HCV, 19.2% compared to 7.2% respectively, of all cancers caused by infectious agents. Hepatitis B virus interferes with apoptosis signaling, promoting viral proliferation by increasing apoptosis and hepatocellular carcinoma progression by decreasing apoptosis [12].

77.2.3 Drug-Induced Liver Injury

Drug-induced liver injury (DILI) can be caused by prescribed medications and drugs of abuse; it is commonly mild but may on occasion be life threatening. A minority of drugs are dose-dependent liver toxins but most cause damage due to idiosyncratic reactions requiring host factors.

77.2.3.1 Cocaine

Cocaine-induced hepatotoxicity may sometimes be fatal, usually hours to a few days after an overdose, generally following or accompanying other major organ involvement (myocardial infarction, stroke, rhabdomyolysis and renal failure are the most frequent); the cause of death is generally not due only to an acute liver failure but to a multi-organ failure. Clinically, the pattern of hepatic injury is usually an acute necrosis with very high levels of serum aminotransferases and a rapid rise in prothrombin time. Most liver damage associated with cocaine is shock liver, secondary to hypotension, though DILI may occur due to conversion to a toxic metabolite as a result of P450 metabolism. The liver injury due to cocaine is self-limiting and resolves rapidly.

77.2.3.2 Ecstasy (MDMA)

Many cases of acute liver failure after ecstasy use have been reported. The clinical features may differ from acute liver failure with hyperthermia often prominent to the commonest presentation of a mild hepatitis. The mechanism of MDMA-induced hepatic damage is unclear as histological changes vary from a mild to moderate lobular hepatitis to massive hepatic parenchymal collapse with areas of nodular regeneration and cholestasis. The severity of liver failure does not seem to correlate with the amount or the frequency of ingested MDMA, suggesting an individual susceptibility for the related hepatic damage. Ecstasy users are also at increased risk of heatstroke because of the direct effect of MDMA on thermoregulation via central serotonergic nerve terminals; it is difficult to establish if ecstasy is directly hepatotoxic or if liver injury results from the hyperthermia. In acute liver failure without hyperthermia, liver damage can progress to need for liver transplantation.

77.2.3.3 Heroin, Marijuana and Amphetamines

Liver damage due to heroin, amphetamines and marijuana without co-factors is unproven, and reported cases may represent idiosyncratic liver injury.

77.2.3.4 Anabolic Steroids

Synthetic androgenic steroids are widely consumed for body building because of their anabolic effects; they can rarely cause cholestatic liver injury, and after a long-term use, they can be associated with liver tumours. The mechanism of hepatic injury is not well defined for the acute cholestatic disease, while an unregulated growth stimulus to hepatocytes is the cause of nodular regeneration and hepatic tumours.

77.3 Investigation and Staging of Liver Disease

In the patient with abnormal LFTs or physical signs of liver disease, the aim of investigation is to diagnose the aetiology and stage how advanced the disease is. Patients with hepatic steatosis or fibrosis are often asymptomatic, occassionally becoming symptomatic once steatohepatitis occurs or cirrhosis is established. Clinical signs are also sparse in steatosis or fibrosis and are mainly consistent with those related to the underlying aetiology. In alcohol-related liver disease (ARLD), these may include bilateral parotid gland hypertrophy, muscle wasting, malnutrition, Dupuytren's contracture, bilateral peripheral neuropathy and hepatomegaly [4]. In drug-related liver disease these may include evidence of drug use such as track marks or sinus formation at injection sites.

Diagnosis of the earlier stages of liver disease is commonly made incidentally on bloods or imaging requested for other reasons. A diagnosis of ARLD can be made clinically and biochemically in patients with heavy alcohol consumption after other causes of liver disease are ruled out [13]. This can be done with a careful history to assess patients' risk and an appropriate biochemical liver screen. Clinical history should include an in-depth discussion about alcohol intake behaviour; drug history, including prescribed, over-the-counter, herbal and illicit drugs, in particular any risky behaviours associated with increased risk of contracting blood-borne viruses such as HBV and HCV; travel history; occupational risk; social risk (tick bite, muscle injury, tattoos, piercings); sexual

history and any features of metabolic syndrome. A liver screen should include hepatitis B surface antigen, hepatitis C antibody, ferritin and transferrin saturation, and an autoimmune liver disease antibody screen (anti-mitochondrial antibody, anti-smooth muscle antibody, anti-nuclear antibody and serum immunoglobulin screen). α1-antitrypsin and caeruloplasmin should be tested for in young patients [14].

77.3.1 Biochemical Markers

Biochemical markers can point towards the aetiology or stage of liver disease:

- Macrocytosis is commonly seen in heavy alcohol consumption secondary to direct toxicity of alcohol on bone marrow, folate or vitamin B12 deficiency due to malnutrition or increased lipid deposition in erythrocyte membranes [15].
- Serum gamma-glutamyl transpeptidase (GGT) can be raised in heavy alcohol consumption with or without liver disease. Values 2–3 times the upper limit of normal with resolution on abstinence in 80% of cases are seen in those without liver disease. Values in those with liver disease are raised to a greater extent, 8–10 times the upper limit of normal and often remain elevated on abstinence. These values are raised disproportionately to any alkaline phosphatase (ALP) rise, with a proportionate rise in GGT and ALP more consistent with biliary disease [16]. An isolated ALP rise points to an extra-hepatic source, such as bone, intestine, kidney, placenta or white blood cells [14].
- Hepatitis of any aetiology causes raised aspartate aminotransferase (AST) and alanine aminotransferase (ALT) secondary to hepatocyte injury. These give an idea of the level of injury sustained rather than level of liver dysfunction which can be gauged by measuring albumin, prothrombin time ratio and bilirubin. ALT is more specific to liver injury as AST is also found in cardiac, skeletal and smooth muscle and can be raised secondary to damage of any of these tissues [14].
- Along with elevated aminotransferases (AST/ALT), hepatocyte inflammation reduces the livers ability to process bilirubin, causing hyperbilirubinaemia. A leucocytosis may also be seen in severe inflammation. Evidence of hepatic synthetic dysfunction can be seen at this point with hypoalbuminaeamia and coagulopathy in the form of a raised prothrombin time ratio (PTr). Coagulopathy can also be a result of dietary deficiency of vitamin K in malnourished patients, a common scenario in patients with alcohol and drug misuse [17].
- When hepatic fibrosis accumulates, leading to cirrhosis, the distorted liver architecture and abnormal pressures on vasculature cause portal hypertension. Biochemically this is seen as thrombocytopenia secondary to hypersplenism.
- Heavy alcohol consumption can also cause a pancytopenia secondary to a direct toxic effect on the bone marrow or reduced thrombopoietin production in synthetic liver dysfunction [18].

77.3.2 Imaging

Ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) can help determine the stage of liver disease but cannot confirm aetiology.

For initial assessment of liver disease, US is an adequate, non-invasive test that delivers no radiation. Steatosis is described as a hyperechoic echotexture with smooth outline, often with coexistent hepatomegaly. A fibrotic liver maintains the smooth outline but the echotexture becomes coarse. The smooth outline is lost in cirrhosis, replaced with a nodular outline and shrunken liver with a coarse echotexture. Associated features of cirrhosis, related to portal hypertension such as splenomegaly, varices and ascites, may also be seen. CT and MRI may be more sensitive and specific than US and are used to delineate any focal liver lesions but are not cost-effective for initial assessment [13]. The main role of imaging is to exclude other causes of LFT abnormality including biliary pathology, HCC and metastatic disease.

77.3.3 Staging of Liver Disease Using Non-invasive Fibrosis Scores

There are multiple non-invasive fibrosis scores that aim to quantify fibrosis stage, including FibroTest, NAFLD Fibrosis score, APRI and ELF. These scores were initially validated in viral hepatitis and NAFLD. Some studies have shown accuracy in distinguishing between mild and severe fibrosis in ALD, but they poorly differentiate intermediate fibrosis and are not yet validated for use in ALD [19].

Transient elastography (TE) can be used to identify and quantify fibrosis and cirrhosis by measuring the stiffness of the liver using shear waves. Reduced shear wave velocity correlates to increased liver stiffness, and numerical cut-offs specific to aetiology relate to the level of fibrosis or cirrhosis present [20]. TE is better validated in chronic viral hepatitis and non-alcoholic fatty liver disease (NAFLD), and there are few studies relating to ALD, but they have shown accuracy when compared to liver biopsy of those with alcoholic liver disease [21]. Co-existent alcoholic hepatitis can falsely raise the liver stiffness, and therefore a period of abstinence improves diagnostic accuracy. The falsely elevated scores correlate with raised ALT or AST [22]. The EASL-ALEH guidelines recommend caution when interpreting TE in patients with ongoing heavy alcohol consumption and raised ALT or AST greater than five times the upper limit of normal, along with obesity, congestive liver, extra-hepatic cholestasis and an interquartile range larger than 30 during TE measurement [20].

77.3.4 Liver Biopsy

Although liver biopsy was previously thought to be the gold standard in diagnosis of liver disease, it is a costly and invasive procedure that does not come without risk. Inter-observer error is possible and there is a risk the small area of tissue sampled may not be representative of the organ as a whole. With the introduction of non-invasive fibrosis scores, liver biopsy should be reserved for those with complex disease, uncertain aetiology or where there is a discrepancy between the clinical picture and non-invasive scores to clarify disease staging [20].

77.4 Diagnosis of Alcohol and Drug-Related Liver Disease

A diagnosis of ALD should be suspected in patients who regularly consume excess alcohol (>20 g/day in females and > 30 g/day in men) and have clinical or biochemical evidence of liver damage. Similarly, drug related liver disease should be suspected in patients who abuse offending drugs. Other causes of liver disease should be ruled out with a careful clinical history, examination and an appropriate biochemical liver screen [19].

Diagnosis can often be difficult as many patients are asymptomatic so a high index of suspicion is imperative. In patients who are suspected to have liver disease, baseline biochemical investigation should including LFTs (ALT, AST, GGT, bilirubin, albumin), U&Es, FBC, coagulation screen and liver screen, structural imaging in the form of USS and fibrosis scoring via TE [19]. These investigations should provide enough information to diagnose aetiology and stage of liver disease along with any complications.

77.5 Clinical Management of Advanced Liver Disease

Regardless of aetiology, the patient with sufficient remaining functioning liver is termed as having compensated cirrhosis, and when they develop liver failure or a complication, they are described as having decompensated cirrhosis.

77.5.1 Compensated Cirrhosis

Although compensated liver cirrhosis may be asymptomatic, clinical signs may be evident at this stage. Along with signs visible in earlier stages of ARLD, there may be stigmata of chronic liver disease, including spider angiomata (supe-

rior vena caval distribution), gynaecomastia, testicular atrophy, palmar erythema, finger clubbing, hypertrophic osteoarthropathy and hypoalbuminaemic nail changes. The liver may be enlarged, normal or shrunken in cirrhosis with a firm, nodular edge. If portal hypertension is present, there may be signs of splenomegaly, caput medusa and hepatic fetor [13].

Along with biochemical changes seen in earlier stages, there may be evidence of hepatic synthetic dysfunction (hypoalbuminaemia and coagulopathy) and hypersplenism if portal hypertension is present (thrombocytopenia) [17].

Abstinence is the cornerstone of management at every stage of ARLD, whether the aim is to prevent fibrosis occurring in the early stages of steatosis, promote resolution of fibrosis already sustained, prevent decompensation of cirrhosis or prevent alcoholic hepatitis. The benefits of abstinence are clear, so identification of patients who drink alcohol to excess followed by a brief intervention is beneficial in reducing harm, regardless of stage of ARLD [23]. In chronic HCV at any stage of liver disease, cure of HCV with anti-viral medication should be achieved; with the locally preferred regimen, this will often be delivered in shared care models between addictions physicians and specialists in viral hepatitis [24]. Patients with chronic HBV are complex and should undergo assessment by an expert; a minority will need treatment or viral suppression therapy, and this should be supervised by an expert in the subject [25].

77.5.2 Decompensated Cirrhosis

Acute decompensated liver cirrhosis is a medical emergency and requires admission under a physician with expertise in liver disease. It occurs when a cirrhotic patient develops hepatic encephalopathy, ascites, peripheral oedema, variceal bleeding or jaundice. It can occur progressively as a chronic decompensation secondary to chronic liver insult, such as continued alcohol consumption in ARLD, or be precipitated acutely by infection (specifically spontaneous bacterial peritonitis), dehydration, constipation, medication changes, hepatocellular carcinoma or variceal bleeding.

Patients that present in a decompensated state should be investigated and treated for the above precipitating factors [26]. Abstinence from alcohol is the main factor correlating with long-term survival [27] and is important even in cirrhosis secondary to viral hepatitis. Medical management is supportive, focussing on correcting electrolyte derangement; malnutrition; alcohol or drug withdrawal; Wernicke's and hepatic encephalopathy; ascites and prevention of complications such as AKI and infection [19]. Protein malnutrition is common in severe decompensated cirrhosis and is associated with poor prognosis. The European Society for Clinical Nutrition and Metabolism recommends a daily energy and protein intake of 35–40 kcal/kg and 2–1.5 g/kg, respectively, with prompt use of nasogastric feeding when goals are not met orally [28–30]. Intravenous vitamin B complex should be administered to reduce the risk of Wernicke's encephalopathy secondary to Vitamin B1 (thiamine) deficiency [19]. The major complications of cirrhosis that define decompensation are ascites, hepatic encephalopathy, variceal bleeding as well as liver failure; a complication particular to alcohol-related aetiology is alcoholic hepatitis.

77.5.2.1 Hepatic Encephalopathy

Hepatic encephalopathy is defined as a spectrum of neurological or psychiatric abnormalities ranging from sub-clinical alterations to encephalopathic coma secondary to liver dysfunction and portosystemic shunting. Clinically it is subdivided into four grades [31].

Grade	Description
I	Trivial lack of awareness, euphoria, anxiety, shortened attention span, impairment of addition or subtraction, altered sleep rhythm
II	Lethargy, apathy, disorientation to time, obvious personality change, inappropriate behaviour, dyspraxia, asterixis
III	Somnolence to semi-stupor, responsive to stimuli, confused, gross disorientation, bizarre behaviour
IV	Coma

Ammonia is the main neurotoxin involved in the development of hepatic encephalopathy. Liver dysfunction and portosystemic shunting

reduce excretion of ammonia, which crosses the blood brain barrier and is converted into glutamine in the astrocytes, leading to astrocyte swelling and cerebral oedema [32]. The use of lactulose as first-line therapy for hepatic encephalopathy and secondary prophylaxis has been validated in many randomized controlled trials [33]. The non-absorbable disaccharide is metabolized to lactic acid by colonic bacteria with the resultant acidic intestinal environment leading to transfer of ammonia into the lumen for excretion and reducing ammonia producing colonic bacteria [34]. Clinically, increasing the dose to achieve 2–3 soft stools daily is adequate.

Rifaximin, a semi-synthetic, non-absorbable antibiotic with gut-selective, non-pathogenic antimicrobial activity can be used as an adjunct to lactulose in secondary prevention of hepatic encephalopathy by reducing the number of ammonia producing luminal bacteria [32].

77.5.2.2 Ascites

The development of ascites is the most common form of cirrhotic decompensation with a marked increase in mortality after its development (40% at 1 year, 50% at 2 years). Increased levels of vasodilators are present in cirrhotic patients with portal hypertension, causing splanchnic vasodilatation and reduced mean arterial pressure. This leads to activation of the renin-angiotensin-aldosterone system (RAAS), increased antidiuretic hormone (ADH) and increased activation of sympathetic nervous system. The RAAS retains sodium and water from the renal collecting tubules, ADH retains free water from the renal collecting tubules and sympathetic activity causes systemic/renal vasoconstriction, all in an attempt to raise circulating volume. The net effect is sodium retention and free water retention leading to accumulation of fluid in the peritoneal cavity and subcutaneous tissues (ascites and peripheral oedema, respectively) [35].

Dietary sodium restriction and diuretic therapy are the mainstays of ascites management. Potassium sparing diuretics such as spironolactone should be used initially and loop diuretics such as furosemide used adjunctively. Spironolactone can be initiated at 100 mg once daily, increasing by 100 mg daily each week to a maximum dose of 400 mg. Furosemide can be initiated at 40 mg once daily, increasing by 40 mg daily each week to a maximum dose of 160 mg. Renal function, sodium and potassium should be monitored weekly over this time [35, 36].

Patients who fail to respond to these measures, whether due to lack of drug effectiveness or development of complications (hyponatraemia, hyperkalaemia, renal dysfunction), are deemed to have refractory ascites and should be treated with large volume paracentesis and considered for liver transplantation [26]; if not suitable, TIPSS can also be considered. Refractory ascites confers a further increase in mortality to 75% at 1 year [36].

77.5.2.3 Variceal Bleeding

Variceal bleeding is the second most common presentation of cirrhotic decompensation and confers the most immediate mortality risk [26]; it presents with haematemesis and is a medical emergency requiring urgent admission. Splanchnic arteriolar vasodilatation increases portal venous inflow; distorted hepatic sinusoids and intrahepatic vasoconstriction increases resistance to portal venous outflow; the net effect being increased portal pressure. When the hepatic venous pressure gradient between the portal and hepatic veins is greater than 10 mmHg, portosystemic collaterals (varices) form in an attempt to decompress the portal venous system. The risk of bleeding depends on the portal pressure, variceal radius and wall thickness [37].

The aim of management is prevention of bleeding. Current guidelines recommend that all patients should be screened for varices at diagnosis of cirrhosis and at each decompensation. If no varices are detected, screening should be repeated every 2–3 years and annually if grade 1 varices are seen [26]. Non-selective beta-blockers (NSBB) such as propranolol and carvedilol are used as primary and secondary prophylaxis of variceal bleeding as they reduce cardiac output and splanchnic vasodilatation leading to reduced portal pressure [38–40]. Endoscopic band ligation to eradicate varices is recommended as secondary prophylaxis in combination with NSBB

after variceal bleeding has occurred due to the high mortality and 60–70% re-bleeding risk without intervention. Repeated endoscopy with variceal band ligation until no varices remain eliminates current varices but does not reduce the underlying problem of portal hypertension, leading to risk of recurrence [26].

77.5.3 Alcoholic Hepatitis

The term alcoholic hepatitis (AH) is used to describe both a histological appearance and a clinical syndrome that are not the same. Histological AH has features of fatty liver with additional necro-inflammation; it does not correlate directly with the clinical syndrome. Clinically AH is the sudden onset of jaundice in the context of sustained alcohol excess which features an inflammatory state without overt sepsis; it can occur with any degree of alcohol-related liver disease [41]. AH should be suspected in any patient developing acute onset jaundice with heavy alcohol use within the past 3–4 weeks; some patients stop or reduce drinking with the onset of the symptoms. There are often associated features of a systemic inflammatory response, decompensated cirrhosis, alcohol withdrawal and malnutrition with the differential diagnosis including sepsis and end-stage liver failure. Excluding sepsis is key, so a full sepsis workup (CXR, blood cultures, ascitic tap, urinalysis and abdominal imaging) should be carried out, as well as considering and excluding other causes of cirrhotic decompensation [42].

The severity of alcoholic hepatitis can be predicted using scoring systems such as Maddrey's discriminant function (mDF) or the Glasgow alcoholic hepatitis score (GAHS) [43]. An mDF score of more than 32 identifies severe disease and need for medical management. Untreated 1 month mortality in this group is 50%, with those scoring less than 32 (non-severe disease) having a 1 month mortality of less than 10% [19]. A GAHS score >/=9 identifies a high-mortality group.

Maddrey's Discriminant Function (mDF)

$$= [4.6\times (\text{Patient PT} - \text{Control PT})] + \text{Bilirubin}.$$

Glasgow Alcoholic Hepatitis Score (GAHS)

Score given	1	2	3
Age	<50	≥50	–
WCC (109/L)	<15	≥15	–
Urea (mmol/L)	<5	≥5	
PTr/INR	<1.5	1.5-2.0	>2.0
Bilirubin (μmol/L)	<125	125-250	>250

WCC white cell count, PTr prothrombin time ration, INR international normalised ratio

Treatment is supportive, as described for decompensated cirrhosis above. Corticosteroids are the mainstay of treatment for severe AH although conflicting evidence exists regarding their use. The STOPAH trail showed that patients with severe alcoholic hepatitis (Maddrey's discriminant function ≥32) treated with prednisolone 40 mg daily for 28 days had slightly reduced 28 day mortality, compared to those treated with placebo or pentoxifylline. Unfortunately this

reduced mortality was not seen long term with no mortality difference at 90 days and 1 year [44]. A recent Cochrane review of 16 trials looking at prednisolone versus no treatment or placebo in severe AH found no evidence of difference between these groups on all-cause mortality, health-related quality of life or serious adverse events during treatment, conceding that the level of evidence in all trials reviewed was low with high bias [45].

Both AH, cirrhosis and corticosteroid use can increase the risk of developing infection. Corticosteroids significantly increase the risk of serious infections during treatment and after treatment. If an infection is present at diagnosis of AH, a course of antibiotics prior to and during corticosteroid therapy confers a mortality advantage over an antibiotic course commencing after corticosteroids [46].

77.5.4 Hepatocellular Carcinoma

Eighty to ninety percent of hepatocellular carcinoma (HCC) occurs in cirrhotic patients, secondary to chronic inflammation and severe oxidative stress. One-third of cirrhotic patients, regardless of underlying aetiology, will develop hepatocellular carcinoma in their lifetime. The highest risk is associated with chronic viral hepatitis; chronic hepatitis B patients are at risk prior to the development of cirrhosis. Worldwide incidence of HCC is increasing with a male preponderance (M:F 2–2.5:1) [47]. There are many mechanisms through which heavy alcohol consumption can cause carcinogenesis, including acetaldehyde as a carcinogenic, upregulation of CYP2E1 increasing reactive oxygen species and immunosuppressive effects of both liver disease and excessive alcohol consumption [48].

Due to the high mortality associated with HCC, cirrhotic patients who are well enough to undergo HCC treatment should be surveyed with USS of abdomen every 6 months. If any suspicious lesions are seen, this should be followed with a CT or MRI of the liver. Depending on both degree of cirrhosis and stage of HCC, there are options for treatment and discussion of possible therapeutic options should be held at dedicated multidisciplinary meetings. Therapeutic options include liver transplant, liver resection, ablation, chemo-embolisation, systemic chemotherapy or supportive care [47].

77.5.5 Liver Transplant

Liver transplant is the only curative treatment for liver cirrhosis. With prevalence of liver cirrhosis increasing and the number of liver donors plateauing, it is important that all cirrhotic patients are effectively managed to slow the progression of cirrhosis, prevent complications that can lead to decompensation and therefore reduce the need for liver transplantation [38]. Withdrawing the insult to the liver, for example, abstinence in ARLD and anti-viral treatment in viral hepatitis, has a positive impact on both of these goals.

All patients who develop complications of their cirrhosis (ascites, variceal haemorrhage, hepato-renal syndrome and encephalopathy) should be considered for transplant assessment as the high mortality associated with liver failure outweighs the risk of liver transplantation. The model of end-stage liver disease (MELD) score predicts short-term mortality pre-transplant and is used to select patient for assessment and prioritise patients on the waiting list. It is a function of renal function, PTr, bilirubin and sodium, and all patient with a score greater or equal to 15 should be referred for liver transplant assessment [49].

Assessment for liver transplant is a complex medical, physical and psychological assessment. In alcohol-related disease, the psychological assessment is important to ascertain the risk of recurrence of alcohol misuse and is usually performed by an addictions psychiatrist. This risk is currently estimated at 15–40% and is related to length of follow-up post-liver transplant and length of abstinence pre-transplant. In the UK most transplant centres require a period of alcohol abstinence of 6 months prior to transplant assessment as this can often reduce the severity of liver disease, negating the need for transplant, and is an indication of compliance that could be expected post-transplant [49].

Key Points

1. Regardless of aetiology, the basic spectrum of liver disease is similar. This ranges from steatosis through hepatic fibrosis, cirrhosis and hepatocellular carcinoma.
2. Removing the liver insult (e.g. alcohol cessation or antiviral treatment) can allow hepatocyte regeneration and reversal of steatosis and fibrosis. Once progression to cirrhosis has occurred, reversal is not possible and removing the insult aims to maintain a compensated liver.
3. Many drugs of abuse can cause a wide range of liver disease, from mild cholestasis or hepatitis to fulminant liver failure.
4. Initial investigation should include baseline bloods (FBC, U&E, LFT, coagulation screen), US abdomen and a liver screen (hepatitis B surface antigen, hepatitis C antibody, ferritin and transferrin saturation and an autoimmune liver disease antibody screen, α1-antitrypsin and caeruloplasmin).
5. Referral to local gastroenterology services should be sought if any evidence of liver disease is found.
6. Acute decompensated liver cirrhosis (hepatic encephalopathy, ascites, peripheral oedema, variceal bleeding or jaundice) is a medical emergency and requires admission under a physician with expertise in liver disease.
7. Alcoholic hepatitis is a medical emergency, requiring admission under a physician with expertise in liver disease, and should be suspected in any patient developing acute onset jaundice with heavy alcohol use within the past 3–4 weeks.
8. Hepatocellular carcinoma incidence is high in cirrhotic patients, with high mortality. Six monthly screening aims to reduce this by allowing early detection and treatment.
9. Liver transplant is the only curative therapy for liver cirrhosis and should be considered in all patients who have decompensated cirrhosis. Six months abstinence from alcohol is required for assessment of patients with alcohol-related liver disease.

Clinical Relevance

High morbidity and mortality are attributed to both alcohol and drug misuse with a large proportion of this related to liver disease which can often be asymptomatic. This necessitates a high level of suspicion at every clinical consultation. If liver disease is diagnosed prior to the development of cirrhosis, cessation of alcohol and drug misuse can have a greater impact on the disease course and reduce morbidity and mortality. As many patients that are at risk of liver disease secondary to alcohol and drug misuse are users of addiction medicine services, it is important that the investigation, diagnosis, treatment and prognosis of these conditions are understood so that appropriate referral to gastroenterology services can be sought.

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78 Kidney Disease and Electrolyte Disorders in the Context of Drug Use

Brendan Smyth, Anna Haber, and Annemarie Hennessy

Contents

B. Smyth
Department of Renal Medicine, St George Hospital, Sydney, Australia

A. Haber · A. Hennessy (✉)
Western Sydney University School of Medicine, Sydney, Australia
e-mail: an.hennessy@westernsydney.edu.au; an.hennessy@uws.edu.au

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Abstract

The kidneys receive approximately 25% of cardiac output and are highly exposed to the influence of drugs of addiction. While many drugs have long been known to cause kidney injury or other metabolic derangements, such as electrolyte and acid-base disorders, the mechanism and the longer-term implications of many drug-induced kidney diseases often remain poorly understood. However, both drug-induced kidney injury and pre-existing kidney disease are frequently encountered in primary care, acute medicine and critical care and when treating people with a history of drug use or addiction. Here, we define the classification and presentation of renal disease before describing the wide spectrum of renal disease associated with drugs of addiction. Both direct nephrotoxicity and indirect injury stemming from injecting drug use, such as the renal complications of blood-borne viruses, are reviewed. In addition, the interaction between drug use and chronic kidney disease and renal replacement therapy is briefly considered. Finally, we describe the spectrum of electrolyte and acid-base derangements associated with drug use.

Keywords

Acute kidney injury · Chronic kidney disease
Nephrotoxicity · Rhabdomyolysis
Blood-borne virus · Electrolyte disorders

Abbreviations

AIN	Acute interstitial nephritis
AKI	Acute kidney injury
ANCA	Anti-neutrophil cytoplasmic antibody
ATN	Acute tubular necrosis
AVP	Argenine vasopressin
CHS	Cannabis hyperemesis syndrome
CK	Creatine kinase
CKD	Chronic kidney disease
DAA	Direct acting antivirals
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
FSGS	Focal sclerosing glomerulonephritis
GIT	Gastrointestinal tract
GN	Glomerulonephritis
HAART	Highly active anti-retroviral therapy
HAN	Heroin associated nephropathy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIVAN	HIV associated nephropathy
HIVICK	HIV-immune complex kidney disease
IVDU	Intravenous drug use
KDIGO	Kidney disease: Improving Global Outcomes
MDMA	3,4-Methylenedioxymethamphetamine
MPGN	Mesangioproliferative glomerulonephritis
NSAIDs	Non-steroidal anti-inflammatories
ODS	Osmotic demyelination syndrome
PrEP	Pre-exposure prophylaxis
RTA	Renal tubular acidosis
SIADH	Syndrome of inappropriate secretion of ADH

78.1 Introduction

The relationship between drug use and renal disease is frequently indirect. Drug-associated behaviour or injuries may lead to nephrotoxicity (as in rhabdomyolysis following a prolonged lie after a drug overdose), blood-borne infections or their treatment may result in kidney disease (as in the glomerular diseases associated with hepatitis C or the renal tubular toxicity of some highly active antiretrovirals (HAART)) or other pathologies owing to drug use may cause secondary renal disease (as in hepatorenal syndrome following alcohol-related cirrhosis or hypertensive kidney disease in the context of excess alcohol intake). Finally, the continued development of novel drugs of abuse (‘designer drugs’) results in an ever evolving field as many of these agents can be associated with unpredictable nephrotoxicity.

78.2 Classification and Assessment of Renal Disease

The kidneys perform a wide variety of functions: clearance of toxins (including drugs and their metabolites) and waste products of metabolism; maintenance of acid-base and electrolyte homeostasis; and regulation of blood pressure, sodium and water balance and hormonal functions involving bone and mineral metabolism and haematopoiesis. Of these, it is the first that is most typically recognised via the measurement of serum urea and creatinine, but it is useful to recognise that derangement of all of the normal functions of the kidney frequently coexist and may have implications for clinical management.

Recognition of renal disease frequently begins with the finding of abnormalities in serum creatinine and its derived parameter – estimated glomerular filtration rate (eGFR). Creatinine originates in muscle and is excreted via both glomerular filtration and direct tubular secretion. Consequently, the amount in serum is dependent on muscle mass relative to overall body size. The equations utilised to calculate eGFR are based on population averages with the result that people at the extremes of body habitus may have renal function that deviates substantially from that provided by eGFR. Alternative equations such as the Cockroft-Gault may be useful in determining whether eGFR is over- or underestimating true glomerular filtration.

Acute kidney injury (AKI) is a rapid decline in renal function defined by a rise in serum creatinine and/or a reduction in urine output. Various classification schemes are in use, but from a practical standpoint, it suffices to understand that the risk of life-threatening complications and need for transfer to a facility with the ability to provide urgent dialysis increases along with the magnitude of rise in creatinine and the extent of the reduction in urine output. Chronic kidney disease (CKD) is the presence of a sustained, and typically permanent, reduction in renal function or the presence of persistent abnormalities of urine sediment (i.e., proteinuria or microscopic haematuria). Both acute and chronic kidney injury can be approached by considering the primary site of pathology within the renal parenchyma. Broadly, kidney diseases may be glomerular (e.g., glomerulonephritis), tubular (i.e., affecting the cells lining the tubules of the nephrons) or interstitial (e.g., acute or chronic interstitial nephritis). To this must be added renal pathology resulting from insufficient renal perfusion (i.e., pre-renal) or obstruction to urine outflow (i.e., post-renal).

In addition to a thorough history and examination (including blood pressure and fluid status), the assessment of an individual with an elevated creatinine involves testing for the presence of haematuria and proteinuria (with quantification most simply achieved with a spot urine albumin/creatinine or protein/creatinine ratio) and exclusion of important derangement of electrolytes and acid-base balance. Radiological imaging to exclude hydronephrosis or an unexpected anatomical abnormality is also often warranted. The results of these tests will help to refine the differential diagnosis and direct further testing and management.

78.3 Acute Kidney Injury

78.3.1 Overview

The causes of AKI are manifold but may be loosely categorised as pre-renal, intra-renal and post-renal. This schema aids in assessing patients with AKI by directing the history and clinical examination (Table 78.1).

78.3.2 Pre-renal AKI

Hypotension or hypovolaemia triggers neurohormonal reflex constriction of renal efferent glomerular arterioles. This acts to maintain glomerular filtration rate despite reduced renal blood flow. However, this autoregulatory mech-

Table 78.1 Drugs of abuse and renal pathology

Pattern of renal injury	Substance use association
Pre-renal AKI in the setting of cardiogenic shock, hypovolaemia, multi-organ failure or septic shock. May lead to acute tubular necrosis if prolonged or severe	Any severe overdose including acute alcohol poisoning
	Hepatorenal syndrome in the context of alcohol-induced cirrhosis
	Severe bacterial infection (e.g., associated with intravenous drug use, chronic alcohol abuse and malnutrition)
	Dehydration in the context of stimulant-induced exertion
Rhabdomyolysis resulting in acute tubular necrosis	Overdose resulting in long lie and pressure injury (alcohol, opioids)
	Stimulant-induced exertion (amphetamines, MDMA, cocaine, 'bath salts', PCP, 'herbal ecstasy')
	Hyperthermia, serotonin syndrome, seizures (amphetamines, MDMA, other stimulants)
Malignant hypertension	Cocaine, MDMA, amphetamines, chronic alcohol abuse
Renal vasoconstriction and renal infarction	Cocaine, methamphetamine
Acute interstitial nephritis	NSAIDs, cocaine, amphetamines, 'herbal' ecstasy, synthetic cannabinoids
Acute tubular necrosis (unrelated to rhabdomyolysis or pre-renal AKI)	NSAIDs, synthetic cannabinoids
Renal complications of intravascular infection (e.g., immune-complex-mediated glomerulonephritis secondary to bacterial endocarditis)	Any intravenous drug use
Blood-borne viruses with renal consequences	
HCV-related cryoglobulinemia	
HBV-related minimal change disease, membranous or mesangiocapillary glomerulonephritis	
HIV-related nephropathies	
Amyloid-A amyloidosis from chronic infection and inflammation	
Vasculitis (including anti-glomerular basement antibody disease) causing acute glomerulonephritis	Cocaine
Chronic glomerulonephritis	Heroin
Renal consequences of cirrhosis Hepatorenal syndrome IgA nephritis	Alcohol, viral hepatitis due to intravenous drug use
Obstructive uropathy	Chronic ketamine use, (rarely) MDMA, lithogenic antiretrovirals, NSAID-induced renal tubular acidosis causing nephrolithiasis

anism may be insufficient in the face of severe or prolonged hypotension or in the presence of nephrotoxins, inflammatory mediators or drugs that interfere with intrarenal signalling (e.g., non-steroidal anti-inflammatories [NSAIDs]). In these cases, pre-renal AKI may progress to acute tubular necrosis (a form of intra-renal AKI) resulting in a more prolonged and potentially incomplete recovery. Pre-renal AKI is a frequent contributor to drug-associated renal injury.

78.3.3 Intra-renal AKI

Any AKI that is not reversible by restoration of poor renal perfusion or urinary outflow is termed intra-renal. The causes of intra-renal AKI can be practically subdivided by common histo- and pathophysiologies into glomerulonephritis (typically autoimmune), acute tubular necrosis (typically due to toxins or a severe pre-renal insult) and tubulointerstitial nephritis (typically drug-induced). In some cases, for instance, bacterial

endocarditis, all of these causes may be possible diagnoses for a single patient.

78.3.4 Post-renal AKI

Obstruction of the ureters or bladder outflow tract should be considered in all cases of AKI and can be rapidly identified with renal ultrasonography or computed tomography. Although rarely related to drug abuse, a number of uncommon associations do exist. These include urinary retention due to MDMA; renal calculi due to protease inhibitors indinavir, atazanavir and darunavir [48]; and calcium calculi in the presence of renal tubular acidosis due to non-steroidal inflammatory (NSAID) use. In addition, around one-third of chronic ketamine users have urological disorders, ranging from haematuria and urinary frequency to ureteral strictures, hydronephrosis and papillary necrosis. Severe cases have resulted in the need for surgical ureteric diversion [65].

78.3.5 Management of AKI

While pre-renal or intra-renal acute tubular necrosis is most common, the clinician should be alert to signs or symptoms suggestive of systemic autoimmune disease, unexplained pulmonary and renal disease (e.g., as seen in ANCA vasculitis or anti-glomerular basement membrane disease), infection or urinary tract obstruction, which might point to other forms of renal injury. A thorough drug and medication history is essential. Analysis of urine sediment is also essential; although moderate amounts of blood and protein may be present in acute tubular necrosis, the presence of a significant degree of proteinuria and/or microscopic haematuria should prompt consideration of glomerulonephritis (see below). Pre-renal AKI is associated with a bland urine sediment and urinary sodium concentration <20 mmol/l. If acute tubular necrosis has developed then granular casts may be present, these may be pigmented if rhabdomyolysis is present. In most instances, the treatment of AKI is purely supportive and is focused on restoring intravascular volume and managing concurrent electrolyte or acid-base disorders. Treatment of severe hypertension or hyperthermia may also be required. Monitoring of urine output (with or without use of a urinary catheter) is also important as oliguric renal injury has a worse prognosis. The presence of oliguria (<30 ml/h) and/or severe acidosis, derangement of electrolytes or elevation of creatinine should prompt transfer to a unit capable of providing acute dialysis. In such cases, it is also imperative that intravenous fluid administration is carefully monitored given the risks of iatrogenic fluid overload.

78.3.6 Drug-Specific Associations with AKI

78.3.6.1 Alcohol

AKI in the context of acute alcohol intoxication is likely to be pre-renal. Alcohol causes the suppression of pituitary secretion of vasopressin, leading to diuresis and risk of hypovolaemia [29], which is often compounded by fluid loss from vomiting. In the presence of drugs that impair renal autoregulation (such as NSAID or cocaine) or nephrotoxins (as occurs in rhabdomyolysis), intra-renal injury may occur and the presence of such exacerbating factors should always be considered [74, 96]. There is also evidence of alcohol causing direct muscular toxicity [92] contributing to the development of rhabdomyolysis, either isolated or in combination with immobility, the mechanism of which is not fully understood, although oxidative stress, mitochondrial dysfunction and inflammation are thought to be contributing factors [46, 99].

78.3.6.2 Cocaine

The classic form of cocaine-associated renal injury is renal infarction resulting from intense renal vasoconstriction. In addition to vasoactive properties, cocaine also upregulates vascular endothelin-1 receptors, causing decreased renal perfusion and which in severe cases may manifest as intravascular thrombosis within small renal arterioles (known as thrombotic microangiopathy) [8, 49, 59, 109]. The presentation may be

marked by severe hypertension, although this is not universal [68]. The risks of co-ingestion of other drugs with renal vasoactive properties (including NSAIDs) cannot be underestimated in this setting. Other precipitating factors may include dehydration caused by poor oral intake combined with excessive physical activity and high heat environments [13], rhabdomyolysis (which may also be exacerbated by hyperthermia and impaired thermoregulation) [30, 109] and concurrent alcohol abuse [68]. Cocaine-associated acute interstitial nephritis has also been reported, although this appears to be rare, and it remains unclear if these instances were due to the drug or to contaminants (especially when used in the form of crack cocaine) [2, 6, 39].

78.3.6.3 Amphetamines and Other Stimulants

Like alcohol and cocaine, amphetamine derivatives are associated with pre-renal AKI owing to dehydration following exertion at dance parties and may be compounded by toxicity from non-traumatic rhabdomyolysis. Acute tubular necrosis and renal infarction have been described and are believed to be due to vasoconstriction and malignant hypertension. Post-renal AKI due to bladder outlet obstruction following MDMA has also been reported, although the precise mechanism of anti-cholinergic and/or alpha-adrenergic stimulation responsible for this is not clear [12, 15]. Rarely, like cocaine, MDMA has also been associated with thrombotic microangiopathy [53]. In addition to renal pathology, MDMA is also associated with severe and sometimes fatal hyponatraemia (discussed in detail at the end of this chapter). Serotonin syndrome is a potentially lethal complication of MDMA and especially of derivatives such as PMMA, characterised by malignant hyperthermia, rhabdomyolysis and acute kidney injury [76]. With the emergence of novel synthetic compounds – particularly stimulants such as synthetic cathinones (e.g., 'bath salts') and phenylpiperazine derivatives (e.g., 'herbal ecstasy') – a variety of types of AKI have been reported. Most instances represent pre-renal AKI and/or rhabdomyolysis, and the renal pathology is hypothesised to be similar to that associated with MDMA or cocaine, given the structural and pharmacological similarities [82, 83]. Finally, rare cases of acute interstitial nephritis (a type 4 hypersensitivity reaction) have been reported with amphetamines and with phenylpiperazine derivatives (e.g., 'herbal ecstasy') [35, 65].

78.3.6.4 Opioids

Heroin is most commonly associated with renal injury due to various forms of glomerulonephritis, which are discussed elsewhere in this text. However, heroin and other opioids have also been associated with rhabdomyolysis secondary to prolonged immobility in overdose or local necrosis caused by intravenous drug use (IVDU) [42, 77, 87]. More recently, a form of crystal nephropathy caused by precipitation of heroin or its metabolites in tubules in association with volume depletion and elevated urinary pH has also been reported [7].

78.3.6.5 Cannabis and Synthetic Cannabinoids

Although cannabis and the active substance (delta-9 tetrahydrocannabinol) do not appear to be nephrotoxic, cannabis hyperemesis syndrome caused by chronic cannabis may cause hypovolaemia leading to pre-renal AKI [43]. A related issue however is the relatively recent rise in cases of AKI associated with synthetic cannabinoids (e.g., 'Spice'). Synthetic cannabinoids consist of a variety of chemicals, both related and unrelated chemically to natural cannabinoids. These mixtures can stimulate both CB1 and CB2 receptors, which may play a part in the increased incidence of AKI [18]. Renal biopsies have most commonly demonstrated ATN as causative process, although AIN has also been seen [65, 107].

78.3.7 Rhabdomyolysis

Rhabdomyolysis is a common form of indirect renal injury, and this can arise from significant drug use, including acute alcohol poisoning, cocaine, MDMA and narcotic use and overdose

(prolonged immobilisation). Novel synthetic drugs have also been associated with rhabdomyolysis, including phenylpiperazine derivatives, synthetic cathinones and phencyclidine [65]. It is of particular concern in the setting of dehydration, hyperthermia and drug toxicity from MDMA used in dance settings. The specific pathophysiological abnormalities include direct tubular toxicity from myoglobin metabolites such as ferrihemate, vasoconstriction induced by these agents, and lipid peroxidation. Myoglobin casts can also form, leading to tubular obstruction. The diagnosis of rhabdomyolysis is confirmed by elevated levels of creatine kinase (CK) in the circulation. For AKI to occur, generally high CK levels (>15,000 U/l) are required except when the rhabdomyolysis is accompanied by acidosis, dehydration and/or sepsis.

Treatment involves fluid resuscitation and restoration of electrolyte disturbances. Recommended practice includes aggressive IV hydration to achieve a target urine output of at least 300 ml/h, with administration of alkali to establish urine pH > 6.5 [24]. A small randomised trial (n = 28) in doxylamine-induced rhabdomyolysis suggests that hydration with balanced crystalloid (e.g., Ringer's lactate) results in higher urine pH than 0.9% saline, although no differences in patient outcomes were identified [26]. A larger trial (n = 98), also in doxylamine-induced rhabdomyolysis, found lower CK levels at 6 h in participants treated with sodium bicarbonate containing fluid than in those treated with 0.9% saline [56]. No differences in renal outcomes were observed. The importance of these results is not clear. The principle underlying alkalinisation is not to reduce serum CK levels, but to prevent acute kidney injury. In practice, treatment intensity should be matched to the severity of rhabdomyolysis and of concomitant acute illness, with recognition that risk of AKI is greatest in the presence of dehydration and oliguria.

78.3.8 Hepatorenal Syndrome

Hepatorenal syndrome is a well-described and often terminal complication of cirrhosis of all causes. It is almost invariably associated with portal hypertension and the pathophysiology is linked to profound renal vasoconstriction in response to intense neurohormonal stimulation, including activation of the renin-angiotensin-aldosterone system. Additional pathological pathways may also contribute, including systemic inflammation and bile-salt-induced tubular damage [3]. Hepatorenal syndrome is classified as type 1, defined by rapidly progressing acute kidney and poor prognosis, and type 2, when renal deterioration is slower in onset and associated with ascites; the prognosis is still poor although survival is typically longer (months rather than weeks). Treatment of type 1 disease involves treatment of any precipitants, such as dehydration or over-diuresis, active upper GIT bleeding or bacterial peritonitis and albumin replacement and terlipressin, a vasopressin analogue. The addition of terlipressin significantly improves survival and transplant-free time, although mortality rates still average 45% [103].

78.4 Glomerulonephritis Associated with Drug Use

A variety of diseases associated with drug use specifically affect the glomeruli, causing glomerulonephritis. It is important to distinguish these cases from more common causes of renal injury as their prognosis and management can be distinct.

78.4.1 Diagnosis of Glomerulonephritis

The hallmark of glomerular disease is proteinuria – i.e., the excretion of greater than 300 mg/day of urinary protein (loosely approximated by a spot urinary protein-creatinine rate of 30 mg/mmol or 30 mg/g). Microscopic haematuria may also occur with some, but not all, causes of glomerulonephritis. In addition to quantitation of urinary protein excretion, analysis of urine sediment for casts (especially red cell casts – which are highly specific for glomerulonephritis) and

Table 78.2 Glomerulonephritis

	Nephritic	Nephrotic
Urine protein excretion	<3.5 g/day	>3.5 g/day
Microscopic haematuria	Present	Absent
Serum albumin	Normal	Low
Oedema	Mild or absent	Marked
Hypertension	Present	Absent
Reduced eGFR	Present	Absent

dysmorphic red cells will aid in the diagnosis. Note that common causes of chronic kidney disease which may coexist with drug use, notably diabetic nephropathy and, to a lesser degree, hypertensive or atherosclerotic nephropathy, may also exhibit proteinuria.

Glomerulonephritis is classically described as either nephritic or nephrotic (Table 78.2). Nephritic presentations are characterised by acute deteriorations in renal function, hypertension and microscopic haematuria with moderate proteinuria. Such presentations are classically associated with aggressive pathologies such as renal vasculitis, which if not treated can rapidly progress to end-stage kidney disease. Nephrotic presentations (classically, nephrotic syndrome) is defined by marked proteinuria and often dramatic reductions in serum albumin, with no or only mild reduction in renal function. While recognising these different presentations is useful to narrow the differential diagnosis, many patients will exhibit features of both syndromes, particularly in the presence of comorbidities such as chronic liver disease or malnutrition.

78.4.2 Rapidly Progressing Glomerulonephritis

Nephritic syndrome accompanied by a rapid decline in renal function requires urgent investigation and management. Typical causes include anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and systemic lupus erythematosus; however rare presentations are related to drug use. Anti-glomerular basement membrane disease (Goodpasture's disease), a nephritic syndrome presenting with a rapidly rising creatinine, acute pulmonary haemorrhage, haemoptysis and pulmonary oedema has been associated with intranasal and smoked 'crack' cocaine use [79]. The pathophysiology of this 'pulmonary-renal' syndrome is thought to result from exposure of alveolar basement membrane due to pulmonary injury and the formation of antibodies to type IV collagen, which is also found in the glomerular basement membrane. Renal biopsy is essential as serum anti-glomerular basement antibodies have been reported in 'crack' cocaine users with unrelated renal pathology [71]. Treatment with haemodialysis and immunosuppression or plasmapheresis is usually indicated for the specific treatment of uremia and for decreasing the circulating antibody. Cocaine adulterated with levamisole (which contaminates up to 70% of cocaine samples in the USA) has been associated with antineutrophic cytoplasmic antibody (ANCA)-positive vasculitis, which may present with skin purpura and deteriorating renal function [50]. It can result in severe renal failure requiring dialysis and require treatment with immunosuppression. Glomerular diseases associated with blood-borne viruses may be indirectly associated with drug use, and screening for HBV, HCV and HIV should be performed in all cases of rapidly progressing glomerulonephritis. These diseases are discussed specifically below under the heading of 'Blood-borne viruses in drug users and renal consequences'.

78.4.3 Glomerular Disease Associated with Bacterial Infection

Drug use is a common contributor to intravascular bacterial infection, either via bacterial seeding from intravenous injection or nasal disruption from nasal inhalation [58]. Renal dysfunction in this setting occurs in 35–45% of patients and can arise for a variety of reasons [85]. The primary differentials are acute tubular necrosis due to sepsis (or less commonly directly caused by high-dose penicillins, glycopeptide or aminoglycoside antibiotics [72], antibiotic-induced acute interstitial nephritis or immune-complex-mediated glomerulonephritis. Intravascular infections, e.g.,

endocarditis, can also cause renal impairment from infectious vasculitis with mycotic involvement (bacterial microabcesses) as well as necrotising segmental infarction from septic emboli. The time course of the deterioration in renal function and the presence or absence of proteinuria, microscopic haematuria and other features of nephritic syndrome aid in narrowing the diagnosis.

Less common complications of infection include AA amyloidosis which may affect the drug user with recurrent infection and presents with nephrotic range proteinuria, with or without the complete nephrotic syndrome [67]. Rare cases of ANCA-positive renal vasculitis have also been reported and present significant therapeutic challenge [23]. Increasingly, chronic staphylococcal infections (including endocarditis) associated with glomerulonephritis with IgA deposition are increasingly identified in older individuals with predisposing conditions such as cirrhosis, hepatitis C and, especially, diabetes [22, 66, 89]. The presentation of immune-complex-mediated glomerulonephritis is most usually nephritic syndrome (hypertension and haematuria), but in a minority of cases, it can be nephrotic with normal blood pressure.

Treatment of immune-complex-mediated glomerular disease in the setting of infection is directed at control of the infection, supportive care including dialysis if the renal impairment is severe and, if interstitial nephritis is suspected or confirmed, variation in antibiotic use. Renal biopsies are performed if diagnosis of acute interstitial nephritis is required to change the antibiotic choice or if the presentation is atypical or associated with nephrotic syndrome or rapidly progressive disease.

78.4.4 Nephrotic Syndromes

The most common lesion associated with nephrotic syndrome in those with a history of drug abuse is focal sclerosing glomerulosclerosis (FSGS). Historically linked to heroin use (termed heroin-associated nephropathy (HAN)), FSGS was thought to be due to contaminants (bacterial or viral) or poor-quality heroin or morphine as the incidence of these has declined in the era of proven blood-borne virus-related nephropathy. The striking association with FSGS, end-stage kidney disease (ESKD) and African-American ancestry was subsequently linked to the high prevalence (over 40%) of APOL1 variants in this population [60]. It is hypothesised that intravenous drug use provides a 'second hit' to those with underlying susceptibility to renal injury. Similarly, classic human immunodeficiency virus (HIV)-associated nephropathy (HIVAN), which is also disproportionately observed in African Americans and also presents with FSGS, is thought to similarly reflect this predisposing factor.

FSGS is only the most common of a variety of renal lesions found in drug users, which also includes minimal change disease, MPGN, mesangial proliferation, dysproteinemias and diabetic nephropathy, which presumably may, at times, be coincidental to the history of drug use. In a large post-mortem cohort of German drug users, hypertensive-ischemic nephropathy was identified as the most common renal histopathological abnormality, highlighting the importance of comorbid cardiovascular disease and hypertension in this group [16]. In this study, heavy IVDU was associated with interstitial inflammation and calcification, whereas cocaine abuse was strongly associated with hypertensive-ischemic changes. Anabolic steroid use is also associated with glomerular pathology, with case reports and one case series indicating that chronic use of these agents can result in variable degrees of proteinuria and impaired renal function. Biopsy reports indicate focal sclerosing glomerular sclerosis as the underlying pathology. The role of high protein intake–induced glomerular hyperfiltration is also likely to play an important role and the relative contribution of steroids alone is not clear [80].

78.4.5 Cirrhosis-Associated IgA Nephropathy

IgA disease (deposition of IgA in the mesangium of the glomerulus) can arise in the setting

of alcoholic cirrhosis, and IgA deposition is detected in up to 64% of autopsies from chronic alcoholics [90, 95]. Intriguingly, as in primary IgA nephropathy, circulating IgA molecules in cirrhotic patients display abnormal glycosylation, but the pattern of abnormal glycosylation appears distinct. While frequently of little clinical consequence, this secondary form of IgA nephropathy can result in proteinuria, haematuria and chronic kidney disease [93]. Case reports of nephrotic syndrome due to IgA deposition also exist [94]. Increased serum IgA levels in cirrhosis are thought to be due to increased production from intestinal lymphocytes as well as impaired hepatic clearance and porto-systemic shunting [31].

78.4.6 BBV in Drug Users and Renal Consequences

78.4.6.1 Hepatitis B

Hepatitis B is associated with membranous nephropathy and mesangiocapillary pattern (membranoproliferative) glomerulonephritis, the former presenting as nephrotic syndrome (more commonly in infected children) and the latter as nephritic syndrome with progressive renal failure if left untreated. Males are more likely to be affected. Other rarer manifestations are minimal change nephropathy (nephrotic syndrome) and polyarteritis nodosa (an aggressive form of glomerular disease associated with progressive renal damage). These are widely thought to represent a spectrum of immune disease ranging from in situ immune reactions to hepatitis antigens present in various components of the glomerulus (membrane and subepithelial locations) to the deposition of immune complexes arising from the chronic antigenemia in the circulation [101].

Treatment strategies in hepatitis B-related GN have been revolutionised by the use of effective antiviral therapies, which are associated with much higher rates of remission of renal disease than seen with supportive therapy alone [63, 102]. The role of adjunctive immunosuppressive therapy remains unclear. Meta-analysis (including 1 RCT and 11 non-randomised studies) suggests that the addition of immunosuppression (predominantly corticosteroids with an antiproliferative (mycophenolate or leflunomide)) to antiviral treatment results in more rapid remission of proteinuria without additional risk [108]. It is also important to note that antibodies to phospholipase-A2 receptor (PLA2R), often considered as synonymous with ‘idiopathic’ membranous GN, may also be common in patients with HBV-associated membranous GN [106]. It is not known if this identifies a subgroup more likely to benefit from immunosuppression, although successful use of rituximab has been reported [9].

78.4.6.2 Hepatitis C

Hepatitis C can be associated with cryoglobulinemic renal disease, which causes a membranoproliferative GN and can rapidly progress to irreversible renal injury. Presentation may include extra-renal manifestations such as purpura in the distal limbs, arthralgia and neurological symptoms [20]. Management of HCV-associated cryoglobulinemic glomerulonephritis is changing in the era of directly acting antivirals (DAA). Previous treatment frequently included immunosuppression with glucocorticoids and rituximab with consideration of plasmapheresis. However, provision of DAA now allows use of immunosuppression to be restricted to cases of severe vasculitis [86]. Less common associations of HCV are membranous nephropathy, fibrillary glomerulopathy, immunotactoid glomerulopathy and IgA nephropathy [63].

78.4.6.3 HIV

HIV is associated with a wide variety of renal pathology. Classic HIV-associated nephropathy (HIVAN) is a podocytopathy resulting in focal segmental glomerulosclerosis (FSGS), nephrotic syndrome and eventual progression to ESKD [63]. Some population subgroups, notably African-Americans, are at much greater risk for nephropathy in the presence of HIV infection. This appears to be mediated by a higher prevalence of APOL1 gene variants that increase the risk of FSGS. Fortunately, suppression of viremia with HAART is associated with slower pro-

gression of renal disease and a lower likelihood of reaching ESKD [70].

HIV immune complex kidney disease (HIVICK) is a separate entity to HIVAN and results in nephritic syndrome with proliferative GN and extensive immune activity ('full house' immunofluorescence staining for IgM, IgG, IgA, C3 and C1q) on biopsy [63]. Other renal pathologies associated with HIV include IgA nephropathy, membranous GN, immunotactoid GN, interstitial nephritis and amyloidosis, which highlights the importance of renal biopsy in patients with HIV and renal disease [64]. In general, treatment consists of HAART with additional therapies (including immunosuppression) guided by usual practice in the non-HIV population.

HIV-infected individuals have higher rate of chronic kidney disease, not only due to glomerulopathies described above but also likely due to chronic inflammation and exposure to the metabolic and nephrotoxic effects of HAART. In particular, tenofovir is associated with renal tubular toxicity manifesting as proteinuria, phosphaturia, glycosuria and variable degrees of reduction in renal function [44]. It should also be noted that a number of antiretrovirals (tenofovir, rilpirivine, dolutegravir and the boosting agent cobicistat) inhibit renal tubular creatinine secretion, which results in a persistent but reversible elevation of serum creatinine without underlying renal toxicity [44, 64]. The use of tenofovir in patients who have, or who develop, CKD is controversial, with studies conflicting as to the risk of further loss of renal function with tenofovir. It is suggested that tenofovir is best avoided in patients with an eGFR <60 ml/min/1.73 m^2, but that it may be used when other agents are not available, provided renal function is appropriately monitored [64]. The potential for renal toxicity from tenofovir should also be considered when using pre-exposure prophylaxis (PrEP). While the reductions in renal function identified are modest (and of uncertain clinical significance), they are greater in those with baseline impairment or renal function or older age [38].

78.5 Chronic Kidney Disease Associated with Drug Use

78.5.1 Classification

Chronic kidney disease (CKD) affects up to 1 in 10 individuals globally and a growing contributor to morbidity and mortality.It is defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or by the presence of proteinuria (regardless of eGFR). The risk of progression is related to the degree of reduction in eGFR and degree of proteinuria, which can be used to define stages of CKD (see Fig. 78.1).

78.5.2 Approach to Chronic Kidney Disease in the Drug User

Use of illicit drugs is a risk factor for chronic kidney disease, which likely reflects the co-incidence of multiple renal risks, including infection with HIV or HCV and nephrotoxicity from drug abuse or from complications such as bacterial infection [17, 69]. More broadly, some authors hypothesise that drug addiction results in the premature appearance of diseases associated with ageing, such as cardiovascular disease and chronic kidney disease [5]. Whether this reflects a fundamental shift towards physiological stressors (e.g., oxidative stress, inflammation and mitochondrial dysfunction) or is more simply understood as the result of the presence of multiple risk factors such as cigarette smoking, alcohol-driven hypertension and metabolic disturbances and repeated infections or inflammatory insults is not clear. Alcohol may indirectly affect renal function by means of chronic hypertension and via its contribution to increased caloric intake, obesity and thus risk of diabetes mellitus. However, these relationships are complex. At a population level, moderate levels of alcohol use have been associated with both worse and better renal function [57, 78], and a recent meta-analysis suggested that higher alcohol consumption is associated with a lower risk of CKD [25]. Alcohol use has also been associated with albuminuria, although the degree to which this represents causation ver-

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 30–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk, Red: very high risk.

Fig. 78.1 Prognosis of CKD by GFR and albuminuria category

sus unmeasured confounding by other behaviours or risk factors remains unclear [104]. Differences between populations (including between the form in which alcohol is consumed) and in study methodology may in part explain these differing results. Moreover, general population studies do not reflect the pathology of individuals with alcohol abuse disorders; a recent study focusing on individuals with a diagnosis of alcohol use disorders identified a twofold increase in the incidence of CKD [78]. As such, screening patients with alcohol abuse disorders for renal disease and for risk factors for CKD (e.g., hypertension and diabetes mellitus) appears prudent.

Core principles of the management of CKD can be found in guideline documents [54] or, more helpfully, in summary resources [55, 97, 100]. Essentially, it consists of optimisation of blood pressure, diabetes and cardiovascular risk factors as well as the use of angiotensin system blockade in patients with macroscopic proteinuria. Additional factors include drug dosing adjustments and avoidance or cautious use of potentially nephrotoxic agents.

Treatment of drug addiction may be affected by the presence of chronic kidney disease [4]. Disulfiram metabolites are renally excreted and its use should be carefully monitored in patients with impaired renal function. Acamprosate is contraindicated in severe renal impairment and dose reduction is recommended for those with moderately impaired renal function. Opioids and their derivatives (including methadone, naltrexone) are generally not nephrotoxic; however renal elimination of drug or active metabolites is common and reductions in dosage or frequency of administration should be considered along with cautious uptitration. Similar consid-

erations apply to baclofen, which is renally excreted and which has been the cause of life-threatening sedation when used in standard doses in patients with advanced renal disease [4]. Buprenorphine and methadone are primarily hepatically cleared; however in advanced (stage 4–5 including dialysis) CKD, small (50–75% normal) starting doses and cautious uptitration are still recommended [91].

78.6 Renal Replacement Therapy in the Setting of Drug Use

Although end-stage renal disease rarely arises de novo from drug use, this has been described with prolonged MDMA and cocaine use causing malignant hypertension. Providing long-term dialysis to individuals with drug and addiction issues can be complex. Issues of vascular access, repeated intravascular infection, difficulties with pain management and compliance with fluid restriction regimes are just a few of the complications. Use of illicit drugs at haemodialysis initiation is associated with shorter survival, particularly in younger patients whose adjusted risk of mortality is up to 9 times higher than similar patients without a history of drug use [41].

As in CKD, altered pharmacokinetics also needs to be considered. Drug clearance may be markedly reduced in the presence of advanced kidney disease, with clearance of drug on haemodialysis also needing consideration as dose may be best delayed until after dialysis. There is enormous variability within drug classes in the need to adjust dosages for renal impairment or renal replacement therapy. Opioids provide an illustrative example of this variation. Morphine undergoes hepatic metabolism to glucuronide conjugates, which are pharmacologically active and dependent on renal excretion such that toxicity is relatively more likely in those with marked reductions in renal function, primarily due to the unpredictable accumulation of active metabolites. Hydromorphone is preferred in advanced renal failure as its metabolites are better tolerated. In contrast, both methadone and buprenorphine are subject to hepatic metabolism with renal clearance of metabolites; however as these metabolites are inactive, no dose reduction is required in the presence of kidney disease (although 50–75% dose reduction is still recommended for those on dialysis or with eGFR <10 ml/min/1.73 m^2) [32]. Dialysability also differs widely. Hydromorphone and morphine to a lesser extent have relatively lower volumes of distribution and low protein binding, allowing them to be partially cleared on haemodialysis. The large volume of distribution and high protein binding of buprenorphine and methadone mean that they are not cleared to any significant degree on haemodialysis. In practice, even with potentially cleared drugs such as hydromorphone, additional opioid dosing after dialysis is rarely required. The core principle of opioid dosing in renal impairment is ‘start low and go slow’, and consult one of the many specialised resources available [91]. Kidney transplant recipients are most at risk of adverse events from drug interactions with their immunosuppressive agents (especially calcineurin inhibitors), and pre-emptive adjustments and close monitoring of drug levels may be required.

The optimal form of renal replacement therapy for most patient is kidney transplantation; however patients with a history of drug abuse or with blood-borne viral infections are less likely to be listed for transplantation and wait longer once listed [28, 88]. The reasons for this are complex as transplant in addicted individual poses particular challenges. Issues include peri-transplant pain management and vascular access and longer-term management chronic immunosuppression and its associated infection and cancer risk in individuals with ongoing high-risk behaviour, comorbid psychiatric diagnoses and/or minimal social support [61]. The role of clinician beliefs or biases in transplant listing should also be considered, in particular the perceived association between substance abuse and medication non-adherence – a strong risk factor for graft rejection, especially in young adults [88]. While evidence to support this association exists [19], interventions to improve compliance are available [36], and it is essential to individualise risk assessment and treatment decisions.

Transplantation may be preferable to the complexity of continuing dialysis in this setting.

Infection with hepatitis B, C or HIV is not a contraindication to renal transplantation. Despite the intensive immunosuppression required for successful transplantation, modern HAART and DAA now provide the ability to reliably eradicate (HCV) or suppress (HIV and HBV) blood-borne viruses [62]. While transplant recipients with chronic HCV infection have increased risk of graft loss and mortality, they still stand to gain substantial benefit as compared with remaining on dialysis [86]. Given that much of the existing data is from the pre-DAA era, it is likely that outcomes for HCV-positive recipients are improving. The success of HCV treatment with DAA, with sustained virological response in >95% of those treated [86], has encouraged the use of deceased donor kidneys from HCV-positive donors, typically for HCV-positive recipients who are therefore able to reduce their waiting time [62]. A viable argument is now being made for transplanting kidneys from HCV-positive donors for HCV-negative recipients based on successful case series [40] and observational data [62]. Since the introduction of lamivudine prophylaxis, HBV-positive renal transplant recipients have similar graft and overall survival, although their risk of liver failure remains higher than HBV-negative recipients [81].

78.7 Metabolic Derangements Associated with Drug Use

78.7.1 Dysnatraemias

Hyponatraemia is a potentially fatal consequence of amphetamine, primarily MDMA, use. Hyponatremic encephalopathy (caused by cerebral oedema secondary to the formation of an osmotic gradient between the hypo-osmolar serum and iso-osmolar cerebral interstitium) is the most feared complication. A majority of cases are females under the age of 30 who present with headache and vomiting followed by lowered level of consciousness which may lead to seizures, coma and death [51]. The primary factors appear to be the ingestion of water in the context of sweating and physical exertion along with the release of arginine vasopressin (AVP) under the influence of MDMA metabolites which causes the syndrome of inappropriate secretion of ADH (SIADH) [73, 105]. The risk of hyponatraemia and of hyponatremic encephalopathy appears to be higher in women, thought to be due to increased sensitivity to AVP and to oestrogen-induced differences in cerebral sodium handling. Indeed, one study found that one in four of female MDMA users sampled at a rave party had mild (subclinical) hyponatraemia as compared to only 3% of males, suggesting that particular caution should be exercised by female MDMA users [98]. In addition to MDMA, related compounds methylone and ethcathinone (marketed as 'legal ecstasy') have also been associated with severe hyponatraemia [14]. Hyponatraemia has rarely been reported in association with cocaine use; however three of the four cases involved cocaine adulterated with levamisole (the fourth case was not tested for levamisole), and it is possible that this (rather than the cocaine) may have been the cause of hyponatraemia [37, 52]. Management of severe, symptomatic hyponatraemia due to MDMA or related compounds involves administration of small boluses of hypertonic (3%) saline, with close monitoring and repeated boluses as needed to achieve a controlled rise in serum sodium [73].

Hyponatraemia is commonly associated with moderate to severe chronic alcohol abuse (so-called beer potomania). The pathophysiology relates to continued intake of fluid despite low solute intake. Low solute intake impairs the ability of even normally functioning kidneys to excrete water as urine solute concentration (osmolality) cannot fall below approximately 50 mOsm/l. This means that a minimum of 50 mOsm of solute must be consumed (or generated from catabolism) for each litre of free water consumed. Moreover, non-osmotic release of ADH in response to gastrointestinal losses from chronic diarrhoea, nausea or vomiting can result in the superposition of a state analogous to the syndrome of inappropriate ADH (SIADH), further predisposing to hyponatraemia. Importantly, patients with alcohol-associated chronic hyponatraemia appear to be at especially

high risk of osmotic demyelination syndrome (ODS) with overly rapid correction of hyponatraemia. Hence, cautious initiation of refeeding, close monitoring and a willingness to use hypotonic fluid to slow the rise in serum sodium may be required [47]. Early administration of thiamine is warranted in all cases. Finally, hyponatraemia is common in cirrhosis, regardless of cause of liver disease, and is associated with reduce survival. Management typically relies on fluid restriction and judicious use of diuretics.

78.7.2 Disorders of Acid-Base Balance and Other Electrolytes

Use of many illicit substances is not associated characteristic acid-base or electrolyte abnormalities beyond those that may emerge in with acute or chronic renal injury, but there are important exceptions. Chronic alcohol use is associated with a variety of electrolyte disorders (in addition to hyponatraemia described above), most often via indirect mechanisms such as excessive vomiting/gastritis, chronic diarrhoea and pancreatitis. Electrolyte disturbance from alcohol-induced diarrhoea is well reported**.** There are additional complications related to specific inhibition of magnesium absorption and phosphate malabsorption and poor nutrition, but the major pathology is from rapid GIT transit time, mucosal damage and a range of gastropathies (gastritis, ulceration and paresis) [1]. Chronic alcohol intake is commonly associated with hypomagnesemia [33]. Alcoholic ketoacidosis may be present in malnourished alcohol-dependent patients and results in an elevated anion gap metabolic acidosis [1]. An emerging cause of metabolic acidosis is that associated with abuse of non-steroidal anti-inflammatories (NSAIDs), often via combined codeine-NSAID preparations. Chronic NSAID abuse results in a type-1 renal tubular acidosis (RTA) and is defined by normal anion gap acidosis (low bicarbonate, high chloride) and hypokalaemia, which may be profound [11, 27, 75]. Type 1 RTA also causes hypercalciuria and NSAID-induced RTA has been associated with nephrocalcinosis [34]. This RTA improves with cessation of NSAID use but may not fully resolve.

There are no direct renal consequences of marijuana use; cyclical vomiting can result in renal and electrolyte disturbances. Cannabis hyperemesis syndrome (CHS) is increasingly commonly seen in regions of the USA following legalisation [10]. Case reports have associated CHS with hypophosphatemia, hypokalaemia and acute renal failure, although these complications appear rare [21, 84]. CHS may also complicate the presentation of other illnesses, as shown in a case report of a cannabis user with type 1 diabetes presenting with the unusual combination of ketoacidosis and an elevated serum bicarbonate [45].

78.8 Conclusions

Drug use is associated with a myriad of renal and electrolyte pathologies and drug use should be considered as a potential contributor in all patients presenting with acute renal failure or acute electrolyte disturbances. Conversely, patients with a history of drug abuse are at increased risk of kidney disease and should be screened for elevated serum creatinine and for albuminuria. Despite the increased risks for this patient population, it remains essential that patients with a history of drug abuse receive equitable access to care. The management of CKD continues to evolve and new therapies may offer greater relative benefits to previously disadvantaged groups.

Key Points

- Acute kidney injury or electrolyte derangement can be caused by a wide variety of drugs of abuse, and a thorough drug history is essential in evaluating such presentations.
- Renal pathology in people with a history of drug use is often only indirectly related to drug use. Examples include

acute kidney injury due to rhabdomyolysis following overdose or the glomerular diseases associated with blood-borne viruses and IVDU.
- Chronic kidney disease and especially renal replacement therapy (dialysis or kidney transplantation) complicate the management of people with drug addiction. Additional psychosocial support and careful attention to drug-drug interactions and drug dosage adjustments are required.
- Acute electrolyte derangements, especially hyponatraemia associated with stimulants or chronic alcohol abuse, can be life-threatening and require prompt, but judicious, treatment to avoid potentially fatal brain injury.

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Trauma and Addiction Medicine

79

Michael Dinh and Matthew Oliver

Contents

Abstract

Trauma systems are designed to transport, triage and treat severely injured apatients to maximise chances of survival and functional recovery. Drug abuse and addictions are closely associated with many types of severe physical injuries. Many patients presenting with trauma also have intercurrent and underlying drug- and alcohol-related comorbidities. Recognition of these in the acute setting helps to improve hospital management of these patients and minimise the risks of deterioration and complications. Acute hospital treatment also represents opportunities for interventions to help patients identify and better manage drug addictions.

Keywords

Trauma · Severe injuries · Hospital assessment

M. Dinh (✉) · M. Oliver
Royal Prince Alfred Hospital, The University of Sydney, Discipline of Emergency Medicine, Sydney, NSW, Australia

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79.1 Introduction

Injuries remain the leading cause of death around the world in people under 45 years of age [1]. It is estimated that over 16,000 people die every day from injuries and many more are left with permanent disabilities. As a result of increased urbanisation and road transportation in developing countries over the past 20 years, road trauma has risen to the sixth leading cause of early death in 2017 from eighth in 1990 [2]. In recognition of this, the World Health Organisation set out to reverse this trend by supporting a global decade of action on improving road safety from 2011 to 2020. Disturbingly, intentional or self-inflicted injuries follow closely behind road trauma as a cause of death in these age groups, and, as the population ages, particularly in developed nations, falls have become an increasingly common cause of morbidity in the elderly [3].

Substance abuse, particularly alcohol, has long been recognised as a risk factor for all these injury mechanisms [4, 5]. Causal associations exist on a number of levels. Firstly there are dose-related effects of certain drugs ranging from disinhibition and impaired concentration through to aggression and impaired level of consciousness that increase the risk of road crashes, falls and assaults [6]. Secondly social factors related to the acquisition and distribution of illicit drug use increase exposure to violent crime and penetrating trauma. Thirdly substance abuse often coexists with psychiatric disorders, increasing the risk of self-inflicted harm and harm to others [7]. Finally, major trauma is a well-described risk factor for the development of posttraumatic stress disorder, which itself leads to substance abuse and a vicious cycle of further injury [8]. For these reasons and more, substance abuse exacts an enormous cost to society. In Australia in 2009, the costs of alcohol abuse alone were estimated to be over $15 billion dollars, which includes tangible costs such as costs of road trauma, hospital treatment and crime and intangible costs such as lost productivity and emotional distress [9].

Emergency departments (EDs) function within health systems to identify and stabilise acute undifferentiated health problems [10]. This paradigm is exemplified by the modern trauma system, where the trauma team assesses and manages patients with life-threatening injuries and prepares the patient for definitive surgical treatment. EDs are also an important point of episodic health care for many people through unplanned admissions and exacerbations of chronic conditions. In most societies EDs also provide access to basic level care and a safety net for socially disadvantaged and isolated populations. Therefore EDs commonly identify and treat patients with substance abuse disorders [11].

These patients present to ED with a wide spectrum of problems, some of which are listed in Table 79.1. The effect of alcohol and drugs of addiction on a patient's cognition and physical abilities means that these patients are at a higher likelihood of suffering trauma. A study in Louisiana found that up to 70% of patients admitted after severe injuries had positive drug or etha-

Table 79.1 Common emergency presentations for patients with substance abuse

Drug intoxication or overdose
Drug withdrawal syndromes
Seeking help or counselling regarding substance abuse
Injuries
Blunt and penetrating assault
Road traumas (including motor vehicle, pedestrian cyclists)
Falls
Domestic violence
Self-inflicted harm
Behavioural and mental state disturbance
Aggression and violence
Psychosis
Depression
Confusion
Medical conditions
Liver failure
Hyponatraemia
Renal failure
Cardiac failure
Atrial fibrillation
Stroke
Aortic dissection
Sepsis
Pneumonia
Infective endocarditis

nol urine screens [12]. A similar study of over 1000 trauma patients at the R Adams Cowley Shock Trauma Center in Baltimore found that rates of positive drug screens around 64% (opiates, cocaine and marijuana) in trauma patients [13]. Patients with substance abuse disorders often present with multiple complaints, confounding even the simplest presentations like a sprained ankle, making such patients amongst the most complex patients to deal with safely and successfully in the ED environment. These management difficulties are often compounded by a patient's own impaired judgement and increased risk-taking behaviours [14]. As a consequence the severity of injury and likelihood of suffering trauma tends to be higher in acutely intoxicated individuals than the general population [13, 15, 16]. Despite these increased chances of trauma, the evidence that these patients have a worse outcome compared to non-intoxicated patients is sparse. Only a handful of studies demonstrate worse outcomes for drug- and alcohol-intoxicated patients compared to non-intoxicated patients with the same injuries [17–21] (Table 79.2).

As a consequence this population is at an increased risk of motor vehicle accidents (MVAs), pedestrian injuries, blunt assault, penetrating assault (stab wound or gunshot wound), self-harm and falls [22, 23]. One study reviewing the odds of patients suffering from severe injury following an MVA identified alcohol use as the greatest predictor over other factors such as age, seat-belt use and vehicle crash. The presence of alcohol intoxication more than doubled the risk for serious injury [15].

Table 79.2 Risk behaviours found of acute and chronic alcohol users

Behaviour	Percentage of patients (n = 145) (%)
Driving	
Don't always wear seat belt	37.9
Don't always obey speed limit	71.1
Ridden with driver under the influence	41.1
Driving under the influence	33.8
Additional driving	
Recent citation/arrest/ license suspension	44.1
Prior DWI/DUI arrest	17.2
Violence	
Carried a weapon	10.3
Recent physical altercation	35.2
Prior assault with weapon	30.3
Suicide	
Suicidal ideation in last year	26.9
Prior suicide attempt	13.8
Additional risk factors	
Lifetime drug use	57.9
Current drug use	32.5
Prior alcohol/drug treatment	20.0

Adapted from Field et al. [14]
DWI driving whilst intoxicated, *DUI* driving under the influence

79.1.1 Injury Profiles

A variety of injury profiles are found in drug and alcohol users ranging from minor to major injuries depending on the mechanism. Minor injuries may include orthopaedic injuries such as ankle sprains or rib fractures, minor burns or soft tissue injuries. Although not requiring operative intervention in the majority of cases, minor injuries still account for a large burden on emergency department resources [24, 25]. Major injuries also account for a large burden on emergency departments but also intensive care, operating rooms and inpatient care accounting for a large financial and resource strain on hospitals [26, 27].

79.2 Clinical Considerations

79.2.1 Initial Assessment and Management

When patients arrive at trauma centres, an initial assessment of patient's injuries is made followed by implementations of therapy. Most centres follow an Advanced Trauma and Life Support (ATLS) structure, whereby evaluations of a patient's Airway, Breathing, Circulation and

Neurological state (ABC's) forms part of the 'Primary Survey' [28]. If a life-threatening abnormality is detected during assessment of these areas, then necessary interventions such as endotracheal intubation and blood product resuscitation are commenced immediately. These are usually undertaken in the context of a severely injured patient with limited corroborative history or available information about medical background. Following on from this, a 'secondary survey' is commenced whereby a patient is examined from head to toe, front and back to detect any other significant injuries. Further investigations often include chest and pelvis radiographs, computed tomography (CT) and an extended focused assessment with sonography in trauma (eFAST). Many of these processes occur simultaneously by numerous clinicians working in a resuscitation or trauma team.

Case Scenario

A 24-year-old male presents to an inner city emergency department with head and chest injuries following an assault in which he was beaten about the head with a baseball bat and stabbed with small knife. He has a history of alcohol and cannabis use. He admits to injecting 'ice' prior to the incident. He does not have family and frequently presents to this emergency department where he is well known for being disruptive and aggressive behaviour towards staff. On presentation he is sweaty, agitated, with a GCS of 13, heart rate of 130 and a blood pressure of 90/50. He has multiple facial abrasions, a large occipital scalp haematoma and a small 2 cm penetrating wound to his left upper chest. The patient becomes violent and demands to leave the emergency department stating that there are people out to 'get him'.

A number of variables dictate a patient's disposition and treatment in the emergency setting. For example, if a patient is severely injured and has tachycardia and hypotension, then clinicians will often presumptively treat for haemorrhagic shock with blood product transfusion and consideration for urgent operative intervention. However, without clinical evidence of ongoing haemorrhage or severe injuries, patients may not require urgent operative intervention and many patients can be managed conservatively. Another example may be the patient with a head injury and a normal Glasgow Coma Scale (GCS) of 15 who may not require further urgent management. However, a head injured patient with reduced conscious level, i.e., reduced GCS or focal neurological findings, may require urgent cranial CT and craniotomy if there is evidence of intracranial haematoma.

79.2.2 Acute Physiological Changes Related to Drugs and Alcohol Use

As shown in Table 79.3, there are a number of effects from alcohol and drugs that make standard assessment and management of an intoxicated patient a clinical challenge. The main areas of concern specific to these individuals are (i) haemodynamic status and (ii) neurological status.

79.2.2.1 Haemodynamic Status

Nearly all drug and alcohol use can affect blood pressure or pulse as shown in Table 79.3. The most concerning presentation to any physician managing trauma patients in general is haemorrhage. Signs of haemorrhage in an average non-intoxicated young adult include increased respiratory rate, tachycardia, peripheral vasoconstriction, anxiety and, later on, hypotension. Patients therefore intoxicated with any of the common substances of abuse could fit any of these criteria at any one time. Animal models have demonstrated the increased likelihood of bleeding with alcohol intoxication [29–33], most likely due to the inability to cause peripheral vasoconstriction to shunt blood to vital areas such as the heart, lungs and brain. Stimulant-affected patients such as cocaine or methamphet-

Table 79.3 Physiological effects of common drugs and alcohol

	Cardiovascular effects	Respiratory effects	Neurological effects
Alcohol	Peripheral vasodilation Increased risk of arrhythmias Myocardial dysfunction	Respiratory depression Reduced pulmonary clearance Higher incidence of pneumonia Reduced pulmonary vascular resistance	Reduced conscious level and airway compromise, disinhibition
Stimulants, e.g., cocaine, methamphetamine, ecstasy	Tachycardia, hypertension, vasoconstriction, arrhythmias, myocardial ischaemia	Increased respiratory rate	Agitation, aggression, anxiety, delirium, seizures
Sedatives/depressants Benzodiazepines Opiates Marijuana	Increased systemic vascular resistance	Reduced respiratory drive with opiate used	Depressed conscious level, confusion, psychosis

amine users are typically tachycardic and agitated, giving the appearance of someone who is in hypovolaemic shock. As a consequence, not only is the patient's ability to cope with blood loss affected but also the assessment by treating physicians may be confounded. Drug-affected patients are therefore more likely to get over-investigated due to the concern for missing potentially life-threatening injuries not detected on routine assessment. However, the converse could be true in that physicians may be tempted to attribute exam findings and vital signs to drug intoxication and potentially miss life-threatening injuries, resulting in delays to definitive care and misdiagnosis. This has large implications for healthcare resources as blood transfusion requirements are increased, rates of CT scanning increased resulting in longer in-patient length of stays [19, 26, 27].

79.2.2.2 Neurological Status

All drug use has potential significant effects on cognitive function. The primary difficulty with any intoxicated patient therefore is the assessment of the cognitive state and whether this is due to the intoxication or traumatic brain injury (TBI). Any unconscious patient (GCS < 9) often requires urgent airway intervention and possible endotracheal intubation and mechanical ventilation to prevent the occurrence of gastric aspiration and prevent secondary brain injury. Previous evidence has demonstrated that alcohol-intoxicated patients are more than twice as likely to require airway intubation compared to non-intoxicated patients with head injury [34]. Due to the alteration in cognitive level including aggression, agitation and sedation, intoxicated patients with evidence of head injury or involved in serious mechanisms of injury are more likely to undergo CT scanning [26]. Also due to the inability to perform an adequate physical exam, patients are more likely to require imaging of multiple body areas for evaluation [35]. Part of this imaging will frequently require not only cranial CT but also CT scans of the cervical spine. Well-described criteria are used in trauma patients to evaluate for cervical spine injury; however, patients must be alert and non-intoxicated to meet criteria for cervical spine clearance [36, 37]. Patients failing the criteria such as those with evidence of head injury or concerning mechanism of injury typically require CT cervical spine imaging to adequately clear the cervical spine of clinically significant injury. However the need for CT imaging needs to be balanced with radiation exposure to the neck, especially in younger patients. Waiting for the clinical effects acute drug intoxication to dissipate before reassessing or the use of plain radiographs are alternative strategies, although plain X

rays have similar radiation dose compared to modern CT scanning techniques. Cumulative radiation dose has been associated with increased risk of malignancy although the dose-risk relationship has yet to be defined [38].

79.2.3 Chronic Physiological Effects of Drugs and Alcohol

Intravenous drug use has a number of implications for acute injury management particularly in relation to difficult intravenous access [27]. However, chronic alcohol use is associated with a much more serious problem of coagulopathy and bone marrow suppression making haemorrhage control more problematic. The liver is responsible for production of clotting factors II, VII, IX and X as well as other components, all of which form essential elements of the coagulation cascade. Chronic alcohol users have reduced hepatic synthetic function, and therefore production of these clotting factors is reduced. Patients suffering trauma are at an increased risk of bleeding from a variety of mechanisms [39], and those patients with a pre-morbid reduction in clotting activity therefore have an increased risk of haemorrhage and death. Chronic alcohol use also impairs the immune response and subsequently these patients are at increased risk of post-injury sepsis, acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF) [26].

Managing acute pain in the context of opiate abuse is a significant challenge for many staff in ED. Patients chronically abusing opiates such as oxycodone, codeine, fentanyl or heroin may require higher doses of analgesia compared to opiate naïve patients. Physicians need to be aware of the risks of under- and over-treating patients in this situation, and a multidisciplinary approach should be taken with early intervention from drug and alcohol specialists. Similarly, it has been recognised that the ED is a frequent source of opiates for patients, and therefore other non-opioid pain medications should be considered for patients at risk of addiction where possible [40]. Patients with alcohol dependence are also at serious risks of withdrawal and, as a consequence, are at risk of a myriad of signs and symptoms such as seizures, nausea, vomiting, abdominal pain diaphoresis, tachycardia and hypotension. These symptoms of withdrawal make assessment and management of the trauma victim difficult. Treating physicians need to be vigilant to this condition and take appropriate steps to prevent withdrawal features whilst excluding other trauma-related complications such as sepsis, raised intracranial pressure and ongoing haemorrhagic shock.

79.3 Emergency Department Considerations

79.3.1 Behavioural Management

Patients experiencing the acute effects of illicit drugs particularly methamphetamines are at risk of violent or aggressive behaviour, requiring behavioural control in ED [19, 41–43]. Measures include various de-escalation strategies, physical restraints, chemical sedation and seclusion. The most appropriate strategy is usually one which allows safe and thorough clinical assessment with restraint and sedation strategies considered as a last resort that should be consistent with local and institutional policies. If there is any clinical suspicion of serious head injury in the context of aggressive behaviour, the patient should undergo rapid sequence induction and endotracheal intubation and proceed to CT scanning of the brain and other imaging studies as indicated. Sedating aggressive patients with potential head injury without airway protection increases the risk of lung aspiration and other serious adverse clinical events.

79.3.2 Mental Health Assessment

Patients with self-inflicted physical injuries and attempted suicide can range from superficial lacerations to gun trauma and attempted hangings. Concurrent drug ingestion is common in these presentations. Patients with acute substance use like cannabis or amphetamines may also express

ongoing thoughts of self-harm or hallucinations. A mental state assessment should be made in the acute setting to diagnose the presence of an acute mental health disorder and determine the need to detain a patient for ongoing psychiatric care. Assessment should be repeated as the clinical effects of any drug intoxication abate to determine whether suicidal ideation or thought disorder persists. This becomes a critical decision when a patient with a serious injury requests to leave the emergency department against medical advice. If the patient has a potentially life-threatening condition and the patient's capacity to make an informed choice is impaired through evidence of substance use, then a patient may be detained under the common law principal of duty of care [44]. In this context, a patient who is mentally disordered due to acute drug ingestion should not be released back to the community until drug effects have cleared and potentially life-threatening injuries have been assessed for and excluded.

79.3.3 Social Problems

Patients with substance abuse disorders often access EDs due to poor social supports or financial difficulties [11]. In addition family members, partners or children of individuals with substance abuse disorders may also present with injuries as a result of interpersonal violence. It is important for EDs to have screening tools for these conditions as many jurisdictions have mandatory reporting requirements for suspected domestic violence and child abuse.

79.3.4 Security

Security personnel are often available in EDs to assist in the management of violent behaviour. Additional staff are often required to ensure patient safety by preventing them from absconding or to monitor and prevent harmful behaviours such as further self-inflicted harm whilst in ED. Patients presenting with gun-related injuries, particularly gang-related crime, should be managed as a potential security threat, and patients and visitors should be searched for potential weapons. The police should be notified if the clinician has reason to believe that a patient is in possession of a lethal weapon and poses an ongoing risk to self or others.

79.3.5 Emergency Department Burden

One of the most important challenges currently facing emergency departments around the world is overcrowding [45]. Lack of staffing and beds required to meet the demands of the healthcare system means that many EDs are chronically overcrowded with patients. The main manifestations are longer waiting times, reduced efficiency and patient safety. In this often chaotic environment, patients with substance abuse disorders particularly those with behavioural or mental health problems are more likely to escalate to violent or aggressive behaviour [43]. Some emergency departments have implemented models of care that involve dedicated mental health and drug and alcohol clinicians in an attempt to meet the demands of these patients at an earlier stage of management in ED.

79.3.6 Screening and Brief Intervention

Although systematic reviews have confirmed the effectiveness of screening and brief alcohol intervention in the primary care setting, it is difficult to extrapolate these to the emergency setting for trauma patients [46]. Acute distress due to a combination of injuries, mental health disorders and toxicological effects, in addition to the environmental considerations outlined above, make brief intervention less likely to be effective in this context. Indeed a meta-analysis abuse disorders present to ED, and the ability to connect a patient with the direct consequences of their substance use, screening and brief intervention in ED would appear to be at least an initial opportunity to discuss these issues with the patient and lends itself

to other opportunities such as follow-up referrals to specialised drug and alcohol services.

Level one trauma centre hospitals (those accredited to manage the most severe trauma patients) in the United States are now required by the American College of Surgeons to have an alcohol screening and brief intervention program for patients admitted under trauma. Few studies have investigated the effect of brief interventions in this context, and ones that have are limited by low follow-up rates (50–70%). Screening and brief intervention within trauma in-patient units offers a number of advantages to the ED setting, namely, the more controlled environment where injuries have been definitively treated, concomitant effects of drug intoxication have cleared and the patient more likely to be cooperative.

Clinical Relevance and Key Messages

- Severe injuries and drug- and alcohol-related comorbidities are often interrelated.
- Self-harm is an increasingly prevalent form of severe injury that is often associated with addiction.
- Drug dependence and withdrawal can complicate the acute assessment and management of severely injured patients, particularly with respect to pain control and vital sign interpretation.
- Early intervention with in-hospital drug and alcohol services can help identify and manage severe injuries with drug and alcohol addiction.

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Neurobiological Complications of Alcohol and Substance Misuse

80

Evelien Rooke, Douglas Steele, and Thomas Gilbertson

Contents

E. Rooke
Department of Neurology, Ninewells Hospital and Medical School, Dundee, UK
e-mail: e.rooke@dundee.ac.uk

D. Steele
Division of Imaging Science and Technology, Medical School, University of Dundee, Dundee, UK
e-mail: d.steele@dundee.ac.uk

T. Gilbertson (✉)
Department of Neurology, Ninewells Hospital and Medical School, Dundee, UK

Division of Imaging Science and Technology, Medical School, University of Dundee, Dundee, UK
e-mail: t.gilbertson@dundee.ac.uk, thomasgilbertson@nhs.net

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Abstract

Alcohol and substance misuse can cause a range of neurobiological disturbances. These may result from acute intoxication, following chronic misuse or drug withdrawal. This chapter will address these disturbances on a drug-by-drug basis. Relevant neurobiological mechanisms of drug action will also be described.

Keywords

Neurology · Alcohol · Sedatives · Stimulants · Opiates · Hallucinogens

80.1 Introduction

Neurological complications which result from substance misuse can lead to mortality and morbidity. Neurobiological mechanisms of drug action and their associated clinical neurological consequences occur during three 'phases' of substance misuse: (1) acute intoxication, (2) dependency and (3) withdrawal (Table 80.1). These will be discussed for various drug classes within this chapter.

80.2 Sedatives

80.2.1 Alcohol

Alcohol-use disorders are medical conditions which are diagnosed when a patient's drinking causes distress or harm. The recommended limit for alcohol intake varies across the world, and in the United Kingdom, it stands as 14 units of alcohol per week for both men and women.

Alcohol consumption can have a serious impact on the function of the whole nervous system but particularly the brain, leading to sedative, amnestic and ataxic effects. This occurs via the direct toxic effects of alcohol or indirectly as a consequence of damage to other organs (such as the liver), falls (leading to head injury) or nutritional deficits (in particular thiamine).

Table 80.1 Phases of substance misuse (all definitions adapted from ICD-10)

Acute intoxication
A condition that follows the administration of a psychoactive substance resulting in disturbances in level of consciousness, cognition, perception, affect or behaviour or other psycho-physiological functions and responses. The disturbances are directly related to the acute pharmacological effects of the substance and resolve with time, with complete recovery, except where tissue damage or other complications have arisen.
Dependence syndrome
A cluster of behavioural, cognitive and physiological phenomena that develop after repeated substance use. These typically include a strong desire to take the drug and difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance and a physical withdrawal state.
Withdrawal state
A withdrawal state is a group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a psychoactive subspace after persistent use of that substance. The onset and course of the withdrawal state is time-limited and related to the type of substance and dose being used immediately before cessation of reduction of use.

80.2.1.1 Neurobiological Mechanisms of Action

Alcohol is a psychotropic depressant of the central nervous system (CNS). It enhances gamma-aminobutyric (GABA), the main inhibitory neurotransmitter of the CNS, and inhibits glutamate, which is the main excitatory neurotransmitter of the CNS.

The inhibitory effects of GABA are mediated primarily by potentiation of the $GABA_A$ receptor function, leading to sedation and loss of social inhibitions. Chronic alcohol use eventually leads to GABA receptor downregulation, which is thought to explain the genesis of alcohol tolerance. This deficiency of GABA receptors also leads to withdrawal symptoms upon cessation of alcohol intake, with overactivity within the CNS producing delirium tremens and seizure activity.

Various glutamate receptor types are inhibited by alcohol, including the N-methyl-D-aspartate (NMDA) receptor, which has high sensitivity to low alcohol doses and is strongly involved in the

neuropharmacological effects of acute alcohol intake as well as the neurotoxicity observed in alcohol dependence [24]. In addition, long-term alcohol use leads to an increase in glutamatergic receptors in certain areas of the brain. During alcohol withdrawal the glutamate receptors that were previously inhibited by the continuous presence of alcohol are no longer inhibited. This means that they become hyperactive and trigger seizure activity or even stroke [6]. The glutamate receptor is also the main receptor involved in neuronal death due to increased permeability of the calcium channel associated with the receptor [21]. Inhibition of NMDA receptor activity is believed to be one of the mechanisms contributing to foetal alcohol syndrome, alcohol-related learning disabilities, neuronal loss and cognitive deficits.

Other potential alcohol targets include serotonin, glycine and nicotinic acetylcholine receptors, although the pharmacological mechanisms remain unclear. There are also indirect effects, altering presynaptic neurotransmitter release of dopamine, serotonin and endogenous opioids, which are believed to reinforce alcohol dependence.

The mesocorticolimbic dopamine system is believed to be particularly important in regulating motivated behaviours. The cell bodies of this pathway reside within the ventral tegmental area (VTA) and project along the median forebrain bundle to various targets including the nucleus accumbens, a key structure of the brain reward system. Alteration of dopamine release is therefore likely to be relevant to the propagation of alcohol misuse.

Brain serotonin is also important, being involved in regulation of attention, motivation and emotion. The cell bodies of serotoninergic neurons are primarily located in the medial and dorsal raphe nuclei, from where fibres project diffusely to many brain regions including the limbic system. An association between alcohol dependence and a deficiency of serotonin within the CNS has been reported [27]. This has led to the hypothesis that alcohol is consumed by certain individuals in order to normalise brain serotonin levels. Serotonin may also contribute to alcohol dependence via its interaction the mesolimbic dopamine neurotransmission [11].

Finally, acute alcohol intake increases the release of the endogenous opioids, endorphins and enkephalins in several brain regions, including the VTA and the nucleus accumbens, which is thought to reinforce alcohol dependence as opioid receptors modulate release of dopamine in the nucleus accumbens [17].

80.2.1.2 Acute Intoxication

The effects of acute alcohol intoxication will vary depending on the individual person, as well as the blood alcohol level reached. There may initially be impairment in tasks which require skill, followed by loss of inhibitions and increased social interaction. At a blood alcohol level of 150–200 mg/100 ml, loss of self-control occurs, with poor coordination (ataxia) and slurred speech (dysarthria). This is followed by memory loss, hypothermia, nausea and vomiting. By 400 mg/100 ml the individual is at risk of coma and respiratory depression. Acute ingestion of alcohol also leads to poor temperature regulation and a propensity towards hypothermia. The main mechanism for this appears to be impairment of shivering thermogenesis resulting from alcohol-induced hypoglycaemia, rather than by increasing heat dissipation via vasodilation [15].

80.2.1.3 Complications of Dependence

Wernicke's Encephalopathy and Korsakoff's Syndrome

Wernicke's encephalopathy is traditionally recognised as a clinical triad of acute confusion, ophthalmoplegia and ataxia, although other symptoms may be present. These include nystagmus, memory disturbances, unexplained hypotension with hypothermia and decreased conscious level. It occurs after exhaustion of B vitamin reserves and in particular thiamine. Treatment comprises intravenous administration followed by oral supplementation of this vitamin. Risk factors include intercurrent illness, peripheral neuropathy, delirium tremens, drinking greater than 20 units of alcohol per day, alcohol-related seizures and recent diarrhoea and vomiting. Typical MRI changes are shown in Fig. 80.1a and b.

Korsakoff's syndrome is characterised by a predominant anterograde amnestic syndrome with impaired recent memory (leading to confabulation) and relatively intact intellectual function [44]. It is associated with a lack of thiamine and subsequent disruption of the diencephalic-hippocampal circuitry, particularly between the thalamic nuclei and mammillary bodies.

Central Pontine and Extrapontine Myelinolysis

Hyponatraemia is particularly common in chronic alcohol misuse due to the large volumes of fluid imbibed. Furthermore, patients with alcohol dependence may not be able to maintain protective cerebral mechanisms against osmotic stress [35]. Cerebral oedema can be exacerbated by iatrogenic rapid correction of such electrolyte disturbances, leading to rapid osmotic shifts in the brain and secondary demyelination caused by complement-mediated oligodendrite toxicity [31].

Central pontine myelolysis (CPM) is characterised clinically as a brainstem syndrome with variable degrees of coma, confusion, quadriplegia and a 'locked-in-like syndrome' [28]. Extension of secondary demyelination into extrapontine regions occurs in around two-thirds of cases, although isolated extrapontine myelolysis (EPM) can exist in

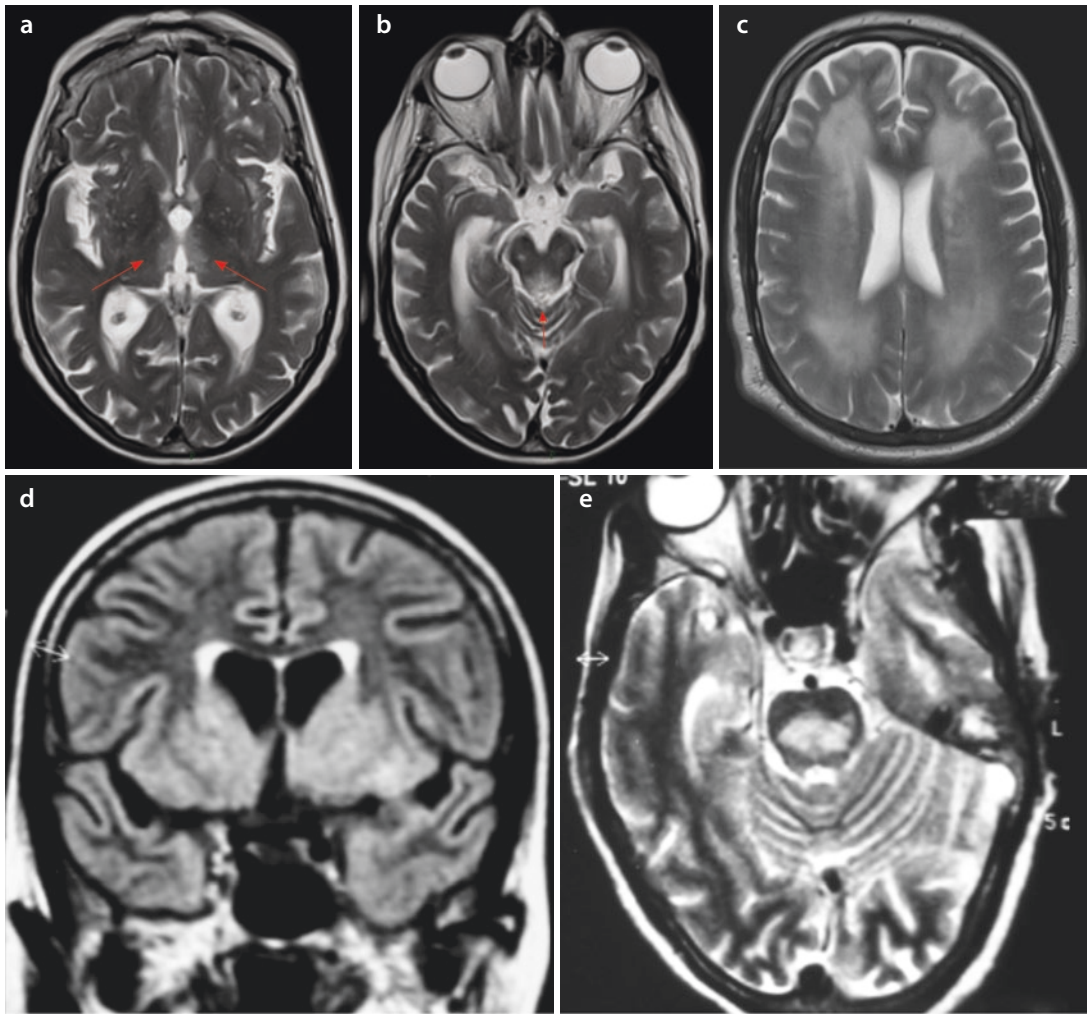

Fig. 80.1 Neuroimaging of neurological complications of drug addiction. T2 MRI sequences demonstrating (**a**) medial thalamic and (**b**) dorsal midbrain signal change in Wernicke's encephalopathy. (**c**) Diffuse white matter change in a patient with toxic leukoencephalopathy secondary to heroin inhalation. (**d**) T2 FLAIR and (**e**) T2 sequences indicative of extrapontine and central pontine myelinolysis

20% of cases [19]. Clinically, the symptoms suggestive of EPM reflect the predilection for basal ganglia structures: Parkinsonism, dystonia and/or choreiform movement disorders are most common. Radiologically, both EPM and CPM produce a striking appearance on MRI with T2 hyperintensity in the lentiform nuclei and brainstem, respectively (Fig. 80.1d and e). Despite the severity of the neurological insult, around two-thirds of patients recover independence. The main prognostic factor is the provision of medical treatment to avoid complications such as infection or thromboembolic events.

Hepatic Encephalopathy

This condition affects 60% of patients with liver cirrhosis. As the liver fails, ammonia levels rise. This has a direct neurotoxic effect on the brain. Symptoms include psychomotor slowing, asterixis, extrapyramidal rigidity, choreoathetosis and even dementia in its more chronic form [44]. Cognitively, hepatic encephalopathy (HE) is characterised by impairments in executive functioning, particularly selective attention and psychomotor speed. Recent studies have supported the idea that the cognitive impairment is irreversible with treatment of the hyperammonemic state and accumulative with each episode of HE [8]. Although the precise relationship to other forms of dementia remains unclear, patients with cirrhotic liver disease have accelerated levels of generalised cortical atrophy which correlate with their neuropsychometric impairment [2].

Cerebellar Ataxia

For reasons that are unclear, chronic alcohol misuse is particularly toxic to the cerebellar Purkinje neurons. Chronic alcohol abuse leads to neuronal degeneration within, and relatively selective atrophy of, the anterior and superior part of the cerebellar vermis. This condition affects over 30% of chronic alcoholics [41] and leads to a broad-based, ataxic gait with relative sparing of the arms.

Neuropathy

Alcohol also affects the peripheral nervous system. This may present acutely (e.g., nerve damage by direct compression while intoxicated) or in response to chronic alcohol misuse. The latter causes a symmetrical axonal sensorimotor peripheral neuropathy with early sensory involvement. Prevalence rates vary hugely between studies but may be as high as 67% when subclinical neuropathy is taken into account [1]. When symptomatic, alcohol-related neuropathy causes paraesthesia, burning pain, hyperaesthesia or numbness in the distal extremities, especially the legs. Varying degrees of balance and gait disturbance, as well as weakness, may be present. Clinical examination demonstrates generalised hyporeflexia and length-dependent sensory loss.

Although dietary deficiency of B vitamins (including thiamine) has long been thought to be contributing factor to neuropathy in alcoholics, there is limited direct evidence for this. In their study of 76 chronic alcoholics, Ammedola et al. demonstrated that neuropathy severity was independent of nutritional status. It did, however, correlate with the total lifetime dose of alcohol and disease duration. A dose-related toxic effect was also demonstrated in the absence of a nutritional effect in a cross-sectional study, supporting a direct neurotoxic mechanism [32].

80.2.1.4 Withdrawal

Delirium tremens is defined as the onset of confusion precipitated by abrupt alcohol withdrawal. It occurs in approximately 5% of people hospitalised for alcohol withdrawal [29]. A person requires at least two of the following eight symptoms for a diagnosis of delirium tremens to be made: autonomic hyperactivity, hand tremor, insomnia, nausea and vomiting, transient hallucinations or illusions, psychomotor agitation, anxiety and generalised tonic-clonic seizures (DSM-5 [12]). It is managed using CNS depressants such as benzodiazepines.

Alcohol withdrawal occurs in individuals who are physiologically dependent on alcohol. The latter is primarily secondary to upregulation of NMDA receptors and downregulation of GABA receptions within the brain. When alcohol intake stops suddenly, the inhibitory effects of alcohol cease, whereas these adaptive changes continue, leading to overactivity within the CNS. The clinical presentation of alcohol withdrawal can be defined as minor, intermediate or serious (Table 80.2).

Table 80.2 Clinical features of alcohol withdrawal

Minor 0–72 h	Intermediate 24–72 h	Serious 24–72 h
Anxiety, irritability Restlessness Insomnia Tachycardia Diaphoresis Weakness Anorexia	Minor features + Hypertension Confusion, illusions, disorientation Fear	Intermediate features + Delusions Hallucinations Seizures Arrhythmias Circulatory collapse

80.2.2 Benzodiazepines and Barbiturates

80.2.2.1 Neurobiological Mechanisms of Action

Benzodiazepines bind to the gamma subunit of the postsynaptic $GABA_A$ receptor complex as full agonists to increase the frequency of inhibitory channel opening and to decrease neuronal function. Barbiturates similarly act on the $GABA_A$ receptor but bind to the beta subunit and enhance neuronal inhibition by increasing the mean open time of these ion channels. Barbiturates also inhibit glutamate (AMPA) receptors.

80.2.2.2 Acute Intoxication

Benzodiazepines and barbiturates are anxiolytics and also aid sleep. They are used to treat seizure disorders, and certain barbiturates are additionally utilised in the management of raised intracranial pressure. Both these substances may lead to a reduced conscious level and similar complications to those described in heroin comas, including cardiorespiratory depression (especially barbiturates), aspiration, anoxic encephalopathy and peripheral nerve compression syndromes [13].

80.2.2.3 Complications of Dependence

Benzodiazepines and barbiturates are generally non-toxic to the peripheral and central nervous system, which explains the absence of clearly defined neurological complications of dependence. Most of the consequences of dependence are reflected in the behavioural changes associated with the continued cycle of withdrawal symptoms and drug-seeking behaviour.

80.2.2.4 Withdrawal

Withdrawal from prolonged benzodiazepine or barbiturate use can have life-threatening neurobiological complications. The symptoms of withdrawal consist of cognitive and memory impairment, impaired coordination, multisensory perceptual impairment and hypersomnia. The single most important presentation as part of this spectrum is withdrawal seizures, as these can lead to fatal status epilepticus [34]. Withdrawal seizures typically occur between 5–7 days following benzodiazepine withdrawal and 2–4 days following discontinuation of barbiturates. Benzodiazepine withdrawal seizures are more likely to occur following abrupt cessation from a higher dose and should be promptly treated in order to reduce the risk of mortality and morbidity associated with status epilepticus.

80.3 Stimulants

Common stimulants include nicotine, cocaine, methylenedioxy-methylamphetamine (MDMA), amphetamine, methamphetamine and synthetic cathinones (or 'bath salts'). As nicotine is not associated with any clinically relevant or common neurological complications, we have omitted it from further discussion.

80.3.1 Cocaine

80.3.1.1 Neurobiological Mechanisms of Action

Cocaine binds tightly to the dopamine transporter to block its function. Dopamine subsequently accumulates within the synaptic cleft. This results in prolonged and enhanced dopaminergic signalling in brain circuits which are related to the control of movement and reward, such as the limbic system. The latter reinforces drug-taking behaviours as it adapts to the excess of dopamine and becomes less sensitive to it.

Cocaine also reversibly blocks sodium channels. By doing this, it interferes with the propagation of action potentials and acts as a local anaesthetic. It also acts as a vasoconstrictor via its inhibition of norepinephrine reuptake in the autonomic nervous system [18].

80.3.1.2 Acute Intoxication

Cocaine produces elation and increased alertness, with increased motor activity (tremor, myoclonus) and endurance in the short and longer term. The intense euphoria from snorting cocaine typically lasts 5–10 min. Even though cocaine intoxication generally lasts less than 30 min, it is important to note that its major metabolites (e.g., benzoylecgonine) are broken down and eliminated from the body over a period of several days. Therefore, in conjunction with other complicating events, these active metabolites may continue to build up and contribute to the manifestation of adverse neurobiological complications several days post use.

Several neurobiological complications may occur as a result of cocaine intoxication. Mydriasis; hypersensitivity to sight, sound and touch; increased heart rate; arrhythmia; hypertension/hypertensive crisis and vasoconstriction may all occur. Hyperthermia may also result due to the direct effects of cocaine on the hypothalamus and the agitation and hyperactivity that stimulant drugs produce. This contributes, along with muscle vasoconstriction and central rigidity, to the rhabdomyolysis seen in more unwell patients. Cocaine may have a direct toxic effect on the cardiac and skeletal muscle [13]. 'Crack dancing' may also occur, comprising a variable combination of Parkinsonism, tics, choreiform movements and dystonia. This is well recognised by addicts as a transient complication which typically lasts for a week following initial exposure.

Seizures may be induced as a result of any combination of cocaine-induced hyperexcitability, cardiovascular dysfunction (arrhythmia), intracranial haemorrhage (hypertension) and/or cerebral ischaemia (vasoconstriction – seen within minutes of cocaine consumption on MRI angiogram). Sudden death may also occur, following initial misuse or after repeated abuse, as result of seizures followed by respiratory arrest.

Table 80.3 Mechanisms for infarction after stimulant misuse

Vasoconstriction as direct drug effect or secondary to subarachnoid haemorrhage
Cardiac arrhythmias/cardiomyopathy causing infarction by embolism or hypoperfusion
Embolism from infective endocarditis (venous thrombus or particulate contaminant) in those injecting stimulants
Cerebral vasculitis

Stroke is the most common lasting adverse neurological event associated with the use of these stimulant drugs. Cocaine is the leading cause of strokes in people under 45 years of age [10]. About 70% of strokes arising with intranasal and intravenous use are caused by haemorrhage rather than ischaemia [13]. Haemorrhages can be intracerebral (basal ganglia, thalamic, lobar or brainstem), intraventricular or subarachnoid. Fifty percent of intracranial haemorrhage occurs in individuals with pre-existing vascular malformations such as aneurysms and arteriovenous malformations [13]. Most haemorrhages occur within an hour of use, especially for crack and intravenous cocaine. A rapid increase in blood pressure is therefore believed to be the trigger for acute rupture.

Ischaemic infarcts also occur. The various mechanisms for ischaemic infarction after cocaine and other stimulant misuse are listed in Table 80.3.

80.3.1.3 Complications of Dependence

Chronic cocaine use is associated with cognitive dysfunction and cerebral atrophy [37]. This correlates with the duration of drug abuse, supporting the idea of a direct neurotoxic effect of cocaine. Cognitive impairment is marked in domains of executive functioning such as decision-making, judgement, attention, planning and mental flexibility. It remains unclear whether these are related to cortical atrophy induced by cocaine or are mechanistically related to neurovascular changes, as indexed by reduced prefrontal perfusion in abstinent patients [20].

80.3.1.4 Withdrawal

Acute neurological complications of cocaine withdrawal are rare. Strikingly, there are no reported cases of seizure, stroke or any other neurological syndrome associated with the withdrawal of cocaine. However, unpleasant dreams, insomnia, low mood and anxiety, slowed cognition, increased appetite and a craving for the drug are common.

80.3.2 Amphetamines, MDMA and Bath Salts

80.3.2.1 Neurobiological Mechanisms of Action

Amphetamines inhibit monoamine transporters and stimulate the release of norepinephrine via inhibition of vesicular monoamine transport, which is responsible for monoamine reuptake into vesicles for storage from the cytosol. Amphetamines also cause the release of dopamine from the mesocorticolimbic system and the nigrostriatal dopamine neurons, inhibit metabolic enzymes such as CYP2A6 and monoamine oxidase and act as a direct agonist on serotonin receptors.

MDMA induces monoamine neurotransmitters to be released from their storage sites in neurons via an inhibition of the vesicular monoamine transporter. This results in increased concentrations of serotonin, norepinephrine and dopamine in the cytoplasm. Compared to methamphetamine, MDMA causes a greater release of serotonin and a smaller release of dopamine. This relative excess of serotonin release may account for the mood elevating effects seen in MDMA use, as well as many of its neurobiological actions and complications.

Little is currently known about the pharmacokinetics and pharmacodynamics of bath salts, largely because these substances are frequently abused in combination with other substances and their true contents remain obscure. It has been shown that mephedrone and methylone act as substrates at transporters for norepinephrine, dopamine and serotonin, thereby stimulating release of these neurotransmitters [26].

80.3.2.2 Acute Intoxication

Neurobiological complications of amphetamines are similar to those seen in cocaine use and include seizure activity and movement disorders. Acute chorea is more common in amphetamine use than with other stimulants. Amphetamines also induce stroke disease, with similar characteristics and mechanisms as seen in cocaine use. After cocaine, amphetamines are the second leading cause of strokes in people under 45 years of age [10]. In a chronic user, stroke usually occurs in the first few hours after ingestion. Infarction is particularly common in crystal methamphetamine use. Angiography may be normal, but beading of large arteries may be seen, with vasospasm being the likely cause. This may persist for weeks [13]. Amphetamines are less likely to present as a 'typical' stoke – with more diffuse neurological deficits seen, often with a subacute progressive course. There may be headache, encephalopathy and diffuse radiological abnormalities comprising both haemorrhagic and ischaemic change [13]. Amphetamine and methamphetamine are also the drugs most commonly associated with vasculitis, especially when used chronically and intravenously. This, along with a sudden elevation in blood pressure when taking these drugs, may result in subarachnoid or intracerebral haemorrhage.

Acute intoxication with MDMA may lead to a state of confusion, depression, sleep problems and anxiety. The drug's effects last approximately 3–6 h. These neurobiological complications may occur within a few hours post use or present more gradually over a period of days. Toxicity can present with hyperpyrexia, seizures, hypertonia and coma leading to rhabdomyolysis and/or death [13]. On rare occasions, MDMA has also been associated with both intracranial haemorrhage and cerebral infarction.

Hyponatraemia is also a commonly reported complication of MDMA use. This is thought to result from several factors including overhydration in the setting of drug-induced secretion of vasopressin [39]. MDMA induces a large surge in the release of serotonin. In turn, serotonin triggers the release of the hormones oxytocin and vasopressin, which play important roles in love, trust, sexual arousal and other social

experiences and are likely associated with the characteristic feelings of heightened emotional closeness and increased empathy associated with MDMA abuse.

Mild versions of serotonin syndrome often develop. This comprises the triad of autonomic dysfunction (hyperthermia), altered mental status and neuromuscular excitation (hyperkinesia). The latter often presents with trismus (jaw clenching). Rest in a cooler environment generally settles these symptoms, although severe serotonin syndrome requires immediate and aggressive medical intervention with cooling, paralysis and the use of serotonin antagonists such as cyproheptadine or chlorpromazine. Serotonin syndrome has been proposed to have a direct relationship to neurotoxicity [36] and in severe cases can lead to death.

Neurobiological complications commonly associated with mephedrone intoxication include agitation, aggression, fatigue, impaired attention, increased empathy, talkativeness and/or an increased urge to move. Bruxism and teeth grinding can trigger jaw pain and headache. Tremor and seizures have also been associated with mephedrone intoxication [39]. Adverse events are likely to last 1–2 h post use. Patients with extreme agitation and seizures should be treated with benzodiazepines to mitigate hyperexcitability and help control seizures [39].

80.3.2.3 Complications of Dependence

Amphetamines may directly induce neurotoxicity and have direct neurotoxic effects. Some studies indicate that neuronal cell loss may be a consequence of excitotoxicity, mitochondrial dysfunction and/or the subsequent generation of free radicals and nitric oxide [10]. Indirect neurotoxicity may also result as a consequence of drug-induced damage to astrocytes, axons and/or the cerebral vasculature. Imaging studies show cerebral atrophy, with neuronal damage and glial proliferation following chronic amphetamine abuse [42]. Ischaemic infarction is also seen, especially in smaller calibre vessels. This could result from the vasoconstrictive effects associated with stimulant use and/or may be an acute hypersensitivity reaction. In the case of injectors, this could also be attributable to contaminants within the injection solution [13]. These complications may all result in the decreased brain volume seen in amphetamine abuse.

There is evidence that MDMA reduces the concentration of serotonin reuptake transporters in the brain upon repeated administration. There are some preclinical and clinical data to indicate that MDMA is associated with dopaminergic and especially serotonergic neurotoxicity, neurodegeneration and axonal loss, perhaps as a result of increased oxidative stress, excitotoxicity, apoptosis and/or mitochondrial dysfunction [10]. Heavy users of MDMA may experience long-term confusion, depression, sleep abnormalities and/or problems with attention and memory, although it is possible that some of these effects may be due to the use of other drugs in combination with MDMA (especially marijuana) [33].

There are no investigations that directly assess the chronic neurobiological complications of mephedrone abuse to date. Preclinical data indicate that repeated administration of mephedrone did not lower striatal dopamine levels or modify the expression of the dopamine transporter. In addition, it was also reported that mephedrone did not cause microglial activation nor did it increase glial fibrillary acidic protein levels in the striatum [4].

80.3.2.4 Withdrawal

Neurological manifestations amphetamine and bath salt withdrawal have not been extensively reported in the literature. However, approximately 60% of individuals who repeatedly abuse MDMA report withdrawal symptoms. These symptoms include fatigue, depression and trouble maintaining concentration [33].

80.4 Opioids

80.4.1 Neurobiological Mechanism of Drug Action

Opioids act by attaching to three types of opioid receptor: mu, delta and kappa. These receptors are found both pre- and postsynaptically on neu-

rones within the nucleus accumbens, amygdala and cerebral cortex of the brain, as well as the spinal cord, peripheral neurones and gastrointestinal tract. They regulate response to pain but also exert an effect on satiety, thirst and respiratory drive. The euphoric effects of opioids are thought to arise chiefly via activation of mu receptors, whereas the analgesic effects are thought to arise via activation of mu, kappa and delta receptors. In general, mu receptors are thought to mediate the analgesic effects of opioids by presynaptically enhancing the release of GABA via acute disinhibition.

80.4.2 Acute Intoxication

Acute opioid intoxication creates a sense of euphoria. Pupils constrict, and respiratory rate is decreased, with slowing of gut motility and subsequent constipation. There is associated cognitive slowing, sedation or even loss of consciousness. Most of these effects diminish as tolerance develops.

Opioid intoxication can be reversed with naloxone, a competitive mu opioid–receptor antagonist that reverses all signs of opioid intoxication. As opioids are metabolised at varying rates, care should be taken to monitor the patient closely. Reversal of opioid analgesic toxicity after the administration of single doses of naloxone is often transient. Recurrent respiratory depression is an indication for a continuous infusion.

Heart rate or respiratory drive can diminish to such an extent following opioid use that hypoxia results, with subsequent coma, anoxic brain injury and even death. The risk of this is even higher if vomiting and aspiration are involved, as this may further exacerbate hypoxia. Indeed, post-anoxic encephalopathy is one of the more frequent neurobiological complications of heroin abuse.

The seizure provoking property of opiates when administered acutely is supported by the finding that injectable heroin is the third most common cause of a provoked generalised seizure, and around 1% of all patients prescribed Tramadol will have a provoke seizure [16].

Acute heroin myelitis has been reported following inhalation of heroin [30], but is a rare complication.

80.4.3 Complications of Dependence

Opioids do not elevate blood pressure in the way that amphetamines do and thus do not increase the occurrence of ischaemic or haemorrhagic stroke via this mechanism. However, using non-sterile syringes/equipment when taking illicit and injectable opioids such as heroin facilitates the entry and dissemination of organisms into the blood stream. Illicit opiates themselves also often contain contaminants and bacteria. These factors, combined with the finding that intravenous addicts have altered immune systems (humoural, cell mediated and phagocytic defects), increase the incidence of septicaemia and endocarditis in this population. Infective emboli may then occlude cerebral and other vessels, which leads to irreversible necrosis and stroke. Contaminants such as talc or corn starch may also embolise and have been seen in retinal arteries or cause infarction in the brain or spinal cord. Other neurological consequences of infection include meningitis, cerebral abscess, septic arteritis and mycotic aneurysm causing intracranial haemorrhage and osteomyelitis and discitis causing extradural abscesses or spinal cord involvement.

80.4.3.1 Toxic Leukoencephalopathy

Toxic leukoencephalopathy alludes to progressive bilateral and symmetric destruction of the brain white matter, particularly myelin. Activated microglia have been found within affected brain areas, although the exact mechanism remains unknown [10]. Multiple illicit substances may cause this (including alcohol, MDMA and cocaine) but especially smoked heroin (‘chasing the dragon’). Individuals may present with inattention, changes in personality, dysarthria, ataxia, dementia, coma and even death. Pronounced, confluent, subcortical white matter changes are characteristic MRI appearances (Fig. 80.1c), which correlate with vacuolar degeneration of the deep white matter and axonal damage on post-

mortem examination [40]. No systematic case series has been published to date. Case reports nevertheless report the potential for a delayed but significant recovery, sometimes after several months following the initial ingestion [25].

80.4.3.2 Neurodegeneration and Brain Atrophy

An increase in the number and distribution of hyperphosphorylated tau-positive neurofibrillary pretangles has been noted in populations of young, chronic heroin abusers. Interestingly, despite the deposition tau in regions associated with Alzheimer's dementia, this was in the absence of amyloid beta peptides, the main component of amyloid plaques seen in this condition. In conjunction with reports of occasional ubiquitin-positive inclusions in neurones of drug abusers, this indicates that chronic opioid abuse also leads to drug-related neurodegeneration [23]. Consistent with these pathological findings, excessive brain atrophy has been recognised in heroin abusers. The relationship between this and the development of cognitive impairment or dementia is unknown. Lesions in the globus pallidus are also a recognised consequence of heroin abuse and are thought to be related to hypoxic injury [3]. Their clinical significance is also uncertain.

80.4.3.3 Peripheral Neuropathy and Neuromuscular

Subcutaneous injections ('skin popping') have been associated with cases of tetanus and botulism. Injection of heroin also increases the risk of abscess formation, rhabdomyolysis and neuropathies either via direct nerve trauma or secondary to localised oedema and compression. Peripheral neuropathy is common, affecting 25% of patients who inject heroin [9]. Compartment syndrome can also be seen after periods of prolonged coma and immobility.

80.4.4 Withdrawal

Opioid withdrawal symptoms typically occur between 6 and 48 h after cessation of opioid use, although this may be extended in longer-acting opioids such as methadone. Symptoms include dysphoria, restlessness, malaise, chills, yawning, nausea, vomiting, diarrhoea, muscle cramps and insomnia. Clinical signs of withdrawal include dilated pupils, rhinorrhoea, lacrimation and piloerection. While intoxication and iatrogenic reversal can be life-threatening, natural withdrawal is not and requires supportive care only with limited specific neurological syndromes arising.

80.5 Hallucinogens

80.5.1 Cannabinoids

80.5.1.1 Neurobiological Mechanisms of Action

THC is a partial agonist for CB1 and CB2 cannabinoid receptors. CB1 receptors are dispersed widely throughout the CNS including the basal ganglia, substantia nigra, hippocampus and cerebellum. When activated, CB1 receptors inhibit presynaptically both glutaminergic and GABAergic interneuronal neurotransmission, whereas CB2 receptors are expressed mainly in the immune cells of the periphery. Because THC activates CB1 receptors in the CNS, it is considered to be responsible for mediating the addictive effects of marijuana.

80.5.1.2 Acute Intoxication

Marijuana abuse can result in increased appetite, heightened sensory perception, inattentiveness, cognitive slowing and dysfunction, motor incoordination, an altered perception of time and talkativeness. It can also impair short-term memory. Effects can vary dramatically for individuals and, when smoked, typically persist for 1–3 h. With heavier marijuana smoking, toxic psychosis, hallucinations, paranoia and a loss of the sense of personal identity can occur. Stroke is a recognised but uncommon complication of acute cannabis intoxication**.** As with other substances of abuse, the proposed mechanisms for marijuana-induced ischaemic events include vasospasm, vasculitis and/or orthostatic hypotension [42].

A variety of neurobiological complications have also been described for Spice or K2 abusers

who have been taken to Poison Control Centres. Some complications that have been reported include tachycardia, nausea, agitation, confusion and hallucinations. There have also been a series of case reports describing stroke after synthetic cannabinoid use [14]. Synthetic cannabinoids are also a recognised cause of provoked seizure and status epilepticus [5]. In the clinical experience of the authors, this occurs more frequently than the current available literature would suggest.

80.5.1.3 Complications of Dependence

Chronic cannabis use is not thought to be associated with the development of epilepsy, neuropathy or cerebral cortical atrophy. An association with cognitive impairment has been suggested but remains controversial, and direct evidence for neurotoxicity is lacking. More recent data suggest that cannabis-related cognitive impairment resolves after 4–6 weeks of withdrawal [43].

80.5.1.4 Withdrawal

Regular smokers of marijuana or synthetic cannabinoids can experience withdrawal and addiction symptoms. With repeated abuse, CB1 receptors can homeostatically downregulate, which may contribute to cannabis-induced withdrawal symptoms when drug use is abruptly discontinued. Some of the neurobiological complications that regular marijuana smokers may experience during withdrawal consist of irritability, restlessness, anxiety, anorexia and insomnia. Specific neurological sequelae of the cannabis withdrawal syndrome are uncommon and infrequently reported.

80.5.2 Non-cannabinoid Hallucinogens

80.5.2.1 Neurobiological Mechanisms of Action

Many hallucinogens have chemical structures similar to those of natural catecholamine neurotransmitters such as acetylcholine, serotonin, dopamine or norepinephrine. Whereas the exact mechanisms remain unclear, psychedelic hallucinogens such as LSD, psilocin and mescaline appear to exert their effects via agonism of 5-HT2A serotonin receptors, perhaps in conjunction with mGluR2 receptors [22] acting within the prefrontal cortex. By comparison, dissociative hallucinogens such as PCP or ketamine appear to exert their effects by temporarily antagonising glutamatergic NMDA receptors, and deliriants are considered to be anticholinergics. PCP may also exert effects on dopamine, opioid and nicotinic receptors.

80.5.2.2 Acute Intoxication

Following acute intoxication, individuals who abuse low-to-moderate doses of LSD may experience hyperthermia and diaphoresis, sleeplessness and dry mouth. A generalised numbness of the extremities and loss of muscular coordination may occur. At higher doses, nystagmus, drooling and/or ataxia develop. LSD can typically take effect within 30 min of ingestion and can continue to produce symptoms for up to 12 h. The major neurobiological complications following LSD intoxication are psychological. Synaesthesia, where sensations seem to cross over, is well recognised. For example, an individual may ‘hear’ colours, while ‘seeing’ sounds. There have been a few reports of cerebral infarcts with large vessel occlusion, but concomitant substance misuse makes this difficult to interpret.

PCP intoxication results in particularly disturbing psychological symptoms, with suicidal and/or violent behaviour and often a misguided sense that one is invincible. This may be due to the diminution of the perception of pain, which can lead to a propensity to self-mutilate. Autonomic disturbances also occur. Higher doses of PCP cause ataxia, dysarthria and prominent nystagmus, as well as seizures activity, dystonic posturing, coma and death. Cases of fatal status epilepticus have occasionally been reported [33]. It is important to note that PCP-induced death is most likely to result from indirect consequences stemming from accidental injury or suicide than it is from a drug-induced physiological consequence.

Neurobiological complications arising from ketamine abuse are similar to those of PCP. Psychologically, acute intoxication with ketamine produces sensations of detachment

from an individual's perceived reality and one's self. There may be wild paranoid delusions, confusion, difficulty concentrating, agitation, alterations in mood, sleep disruptions/nightmares, catatonia, ataxia and/or deficits in working memory.

GHB can trigger muscle twitching and seizure activity.

80.5.2.3 Complications of Dependence

Most complications secondary to non-cannabinoid hallucinogen misuse are psychological rather than neurological, and will therefore not be discussed in detail here. Repeated abuse of LSD may produce tolerance over time. Towards this, an individual must ingest progressively higher doses of LSD to reach a similar level of acute intoxication that she/he experienced previously. Although LSD does not typically induce addictive-like, compulsive drug-seeking behaviours, this can occur with chronic abuse of PCP.

80.5.2.4 Withdrawal

There is no evidence that LSD produces physical or neurological withdrawal symptoms when chronic misuse of the drug is stopped. However, former LSD users have reported flashbacks, which have periodically been mistakenly diagnosed as brain tumours or other neurological disorders such as focal seizure activity [33]. Unlike LSD, the abrupt discontinuation of chronic PCP ingestion can be associated with withdrawal. Symptoms such as memory loss and depression may persist for up to a year after a chronic user stops taking this hallucinogen.

80.6 Organic Solvents/Inhalants

80.6.1 Neurobiological Mechanisms of Action

Volatile organic solvents are highly lipophilic and therefore neurotoxic. Mechanisms of action for inhalants appear to be similar to those produced by CNS depressants such as alcohol or barbiturates, although their effects are more immediate (within seconds) and shorter lived (commonly disappearing within fewer than 30 min). Some inhalants such as toluene have been shown to decrease neuronal excitability by acting as an NMDA receptor antagonist and a $GABA_A$ receptor positive allosteric modulator.

80.6.2 Acute Intoxication

Acute intoxication with organic solvents such as toluene can produce a variety of feelings including euphoria, exhilaration or giddiness. Because intoxication lasts only a few minutes, abusers frequently seek to prolong the high by inhaling repeatedly over the course of several hours. This is when the neurobiological complications from inhalant abuse become increasingly apparent. They may experience drowsiness and a lasting headache. Nystagmus, diplopia, dysarthria, ataxia and progressive cognitive dysfunction can become increasingly evident over time. In some instances, a protracted confusional state may last for several days [13]. With repeated exposure, inhalant-induced neurobiological complications become increasingly apparent and CNS recovery post abuse may be incomplete. Chronic toluene abuse has led to permanent cognitive changes, ocular motor abnormalities and pyramidal features that do not resolve when drug use has been discontinued. This is believed to be secondary to myelin sheath destruction [7]. Deterioration may continue for 1–4 months post cessation [13]. Demyelination and gliosis in the cerebral and cerebellar white matter have been observed up to 7 years after chronic abuse and appear to be irreversible [42]. Solvent-induced encephalopathy may also result in cognitive dysfunction and cortical and cerebellar brain atrophy [34]. It is also important to note that, in addition to the substance of abuse, other chemical ingredients found within the various types of inhalants may produce a variety of other neurobiological complications.

80.6.3 Complications of Dependence

Addictive-like behaviour is not unlikely to develop upon repeated use/abuse of inhalants.

80.6.4 Withdrawal

Although rare, compulsive use and a mild withdrawal syndrome have been reported in long-term inhalant abuse. Withdrawal symptoms include irritability, restlessness, inattentiveness, anxiety, hallucinations and depressed mood [38]. It has been argued in case reports that these mirror the presentation and severity of alcohol withdrawal symptoms. Despite this, no evidence-based treatment for inhalant use disorders currently exist, and this is still very much an area of ongoing research.

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Neurocognitive Disorders in Substance Use Disorders

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Hamed Ekhtiari, Mehran Zare-Bidoky, and Antonio Verdejo-Garcia

Contents

H. Ekhtiari
Laureate Institute for Brain Research, Tulsa, OK, USA

M. Zare-Bidoky
Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran

School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

A. Verdejo-Garcia (✉)
Turner Institute for Brain and Mental Health, Monash University, Melbourne, VIC, Australia
e-mail: antonio.verdejo@monash.edu

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Abstract

Chronic use of different substances is associated with neural dysfunctions and related cognitive deficits. Neurocognitive disorders encompass reward, negative affect and control deficits underlying core addiction symptoms, and broader cognitive sequela affecting everyday functioning. In the first part of this chapter, we summarise the theoretical models posited to understand the nature and course of addiction-related cognitive deficits, with special emphasis on dual and tripartite models and recent international consensus. Then, we review the specific neurocognitive disorders associated with chronic use of different drugs, including alcohol, cannabis, opioids and stimulants, while acknowledging the role of premorbid cognitive alterations and polysubstance use. In the last part of the chapter, we analyse the neural dynamics underlying these deficits, including development-related changes underpinning the transition between recreational and chronic use and neuroplasticity-related changes that can be achieved via pharmacological enhancement, cognitive remediation and neuro-stimulation. We conclude by providing a critical view of the strengths and weaknesses of current frameworks and assessment and intervention approaches and a perspective of future horizons for neurocognitive research and clinical applications in addiction medicine.

Keywords

Cognitive deficits · Substance use disorders
Neuroadaptations · Neural dysfunctions
Positive and negative valence
Cognitive control

81.1 Introduction

Chronic use of substances (i.e. alcohol, opioids, stimulants, cannabinoids, etc.) changes how our brain works. In a simplified mechanistic approach, both neuroadaptive and neurotoxic pathways contribute in the effect of substances in our brain [26, 68]. These brain changes happen in multiple layers including our neurons (e.g. changes in dopamine secretion patterns), circuits (e.g. changes in connectivity between brain networks) and cognition (e.g. attentional bias towards substance-related stimuli) and can be reflected in our subjective experiences (e.g. feeling craving) and behaviour (e.g. doing risky behaviours to obtain substances). There is also a growing body of evidence that some of our brains are neurodevelopmentally more vulnerable to move from recreational substance use to chronic use and then substance use disorders (SUDs) [70]. In this chapter, we put all these brain changes/vulnerabilities associated with SUDs into a single term of neurocognitive deficits (NCDs) and explore how NCDs can contribute to addiction medicine. Recent advances in neuroscience methods provide us with great opportunities to measure these NCDs and target them in interventions. In this book chapter, we will narrow our methodological approach to the measurement and intervention for NCDs into what human cognitive neuroscience provides. To facilitate dissemination among addiction medicine experts who may not be experts in human neuroscience, we will provide our readers with a straightforward approach to these NCDs using heuristic models. We hope this will make a shared language/terminology between different disciplines active in the field of addiction medicine and provide opportunities to bring more from the field of addiction neuroscience into addiction medicine. Other than shared language/terminology, heuristic models for NCDs associated with SUDs can also organise (1) our mechanistic understanding, (2) specific deficits/assessment targets, (3) temporal dynamics before starting to use towards SUD and then recovery and (4) intervention targets/methods. In the following five sections of the book, we (1) introduce the main domains of NCDs in the cognition level, (2) explore the cognitive mechanisms involved in NCDs, (3) describe NCD dynamics across time, (4) review promising interventions for NCDs and (5) discuss current gaps in our understanding about NCDs and how we can bring neurosci-

ence to addiction medicine in the international level. We encourage interested audience to follow more details on these topics in our books 'Neuroscience for Addiction Medicine' [28] and 'Cognition and Addiction: A Researcher's Guide from Mechanisms towards Interventions' [97].

81.2 Main Domains of NCDs

Novel dimensional approaches to SUDs, inspired by the Research Domain Criteria (RDoC) framework [48] (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/definitions-of-the-rdoc-domains-and-constructs.shtml), posit three neurocognitive domains implicated in SUDs vulnerability and disease progression: positive valence, negative valence and cognitive control [56, 82, 112]. This tripartite structure is similar to that proposed on 'dual models' of SUDs, which emphasise the imbalance between sensitisation of motivational and emotional systems (unpacked into positive and negative affective elements in tripartite models) and deterioration of cognitive control mechanisms [114]. These dimensional approaches provide a neuroscience-informed framework to characterise SUD-related NCDs and facilitate biomarker discovery [55]. Figure 81.1 provides a visual summary of the cross-talk between different neurocognitive dimensions according to recent tripartite models, including the National Institute of Drug Abuse (NIDA) Cognitive Phenotyping model [82] and the Addiction Neuroclinical Assessment (ANA) model [56]. In the following subsections, we describe the three key dimensions common to these models and explain their role in SUDs development and SUDs-related NCDs.

81.2.1 Positive Valence Domain

According to RDoC, the *Positive Valence System* is concerned with responses to positive motivational situations consisting of *reward responsiveness* (i.e. neural reactivity to hedonic responses), *reward learning* (i.e. learning what predicts positive outcomes) and *reward valuation* (i.e. processing ambiguity/risk, delay and efforts needed to gain the reward) constructs. The *reward responsiveness* construct has been widely examined in addiction studies showing disrupted brain activations, increased craving and increased urge to use which predispose users to relapse [54, 110, 114]. *Reward learning* is another major factor taking part in the development of SUDs. It refers to aberrant learning of positive reinforcement of drug and

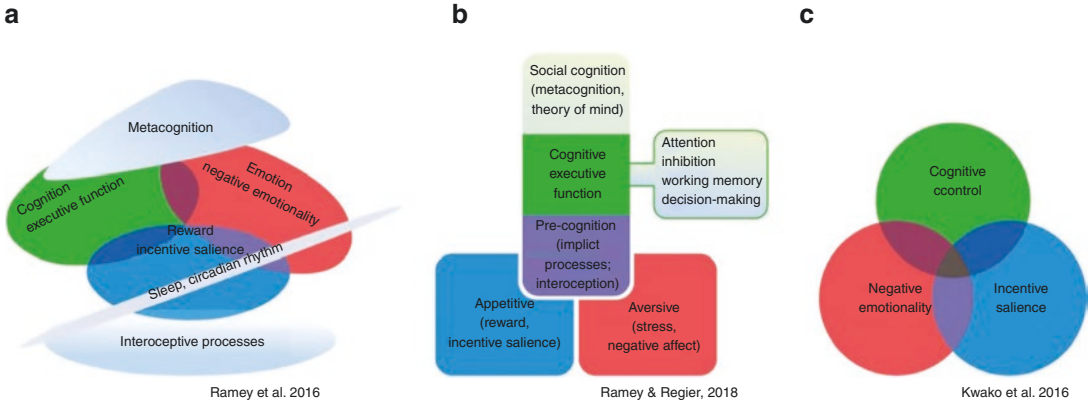

Fig. 81.1 Tripartite models of neurocognitive deficits in drug addiction. All models include (1) positive valence (blue), (2) negative valence (red) and (3) cognitive control systems (green). These three models have a dualistic notion of top-down and bottom-up interactions between positive and negative valence systems (down) and higher cognitive functions (top). (**a**) NIDA phenotyping battery. (**b**) Updated NIDA phenotyping battery. (**c**) Addiction neuroclinical assessments

drug-related stimuli and impairment in learning the association between the stimulus and the reward (or loss) outcomes [26, 51, 67]. For instance, people with SUDs show less successful results in comparison with healthy controls in Iowa and Cambridge gambling tasks (IGT/CGT), two tasks that measure the ability to predict reward outcomes in the context of uncertain and risky choices. *Reward valuation* refers to the attribution of high saliency to drugs' reward value [12, 16, 38, 56, 98]. These aberrant processes may arise from great activation of the brain's ventromedial network (VMN) and dampened activation of salience network (SN) and executive control network (ECN) [24, 27, 114].

81.2.2 Negative Valence Domain

The *Negative Valence System* has to do with responses to aversive stimuli, like fear, loss and anxiety. Drug consumption motivation can be either appetitive, as described in the positive valence system, or driven by negative reinforcement [44], meaning that the person wants to escape from negative feelings that he/she is feeling right now. These feelings can be *sustained threat* (prolonged emotional state of being exposed to aversive stimuli), *loss* (deprivation of something that had been motivationally significant) and *frustrative nonreward* (anhedonia). These constructs are manifested in different addiction models (Fig. 81.1), proposing that insufficient salience is attributed to non-drug-related rewards (frustrative nonreward) and deprivation of the hedonic state of consuming the drug (loss). Withdrawal states are proposed to be substantial to SUDs [6], and this hypohedonia may also explain the higher saliency attributed to drug rewards which leads to craving and drug consumption [27, 43]. *Negative emotionality* is counted as one of the main domains for both the ANA and the NIDA cognitive phenotyping models, as it is seen among people with active substance use and those who are in recovery, as a prognostic factor for relapse [56].

81.2.3 Cognitive Control System Domain

Poor cognitive function is known to be a significant feature of SUDs [39, 41]. Among RDoC constructs, *attention* seems to be biased towards drugs and drug-related stimuli, either as a result of positive or negative motivation; *response inhibition* is disrupted, as users struggle to suppress drug-related impulsive and compulsive responses either emotionally or behaviourally; *limited capacity working memory*, together with *goal setting* impairment, results in susceptibility of the person to relapse, as users may fail to hold goal-related information online (e.g. abstinence strategies) when they are overloaded with craving or stress [82, 89]. It is well known that one of the main mechanisms of addiction is impaired response inhibition, which seems to originate from top-down regulation dysfunctions, mainly in the ECN [21, 38, 56, 114] (Fig. 81.1b). The centrality of this mechanism is consistent with the findings of the neurocognitive literature on SUD (reviewed in Sect. 81.3), which stresses the presence of executive function deficits (i.e. working memory, response inhibition, flexibility and planning) among users of different substances.

81.3 Mechanisms for Neurocognitive Disorders in Substance Use Disorder

81.3.1 Neural Adaptations and Dysfunctions

Substance use–related changes in brain function can be classified in two broad categories: (1) neural adaptations associated with active use of the drug and related craving and preoccupation and (2) neural dysfunctions/toxicity (i.e. loss of integrity or functionality) associated with the long-term sequelae of chronic use (e.g. executive function and general cognitive impairments) [26]. Most drugs have overlapping effects on the dopaminergic mesolimbic system underpinning reward sensitisation and rebound negative affect, i.e. midbrain, striatum, amygdala and medial pre-

frontal cortex regions [53]. These neural adaptations underpin core symptoms of addiction, such as withdrawal, craving and inability to stop use. In addition, chronic use of different drugs generates varied neural dysfunctions, depending on their neuropharmacological effects and neuroadaptive/neurotoxic potential among other factors (e.g. genetic, trait and background characteristics, pharmacokinetics). Specifically, alcohol yields broad-spectrum and potent neurotoxic effects (i.e. loss of integrity and function) across the brain, stimulants such as cocaine and methamphetamine yield potent neuroadaptive and neurotoxic effects on frontal-striatal-limbic-cerebellar systems (i.e. loss of function and to a lesser extent integrity) and opioids and cannabinoids yield more subtle functional effects on dysregulation of frontal-striatal and fronto-limbic dynamics [65, 102, 104]. Neural adaptations associated with active use and craving play a key role in the transition between recreational drug use and addiction. However, neural dysfunctions underlie a range of cognitive deficits (e.g. executive functions, decision-making) associated with reduced treatment motivation and adherence, poorer quality of life and risk for relapse. Thus, in the following sections, we focus on reviewing neural dysfunction–related cognitive deficits.

81.3.2 Substance-Specific Neurocognitive Disorders

The following sections summarise cognitive deficits specifically associated with different drugs of abuse while acknowledging the role of premorbid factors and polysubstance use. We use the terms 'mild', 'moderate' and 'severe', equivalent to small, medium and large effect sizes for differences between substance users and healthy controls [113], to refer to the magnitude of the cognitive deficits described.

81.3.2.1 Premorbid Alterations

Impulsivity – rapid, unplanned reactions in pursuit of short-term gratification – is a premorbid vulnerability factor for SUDs [100]. In the context of cognitive systems, impulsivity traits may translate into difficulties in inhibitory control (or response inhibition) and reward-driven impulsive choice (e.g. steeper delay discounting or preference for smaller immediate rewards versus larger but delayed rewards and high risk/reward decisions). Thus, inhibitory control and impulsive choice deficits can be common across users of different substances. These deficits are more likely to occur among users with history of ADHD, conduct disorder or personality disorders from Cluster B (i.e. borderline, antisocial, narcissistic and histrionic) [1–3, 106]. Given strong genetic overlap and measurement covariance between inhibitory control and other executive functions such as working memory, reasoning and planning, it is plausible that broader executive dysfunctions predate substance use initiation. For example, it has been recently found that among stimulant (methamphetamine) users, school achievement indices were better predictors of current executive dysfunction than history of drug use [22]. Thus, cognitive findings speak to the need to examine executive functions in all cognitive assessments of people with SUDs, regardless of primary drug of choice or severity.

81.3.2.2 Cannabis

Cannabis and cannabinoid synthetic products interact with CB1 cannabinoid receptors. CB1 receptors are densely expressed in brain regions of the default mode network (DMN, i.e. ventromedial prefrontal cortex, posterior cingulate and medial temporal regions involved in introspection and inner experience), striatum, hippocampus and cerebellum [17, 18]. The most common cognitive deficits among heavy cannabis users are mild/moderate learning and memory problems [36, 42]. Specifically, heavy cannabis users have problems to organise new information to facilitate learning and to retrieve that information when needed. Episodic memory is often referred as the ability to engage in 'mental time travel' to retrieve specific details of past events. Heavy cannabis users have problems to make the most of that mental time travel, which might also affect their ability to make detailed plans for the future (i.e. episodic future thinking) [62]. A recent longitudinal twin study has also associated cannabis

use with working memory deficits, affecting their ability to hold and manipulate incoming information on line [66]. Clinicians often refer to motivational problems in cannabis users, and those problems can be related to cognitive difficulties to envisage future goals, to an imbalance between inner-oriented and task-oriented experience (as cannabis interacts with the introspection-related functions of the DMN and damages episodic memory) or to alterations in effort-related reward pursuit (i.e. reward valuation) [32, 57]. Cannabis users carrying genetic polymorphisms associated with poorer catecholamines and serotonin function are also more likely to experience mild working memory, selective attention and decision-making deficits [99].

81.3.2.3 Stimulants

Stimulant drugs including cocaine, amphetamine and methamphetamine damage dopamine signalling in frontal-striatal circuits involved in reward valuation/learning, executive functions and decision-making [11, 13, 20]. Thus, stimulant users frequently exhibit aberrant reward learning (i.e. the ability to learn which actions or stimuli are associated with obtaining a reinforcer) and moderate to severe deficits in working memory, inhibitory control, flexibility and decision-making [33–35]. An innovative strand of research has recently revealed broad social cognition deficits in cocaine users, including problems with social communication, affective empathy and interpersonal decision-making [47, 81, 105]. Interestingly, some of these social cognition deficits stem from core abnormalities in reward learning, as the same brain regions (e.g. medial orbitofrontal cortex (mOFC)) code the value of drug-related and social rewards [80, 94]. Core reward learning problems have been examined using reversal learning tasks and more recently model-based/model-free tasks amenable to computational modelling. These probes suggest that stimulant users have severe problems to generate 'models' of the association between their decisions and subsequent outcomes [107]. These reward learning problems result in erratic patterns of decision-making. Cocaine and methamphetamine users have also shown moderate to severe deficits across a range of higher-order executive function measures (i.e. planning, multitasking) and risk- and reward-based decision-making measures [31, 96]. Methamphetamine users also exhibit prospective memory deficits and thus may have difficulties to comply with planned/scheduled tasks [49, 83]. They also show episodic memory deficits, but at this stage, it is unclear if memory problems arise from executive dysfunction (i.e. difficulties to organise and retrieve stored information) or pure learning and memory encoding problems.

81.3.2.4 Opioids

Opioids, including heroin, morphine and opioid substitution and pain medications such as methadone, buprenorphine or oxycodone, interact with different opioid receptors, as well as dopamine systems. Meta-analytical research has shown that chronic heroin use is associated with moderate deficits in verbal fluency (ability to generate words within specific categories), verbal working memory, inhibitory control, planning and risk- and reward-based decision-making [8, 9]. More recent studies have additionally revealed visual memory and working memory deficits among chronic heroin users, including those enrolled in methadone treatment [10]. Methadone treatment has generally been associated with additional cognitive deficits, although the specific domains affected are unclear and methadone effects may be better explained by generalised cognitive slowing affecting speed of information processing across different tasks, but not core cognitive deficits [7]. Interestingly, buprenorphine seems to be a much cleaner drug in regard to cognitive consequences, with most studies showing cognitive improvement associated with buprenorphine treatment and 'normalising effects' on risk- and reward-based decision-making [76], which may have a preventive effect on relapse risk [72, 73]. There is a need for more research on novel pain prescription drugs, but research available to date has not observed significant cognitive deficits associated with their use [8].

81.3.2.5 Alcohol

Alcohol interacts with widely distributed GABA receptors as well as glutamate (especially during withdrawal) and dopamine, serotonin and cannabinoid systems [104]. Not surprisingly, heavy, chronic alcohol use is associated with broad-ranging, moderate to severe cognitive deficits. Research highlights moderate to severe cognitive deficits in visual-spatial and motor skills, attention, episodic and autobiographical memory, executive functions, decision-making and social cognition [15, 77–79, 88]. Recent reviews have stressed the impact of alcohol use in higher-order executive functions such as planning and cost-benefit decision-making and social communication and interaction, which likely have a significant impact on daily life (e.g. management of workloads and finances personal and social relationships) [88]. In addition to deficits directly associated with alcohol use disorder, chronic alcohol users may exhibit cognitive deficits secondary to well-defined, alcohol-related neurological syndromes, including Korsakoff's syndrome, Marchiafava-Bignami disease, hepatic encephalopathy and central pontine myelinolysis [63]. These syndromes have distinctive cognitive profiles, characterised by more severe memory and motor deficits and more florid neurological symptoms (e.g. confabulation) (see Maillard et al. for a detailed review). Cognitive and neuroimaging studies have also revealed additive or synergistic effects of alcohol + tobacco use, with co-users exhibiting substantially greater neuroadaptations and cognitive deficits and slower abstinence-related recovery [25, 71, 91, 108].

81.3.2.6 Polysubstance Use

Studies examining cohorts with concurrent use of multiple substances (e.g. alcohol + stimulants + heroin) invariably show cognitive deficits of greater magnitude than studies assessing cognition in users who are less exposed to multiple drugs. Recent meta- and mega-analyses of cognitive and neuroimaging data have also highlighted the role of alcohol and cannabis use in explaining the cognitive deficits of users who identified stimulants or opioids as their primary drug of concern [59, 61]. However, there is a dearth of well-controlled studies directly comparing poly- and mono-substance users. In addition, some of these studies have yielded paradoxical effects, e.g. less cognitive impairment in cocaine + alcohol versus cocaine or alcohol mono-users or less cognitive impairment in cannabis + methamphetamine users than in cannabis mono-users [40, 75, 90]. Thus, there is a clear need to conduct more research in this area, especially since polysubstance use is by far the most common and almost ubiquitous clinical presentation of treatment-seeking substance users. For now, we can conclude that chronic use of multiple substances results in more severe cognitive deficits than those described in users with more limited co-use, but that concurrent use of different substances and their specific effects needs to be assessed idiosyncratically; for example, alcohol + tobacco are consistently associated with more cognitive deficits, but alcohol + cocaine seems to be associated with less cognitive deficits.

81.4 Neurocognitive Deficits Across Time

Neurocognitive deficits associated with SUDs are dynamic across the time. These dynamic changes in NCDs can be seen at different levels of time resolution, from minutes to hours, days to weeks and months to years. Having good knowledge about these dynamic changes has critical effects on understanding the pathogenesis of SUDs, disease progression and potential targets for interventions.

81.4.1 Minutes to Hours

A brain that is shaped with the NCDs associated with SUDs responds to any conditioned cue associated with previous substance use with an intensive desire, which is called craving. Drug craving and resulting substance use are the results of the enhanced negative emotionality, the accentuated saliency processing of the drug related stimuli and lack of cognitive

control. These three main groups of NCDs interact dynamically in few minutes in a process to build up an intensive craving. First, environmental stimuli (E) trigger the process and provide the input to the brain, attention (A) provides resources to process information related to the triggers, and saliency (S) with the help of memory is attributed to the cue, leading to an interoceptive (I) state of craving which causes executive control system (Co) to either prepare for drug taking (Re) or inhibit the craving and stay abstinent (Fig. 81.2). Neurocognitive processes by which a trigger results in craving and drug use can also be tracked in the neural circuit level. It starts by attentive processing of the incentive salience of the drug in the VMN (nucleus accumbens (NAcc), ventromedial prefrontal cortex (vmPFC)); it passes then through the DMN, which forms the self-oriented goal; vmPFC-Precuneus generate the drug use scenario, and fronto-parietal networks strategically plan for its execution. Before the brain executes these plans, the SN selects whether to let it happen or inhibit it; if it passes the SN, then somatomotor region executes it [24]. Again, as it is deduced from these processes, the orchestrated NCDs through high salience attributed to drug-related stimuli, negative emotionality felt during exposure to environmental stimuli and interoceptive aversive state and low ability to cognitive control lead to drug taking.

81.4.2 Days to Weeks

SUD cannot be seen as a simple act of drug taking. Instead, the active user falls into a cycle separated into three stages. (1) *Binge and Intoxication:* at this stage, the person is taking the drug which changes the reward circuit and condition learning, leading to high saliency of drug-taking behaviours. (2) *Withdrawal and negative affect:* this stage is when the subject is abstinent, either for an hour to weeks. During this stage, the person loses his/her motivation in non-drug-related rewards and also is more sensitive to negative emotionality feelings. (3) *Preoccupation and anticipation:* when the negative emotionality is felt and the person remembers how valuable the rewards of drug stimuli were, the person feels craving that if not having enough ability to control, it eventually leads to relapse and this vicious cycle of substance use starts again [103] (Fig. 81.3).

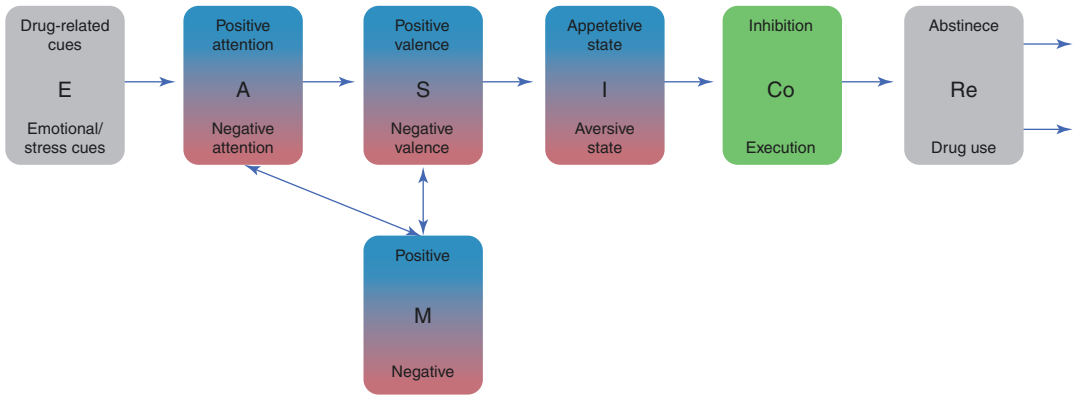

Fig. 81.2 Dynamic contribution of the neurocognitive processes to shape drug craving. This figure shows how environmental stimuli (*E*) trigger attention (A), saliency processing (S) and drug-related memories (M) and end up to an interoceptive (I) state perceived as craving. Perceived drug craving will eventually lead to either successful control (Co) and stay abstinent or failure to control the drug use response (Re) and relapse. Please see Fig. 81.1 for the colour codes (blue, red and green). E Environment, A attention, S saliency processing (significance), M memory, I internal state (interoception), Co control, Re response

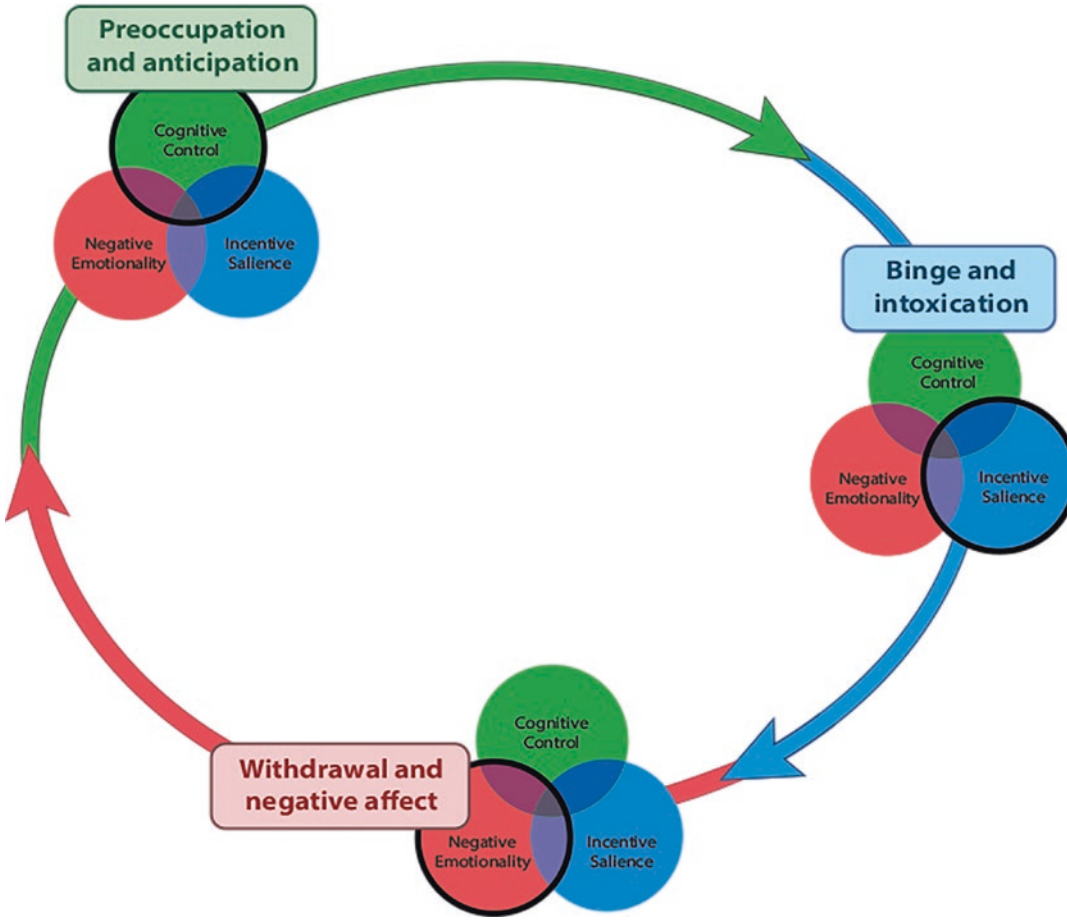

Fig. 81.3 Contribution of the neurocognitive deficits in the drug use cycle. When the person takes the drug during binge and intoxication, it induces an accentuated reward learning. During withdrawal and negative affect phase, negative feelings and stress are increasingly felt . During the preoccupation and anticipation phase, inability to resist and control the temptation of drug use will result in drug taking

81.4.3 Months to Years

As the result of the dynamic change in the NCDs, people's behaviours, experienced feelings and goal of drug consumption change over time with chronic substance use. At their early periods of taking the drug, substance users have voluntary actions to either take the drug or stay abstinent; it then changes to sometimes having trouble stopping taking drug and ends up with impulsive and compulsive actions and dozens of relapses in spite of trying to resist the temptations and stay abstinent. The feelings and goals of drug taking also are affected as the result of chronicity of use. Over time, the *binge and intoxication* phase changes, as in the first experiences the person feels euphoric of drug use, over months and years he/she feels just good, and then he/she takes the drug just to escape from the bad feelings. *Withdrawal and negative affect* phase will also change over time. It starts with the feeling of reduced energy, continues with reduced excitement/interest and eventually ends up with feeling depressed, anxious and restless. Over time, during *preoccupation and anticipation* phase, ability to resist the urges decreases from looking forward to taking the drug to desiring drug and then obsessing and planning to get the drug non-stop [103] (Fig. 81.4).

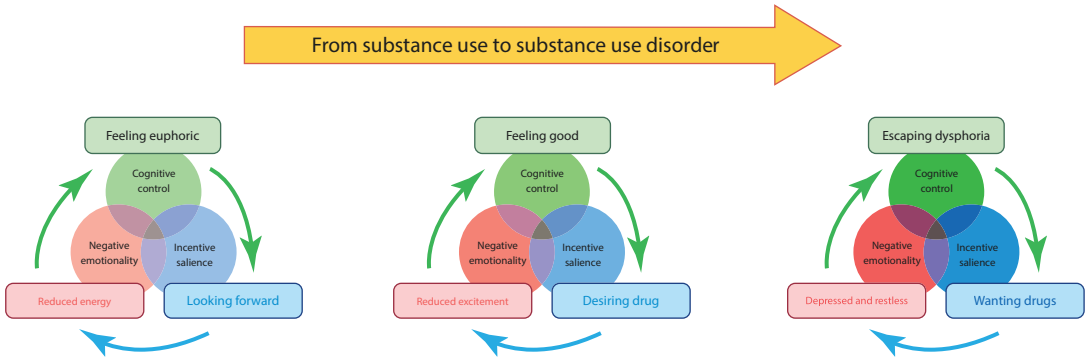

Fig. 81.4 Development of neurocognitive deficits associated with the substance use disorder in years of chronic use. This figure shows how the personal experiences during addiction cycle change over time as the person continues to use in months and years

Approaching NCDs associated with SUD as a series of dynamic processes that can be engaged or disengaged in minutes or reshaped over months and years and drive the behaviour unexpectedly will uncover some aspects of the complexities associated with SUD and its treatment failure.

81.5 Interventions in Neurocognitive Deficits

All three main groups of the neurocognitive deficits introduced in the tripartite models can be targeted by interventions to promote abstinence and recovery from SUD. Interventions may target the *positive valence* systems by reducing the saliency attributed to drug-related rewards and increasing the saliency to non-drug-related (natural/healthy) rewards. The goal of targeting *negative valence* systems is to attenuate negative emotions/body signals, like stress, dysphoria and pain, felt by the person especially during the withdrawal/abstinence state and meanwhile augmenting the negative valence for consequences of drug-seeking/drug-taking behaviour. *Cognitive control* can also be an important target to improve the ability to inhibit pre-potent drug-seeking/drug-taking behaviour and promote goal-directed behaviours (Fig. 81.5). Here we will briefly point out to the three main groups of interventions which aim at normalising and improving these NCDs in addiction medicine.

81.5.1 Pharmacotherapy

Medication, in an ideal scenario, should promote abstinence and aid in regaining the normal functions of the brain by relapse prevention and facilitating goal-directed decision-making [103]. However, we have not reached this aim for many substances yet [45, 52, 69, 92]. From a neurocognitive perspective, the main effects of the medications for treatment of SUDs can be classified as (1) controlling the symptoms of withdrawal and craving by decreasing negative emotionality during detoxification/abstinence states (like clonidine during opioid withdrawal or benzodiazepines for alcohol withdrawal), (2) preventing intoxication effects and decreasing the incentive saliency learned by previous drug-taking behaviours using substitution medications without inducing euphoria (like methadone for opioid use disorder) or using antagonistic medications to block the euphoria (like naltrexone for opioid and alcohol use disorders) and (3) reducing drug-oriented anticipatory and preparatory behaviours by improving cognitive control (for review, see [23]). Most of the currently available approved medications in the field of addiction medicine target the first two effects/goals (negative and positive saliency). However, there are hopes for medications that can promote cognitive control and executive functions to play a clinically meaningful role in addiction medicine [92]. For instance, in a randomised cross-over trial, during

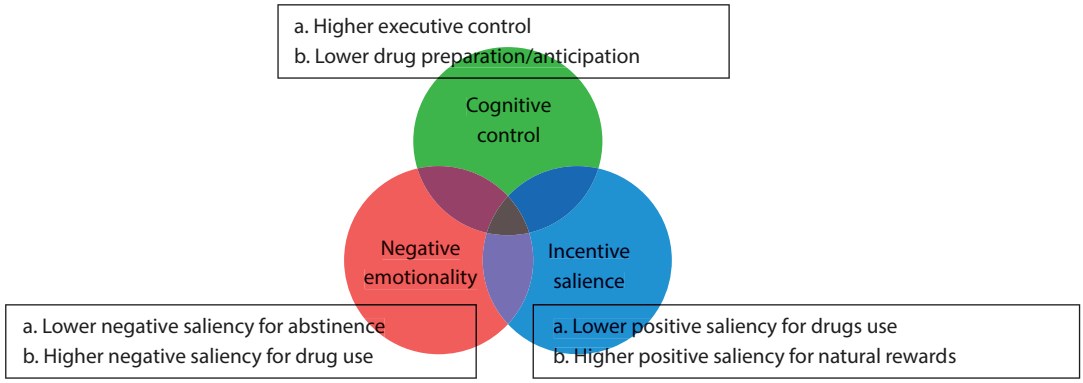

Fig. 81.5 Neurocognitive targets in addiction treatment. According to the tripartite model, aberrant dysfunction of each of the following domains could be a target for intervention. (**a**) Incentive salience can be altered in favour of increasing the non-drug-related rewards and decreasing the drug-related rewards. (**b**) Negative emotionality can be targeted by reducing negative emotional/bodily feelings associated with abstinence and increasing the negative emotional responses associated with drug-related stimuli/behaviours and their negative saliency. (**c**) Cognitive control can be improved by higher executive control ability and lower attention attracted towards drug-related stimuli. Better cognitive control will reduce anticipatory and preparatory drug use behaviours

varenicline administration phase compared to the placebo, people with nicotine use disorder showed improved sustained attention and working memory which were accompanied by reduced withdrawal symptoms and smoking urges [74]. In another study, people with cocaine use disorder who received intravenous methylphenidate showed improved response inhibition in stop-signal task [58].

81.5.2 Cognitive Interventions

Cognitive interventions are able to target all three main groups/domains of NCDs associated with SUDs. Here, we will bring six examples of cognitive interventions frequently used for SUDs treatment. (1) Contingency management (CM), as a behaviour-reinforcement cognitive intervention, gives simple natural rewards (vouchers to buy a simple gift from the clinic's shop) to the patient in the recovery as much as he/she stays abstinent (one voucher for each negative urine test). This intervention gradually increases the incentive salience of staying abstinent [60]. (2) Cognitive bias modification (CBM) is a family of interventions that aims at training attentional biases away from drug-related stimuli and modifying the automatic approach responses to appetitive drug-related stimuli. CBM may affect the top-down regulation by enhancing the activation of lateral PFC and dorsal anterior cingulate cortex (dACC) in craving management. Bottom-top regulation is also targeted by attenuating the activation of the NAcc and amygdala in reducing the effect of previously learned rewards [109]. (3) Mindfulness-based interventions train focused attention and open monitoring, which are reported to improve the activation of prefrontal regions aiding the cognitive control system and decrease the activations of limbic regions in charge of negative saliency [14, 37]. (4) Working memory training (WMT) practices 'online' maintenance and manipulation of increasing streams of information to build working memory capacity, which yields better cognitive control and reduced substance use [46, 82]. (5) Inhibitory control training (ICT) specifically targets cognitive control by applying repeated training of tasks requiring inhibition of pre-potent motor responses like go/no-go and stop-signal paradigms [5]. (6) Cognitive remediation/rehabilitation interventions are mainly designed to target cognitive control and executive functions (cold cognitive functions) using both psychoeducation, metacognitive training and cognitive games/exercises [85, 86]. Hot executive functions are those related to positive and negative feelings like craving, anhe-

donia, dysphoria, etc. They can also be targets for treatments like emotion regulation, reshaping addiction memories and mindfulness-based therapies to increase awareness. Recently, training both cold, i.e. executive functions, and hot, i.e. positive and negative saliency mechanisms, is bringing interesting potentials to the field (for comprehensive information, see [84]). (7) Goal Management Training (GMT) is a manualised group intervention for executive dysfunction that has been shown to improve cognitive control and reduce stress in SUDs [4, 95]. GMT uses instruction, discussion and mindfulness and cognitive exercises (e.g. stop and multitasking tasks) to improve hot and cold executive functions and trains an overarching strategy, i.e. 'Breath – Stop – State Goal – Check' that targets automatic positive and negative biases towards impulsive behaviour ('Breath, Stop') and reorients attention towards goals ('State Goal, Check'). Participants are trained to apply the GMT strategy to everyday scenarios and projects, thus fostering generalisability. (8) Psychoeducation is considered as an effective intervention in different domains of mental health disorders [87]. By informing people with SUDs about their cognitive deficits, we can increase meta-cognitive awareness and treatment motivation [29].

81.5.3 Neuromodulation

There are many ways to use different technologies to externally modulate the brain activities from invasive deep brain stimulation (DBS) to non-invasive technologies like transcranial electrical stimulation (tES) or transcranial magnetic stimulation (TMS). Although they are different in some respects like their feasibility of application and their effects, they have a goal in common and that is to directionally modulate dysfunctional brain activity. There are systematic reviews and meta-analyses which report effectiveness of neuromodulation, especially repetitive TMS (rTMS), tES and DBS [19, 50, 64, 93, 111]. Repetitive TMS creates a magnetic field that induces trains of electrical changes, and tES directly causes electrical induction to the brain, which can either increase or decrease the activation of the targeted region according to what protocol is used. Both tES and TMS techniques exert their effect on cortico-striatal-thalamic pathway by dampening the activations of the reward circuit which shows aberrantly high value to drug-related cues and low to non-drug-related cues; the treatment of the first one causes normalised incentive salience and the latter leads to reduced negative emotionality. It also increase the activation of dACC, anterior insula, DLPFC which lead to higher cognitive control over drug craving and also less saliency to drug which will lead to better self-control (for review, see [24]). DBS aims more at the subcortical areas specifically NAcc and tries to regulate the activations of the reward system to alleviate incentive salience to drug [19]. For more details, you may read [30].

81.6 Clinical Implications and Future Horizons for NCDs in Addiction Medicine

In the previous sections, we have described the existence of significant NCDs associated with different SUDs. These NCDs have meaningful clinical implications, as they underpin key aspects of addiction psychopathology, i.e. compulsive use, withdrawal and craving, and impact a range of clinical processes and outcomes, i.e. treatment engagement, abstinence or reduction of drug use and quality of life. Specifically, we have provided evidence that NCDs in reward valuation and learning fuel compulsive drug use, NCDs in attention and memory compromise treatment engagement and compliance, respectively, and NCDs in cognitive control and decision-making increase the risk of relapse during and after treatment. In addition, impulsivity/reduced inhibitory control has a generalised negative impact on treatment adherence, abstinence and recovery of quality of life. Given the relevance of NCDs for clinical prognosis and outcomes, clinicians and researchers should collaborate to integrate NCDs-specific assessment and interventions in routine clinical practice. Below, we provide spe-

cific recommendations on how to promote this integration.

Harmonised cognitive assessments The consolidation of addiction-specific NCDs framework should lead to harmonisation of cognitive assessment protocols. At this stage, there is relatively high agreement on the cognitive domains that need to be assessed, but no agreement (in fact remarkably low data comparability) on the assessment tools that need to be used [112]. The Neuroscience Interest Group of the International Society of Addiction Medicine (ISAM-NIG) has been recently created to, among other goals, promote an international expert consensus on a minimum set of harmonised tools that can be uniformly applied on addiction neurocognitive studies globally [101]. This set of tool should measure addiction-relevant mechanistic targets, provide useful feedback to patients and clinicians and be relatively culture-free to facilitate upscaling.

Pragmatic implementation of cognitive assessment in the addiction clinic Cognitive assessment will only be relevant if it is integrated in clinical practice. This way patients and clinicians could benefit from its potential applications, including characterisation of addiction severity (e.g. degree of decision-making impairment), prognosis, triage and cognitive-profiles-matched personalised interventions. The best approach to achieve this goal would be to train machine learning algorithms on predictive data generated from a harmonised tool in the context of international research collaboration studies. Machine learning models can then serve to distil the tools and indices that optimise clinical utility, to derive briefer, pragmatic assessments that can be routinely administered in any clinical setting.

Phase III Randomised Controlled Trials of Neurocognitive Interventions

The majority of the cognitive training and remediation interventions that have shown promising results in proof of concept and exploratory trials have not been tested in Phase III or implementation trials. Given the moderate success of the neuroscience-informed interventions that have been clinically tested, such as cognitive bias modification and mindfulness, Phase III trials involving adjunctive cognitive remediation interventions, including cognitive training of executive functions (e.g. working memory, inhibitory control), Goal Management Training and cognitive rehabilitation + psychoeducation, are warranted and needed.

Key Points

- Neurocognitive deficits in three main domains of positive valence (high saliency attributed to drug-related stimuli), negative valance (intense negative feelings during withdrawal state) and cognitive control (inability to execute inhibition) underlie addiction.
- Heavy cannabis use is specifically linked to episodic and working memory deficits.
- Stimulants and opioids are linked to executive function and decision-making deficits.
- Chronic alcohol use is linked to wide-ranging cognitive deficits.
- Mixed polysubstance use is associated with more severe neurocognitive disorders.
- Neurocognitive deficits change dynamically over time as substance use continues and substance use disorder evolves.
- Pharmacotherapy, cognitive intervention and neuromodulation can target specific neurocognitive deficits associated with substance use disorders in positive valence, negative valance and cognitive control domains.

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Substance Use and Co-occurring Infections (Including Immunology)

82

Tianna Magel, Kelli Wuerth, and Brian Conway

Contents

Abstract

Infectious diseases account for over 50% of mortality among substance users. About 1.7 million worldwide are known to be infected with HIV and 6.1 million have chronic HCV infection. Skin and soft tissue infections affect 40% or more of active substance users, while more serious bacterial infections (including endocarditis, osteomyelitis, and epidural abscesses) are much more common than in the general population. Addressing them in a systematic manner will be an important part of a worldwide response to the two great pandemics of this era, namely, HIV and HCV infections. Bacterial infections may be the cause of initial presentation to care, which may provide

T. Magel · K. Wuerth · B. Conway (✉)
Vancouver Infectious Diseases Centre, Vancouver, BC, Canada

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a unique opportunity to secure engagement in long-term, multidisciplinary programs. If we treat substance users as complex human beings with multiple needs, not only will we treat their infections more effectively, we will also help them become better functioning members of society. This must be our ultimate goal.

Keywords

HIV · HCV · Cellulitis · Endocarditis
Osteomyelitis · Epidural abscess

82.1 Introduction

Substance use is a global public health problem, affecting over 275 million people, of which 71 million are diagnosed with a drug use disorder [20, 57]. According to the UN World Drug Report, opioid use remains the most prevalent drug used followed by cocaine and amphetamines worldwide. Globally, there are over 12 million injection drug users with the highest proportions concentrated in areas of Eastern Europe (16%), North America (16%), and Southeast Asia (28%) [57]. Many of these individuals (particularly polysubstance users of amphetamines, cocaine, and/or opioids) are at risk for the acquisition of numerous life-threatening infectious diseases. Injection drug use accounts for 10% of global human immunodeficiency virus (HIV) infections (3–4 million individuals) as well as the majority of prevalent and incident cases of hepatitis C virus (HCV) infections in the developed world. Over 50% of the 12 million active injection drug users are living with HCV infection. Transmission of HIV and HCV occurs primarily through sharing of needles and other drug-related paraphernalia, with unsafe sexual practices as another route of disease acquisition, particularly for HIV [12].

Mortality within the substance use population is 2.35 deaths per 100 person-years (PYs) and, using standard mortality ratios, is 14.68 times higher than that seen in a comparable general population [37]. Causes of mortality are listed in Table 82.1, over 50% of which are related to infectious diseases.

Table 82.1 Worldwide deaths/year among substance users [17]

Hepatitis C	~222,000
Overdose deaths	~190,000
HIV/AIDS	~60,000
Self-harm	~29,000

Beyond mortality, there is also a significant morbidity associated with infections in this population, including hospitalizations and costs to the healthcare system. Bacterial infections are frequently implicated in this regard. Of drug users receiving health care in San Francisco, as many as 32% had an abscess, cellulitis, or both on physical examination [21]. Infective endocarditis may occur in 1.5–20 cases per 1000 injection drug users/year [19]. It is also thought that the onset of infections is associated with more unsafe drug use practices and increased consequences of drug use, including accidental overdose deaths. Presentation of an individual into care for management of an infection may represent an opportunity to intervene to prevent such deleterious outcomes.

In this chapter, we will discuss a physiologic basis for an impaired immune response in this population leading to a higher prevalence of infectious complications and the epidemiology as well as the clinical manifestations of the most common viral and bacterial infectious diseases. We will end by proposing an approach to address this aspect of the management of substance use within the context of a multidisciplinary model of care.

82.2 Immunologic Effects of Substance Use

The immunologic effects of substance use are varied, but immune dysregulation and an increased susceptibility to infection are widely described. The effects of substances on the immune system may be due to the presence of substance receptors on immune cells, although the presence of some opioid receptors on immune cells has been debated [1, 18]. Alternatively, the

effects may be caused indirectly through the presence of opioid receptors or the cocaine receptor sigma-1 in cells of the nervous system or through the release of mediators that affect the immune system, as seen with the release of dopamine after amphetamine use [32]. Substances may also affect the normal functioning of the cardiovascular, respiratory, endocrine, and nervous systems, resulting in physiological changes that may in turn dampen normal host responses to infection.

Numerous studies have demonstrated immunomodulation with substance use. The party drug methylenedioxymethamphetamine (MDMA, or ecstasy) decreases neutrophil phagocytosis, inflammatory cytokine production, and circulating lymphocyte levels [11]. Cocaine use has led to decreased antimicrobial activity and altered the release of cytokines [18]. Opioid effects in humans include decreased phagocytosis, chemotaxis, T cell and natural killer cell activity, and decreased antibody-dependent cellular cytotoxicity [16, 18]. In a real-world study examining blood collected from 19 injection drug users in a needle and syringe program, most of whom used multiple drugs (with 26% reporting crack cocaine use, 56% non-crack cocaine use, and 100% heroin use in at least 16 of the previous 90 days), it was found that the injection drug users had more circulating B cells and systemic inflammation when compared to healthy controls [46].

It has also been reported that substances skew the immune response from Th1, favoring cell-mediated immunity, to the humoral Th2 response [18]. A decreased Th1 response impairs the response to viruses and other intracellular pathogens. A study in rhesus macaques demonstrated that animals given morphine had fewer CD4 T cells and increased viral replication after infection with either simian immunodeficiency virus or a modified simian-human immunodeficiency virus [33].

Taken together, these findings demonstrate negative immunomodulation after substance use, leading to a predisposition to microbial infections among substance users. In general terms, there should be a high index of suspicion for infections of all types among substance users engaged in health care.

82.3 HIV Infection: Epidemiologic Considerations

Since the isolation of the virus in 1981, over 77.3 million individuals have been infected with HIV and 35.4 million people have died due to HIV-related complications. Every year there are nearly 1.8 million new cases of HIV infection reported globally [56]. People who inject drugs are nearly 23 times more at risk of acquiring HIV infection as compared to the general population [56]. Injection drug use is the second leading cause of HIV infection and nearly one in eight injection drug users are living with HIV. Nearly 10% of substance users (1.7 million) worldwide are known to be infected with HIV [61]. Reduced inhibitions and increased risky sexual and drug use behaviors contribute to substance user's exposure and prevalence of disease. Today, most regions in the world have demonstrated an overall relative reduction in HIV transmission among substance users as compared to other populations, such as men who have sex with men. In the past few years, the actual incidence of HIV infection among substance users has remained stable. However, with the rise of synthetic opioids, such as fentanyl, there have been pockets of HIV outbreaks within regions of the United States and the rest of North America. The rate of transmission is increased by the lack of availability of needle and syringe exchange programs, increasing the prevalence of risky behaviors favoring HIV acquisition. Globally, HIV among substance users continues to be prevalent in parts of South America, Eastern Europe, and Central and Southeast Asia, for similar reasons [13].

Even among drug users, the incidence of HIV infection tends to be more prevalent among men. This is in part due to enhanced sexual transmission among men who have sex with men, as well as the incidence of injection drug use being higher among men. In those infected with HIV, the presence of another sexually transmitted infection can increase the risk of HIV transmission as the virus tends to shed more effectively when there is an open sore or genital ulcer [48]. This is especially critical among drug users who tend to engage in increased risky sexual behavior

and acquire such concomitant infections that increase the spread of HIV infection if it is already present.

82.4 HIV Infection: Clinical Considerations

HIV causes immune suppression through attacking the body's white blood cells, in particular CD4 T cells. Reductions in CD4 cell counts leave an individual with a weakened immune system and at increased risk for opportunistic infections or cancers. In the first 2–4 weeks following acquisition of the virus, known as the acute stage, symptoms of HIV infection can mirror those of a flu-like illness, with sore throat, fever, chills, and swollen lymph nodes [58]. In a drug user with significant risk factors for disease acquisition, such a presentation should prompt consideration of testing for HIV infection (as well as HCV testing as co-infection will likely be present), with clinical assays for viral detection being positive even at this very early stage. This could allow for immediate initiation of HIV treatment, not only to preserve the patient's immune system but to reduce the amount of HIV in the circulation of an individual who, having recently acquired the infection, is likely engaged in risk behaviors for its onward transmission.

The acute phase is followed by a long asymptomatic period, which may go on for a decade or more. In a drug user of unknown HIV status, this may offer a unique opportunity to establish a diagnosis and initiate antiretroviral therapy as appropriate [58]. Current clinical guidelines suggest that all HIV-infected patients should receive such therapy and that ongoing drug use is not a contraindication to its prescription. Some individuals may naturally never progress to full-blown acquired immunodeficiency syndrome (AIDS) and they are a small percentage (1–5%) of individuals known as "non-progressors." For all others, if left untreated, progression from HIV to AIDS generally occurs within 10–12 years. Progression to AIDS is characterized by a CD4 cell count below 200 cells/mm^3 [10]. From the time of diagnosis of AIDS, mortality generally occurs within 2–3 years.

The advent of highly active antiretroviral therapy (HAART) in 1996, consisting of three medications inhibiting HIV replication administered simultaneously, led to a dramatic decrease in HIV-associated morbidity and mortality. Over the past 20–25 years, treatments have become more effective, simpler, and with few (if any) short- and long-term side effects. Today the life expectancy of an HIV-infected individual adherent to treatment approaches that of the general population [53].

Current regimens that are recommended as part of the initial therapeutic approach generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) administered with a third agent, most often an integrase strand transfer inhibitor (INSTI). The current preferred combinations, as outlined by the widely accepted US Department of Health and Human Services academic panel, are shown in Table 82.2. For all of these preferred combinations, observational and controlled clinical trials have shown efficacy of over 90% in achieving and maintaining full virologic suppression (undetectable HIV plasma viral load). This is the necessary prerequisite to controlling immune disease progression, preventing the development of AIDS-related complications, and preventing disease transmission [14]. Selection of regimens for drug users should take into account a number of factors including potential adherence barriers, potential drug interactions, and adverse events, with an emphasis on

Table 82.2 What to start: Initial combination regimens for the antiretroviral naïve patient [58]

Regimen	Single tablet regimen	Randomized clinical trial data
Bictegravir/tenofovir alafenamide/emtricitabine	Yes	Yes
Dolutegravir/abacavir/lamivudine	Yes	Yes
Dolutegravir/tenofovir/emtricitabine	No	Yes
Raltegravir/tenofovir/emtricitabine	No	No

liver-related side effects as the majority of HIV-infected substance users are co-infected with HCV.

All of the recommended regimens shown in Table 82.2 can be taken with or without food, addressing an important logistic consideration for the treatment of substance users. Raltegravir has a lower barrier to resistance and some have recommended it not be used in patients who may struggle with adherence to medications. In fact, some have suggested that alternative regimens based on a protease inhibitor (PI) such as darunavir be used rather than an INSTI-based combination, to reduce the likelihood of treatment failure with resistant viral isolates. Finally, tenofovir-based regimens must be used in the presence of HBV co-infection. Other issues are detailed in a number of excellent guideline documents that are updated regularly [58]. Consultation with an expert in the field of HIV medicine should be considered prior to the initiation of lifelong antiretroviral therapy.

Substance users are also at increased risk for HIV disease progression. Many substance users exhibit low or reduced HIV treatment uptake and adherence. As a result, drug users demonstrate suboptimal treatment outcomes and poor virologic response to HIV treatment. Continued drug use, even intermittently, is also associated with a weakened CD4 cell count response as compared to those free of substance use [35]. Various other additional factors contribute to poor HIV outcomes among drug users, such as homelessness and additional psychiatric comorbidities that may independently hinder adherence to therapy [44]. The resulting suboptimal virologic suppression not only reduces treatment efficacy but may also lead to the development of drug resistance. In this context, it will be important for substance users on HIV therapy to be engaged in care so that monitoring of adherence and virologic suppression can be conducted on an ongoing basis. As such, regular monitoring of HIV plasma viral load should be conducted on a quarterly basis at a minimum, more frequently if there are concerns about adherence to therapy.

Substance users living with HIV have a threefold increased risk of death compared to other populations [36]. HIV-/AIDS-related deaths remain the leading cause of mortality in this group. Injection drug use can also decrease the immunological and clinical response to therapy, accounting for part of this observation. Continuous drug use also results in increased risk for opportunistic infections due to the compounding effects of drugs on the immune system of immunocompromised individuals, leaving HIV-infected drug users at increased risk for fatal infections. According to the World Health Organization, nearly one third of AIDS-related deaths are caused by tuberculosis infection, accounting for over 300,000 deaths in 2018, many in substance users who may not be aware of their co-infection status until advanced clinical symptoms develop. HIV-infected substance users are also at increased risk for psychiatric comorbidities and suicide-related mortality. HIV-positive individuals with a history of substance use demonstrate increased rates of suicide [27]. HIV-infected substance users are also overrepresented within the epidemic of overdose deaths, particularly in North America. According to the United States Centers for Diseases Control, overdose deaths among HIV-infected individuals increased by nearly 43% between 2011 and 2015. Increased availability of synthetic opioids and decreased metabolic clearance (due to liver disease) among HIV-infected drug users are considered a major contributing factor to this rapid increase, in addition to a higher prevalence of risky behaviors within this group.

Treatment in HIV substance users requires a multidisciplinary approach in which the individual's medical, social, psychiatric, and addiction-related needs can be addressed in an integrated manner. Peer support, counseling, directly observed treatment, and incentives have been demonstrated as tools to overcome barriers to effective HIV treatment. Co-location of HIV and addiction care has been proven to be an effective tool in addressing HAART adherence and monitoring disease progression. Previous studies have demonstrated the benefits of methadone maintenance therapy (MMT) in HIV treatment adherence and maintenance

[55]. MMT and other opioid agonist therapy (OAT) options have also been demonstrated to be effective tools in primary HIV prevention. Providing harm reduction services is also of critical importance in preventing overdose-related mortality among HIV-infected substance users. A scale-up of multifaceted and integrated treatment approaches are not only the key to success of programs to treat HIV but will also contribute to a more successful approach to the management of addiction itself, including a reduction in the stigma associated with it.

The Joint United Nations Program on HIV/AIDS has set out the 90-90-90 goal for the management of HIV infection in the world, such that 90% of infected individuals are diagnosed, 90% of these linked to care and taking antiretroviral therapy, and 90% of those on therapy exhibit a maximal response to it. However, among substance users in many jurisdictions, suppression rates (the "third" 90%) of 50% or less are achieved [4, 9]. There are many correlates of this lack of success. These include ongoing drug use and poor social conditions, including homelessness. Introducing and scaling-up of evidence-based interventions into the community is critical in addressing HIV among drug users. Interventions such as needle and syringe exchange programs, OAT, and addiction recovery programs must be considered part of the overall approach to HIV infection in substance users. Recent data also show that the provision of HIV pre-exposure prophylaxis (PrEP) to uninfected individuals, shown to be highly effective among men who have sex with men, may also have a role to play among high-risk drug users who are not infected with HIV but are at risk of becoming so. The role of the healthcare practitioner has been stressed as an important tool in mitigating the HIV syndemic among drug users through increased screening and engagement in care [8]. In addition, the design of multidisciplinary programs of care (described below) to attend to the individual's need in a holistic manner may be the key to successful long-term interventions.

82.5 HCV Infection: Epidemiologic Considerations

It is thought that over 71 million people are productively infected with HCV throughout the world [6]. Most people acquired the disease as a result of substance use, with injection drug users being 50 times more likely to become infected as compared to the general population [39]. Most exposure occurs through sharing of needles and syringes, but infection may also occur through pipes, cookers, and other substance use equipment if it is contaminated with blood. In 2014, of the estimated 12 million injection drug users worldwide, six million of those had chronic hepatitis C [41]. According to the World Health Organization, there are about 1.75 million new HCV infections in the world each year, with injecting drug use accounting for 23% of new cases [60]. This is the driving force maintaining this worldwide pandemic. The first few years of injection behavior are particularly important, with up to 40% of individuals acquiring HCV infection during this period of time. In some drug using groups, such as a cohort of drug injectors in St. Petersburg, Russia, prevalence of HCV infection may exceed 90% [43]. Although many people clear the virus spontaneously, as many as 85% will remain productively infected and at risk for the development of cirrhosis and hepatocellular carcinoma (HCC).

Among substance users, a number of factors are associated with the acquisition of HCV infection. The duration of drug use is a key factor, with a meta-analysis showing a 2.4-fold increase in the prevalence of infection with duration of drug use exceeding 5 years [62]. Injection drug use itself confers a tenfold increase in risk of transmission, attesting to the central role played by the injection behavior itself [62]. Sharing of needles/syringes carries a 2.24-fold increase in risk, speaking to the possible benefit of equipment exchange programs in controlling disease spread [62]. A number of social factors play a role, with unemployment, as an example, carrying an independent risk of disease transmission of 1.5-fold [62]. It is likely that other factors such as financial and housing insecurity may be important. Recent incarceration is another key issue, with a meta-analysis showing a

62% increase in HCV acquisition among injection drug users associated with this variable [51]. Finally, it is important to point out the overlap of the HIV and HCV epidemics in the world. An estimated 2.2 million people are co-infected with HIV and HCV and over half of these cases are in people who inject drugs, a fact that must be considered as they are engaged in active medical care.

82.6 HCV Infection: Clinical Considerations

The first 6 months of HCV infection are referred to as acute HCV infection, which is asymptomatic in two-thirds of cases. If symptoms do occur, it will typically occur over a broad period of time after exposure, between 2 weeks to 6 months and usually within 8 weeks. The most common symptoms are jaundice, dark urine/pale stools, nausea, and abdominal pain. In a substance user engaged in care with any or all of these clinical manifestations (particularly jaundice), testing for the presence of HCV infection should be considered. As it may take several months for a positive HCV antibody test to develop, HCV RNA testing should be requested as it is generally positive within weeks of the infection having been acquired. HIV antibody testing should also be requested as 20–25% of individuals may be co-infected. Globally, it is estimated that 9.1% of people who inject drugs are productively infected with HBV, with great geographical variation [13]. It would also be indicated to test for the presence of HBV infection in this context.

Once HCV infection has been diagnosed, the patient must be monitored to determine the outcome of infection, either spontaneous viral clearance or chronic productive infection. Estimates of the frequency of spontaneous clearance vary from 15% to 45% [60]. If this occurs, individuals who continue to use drugs remain susceptible to infection upon re-exposure to HCV and should be re-evaluated accordingly. Some guidelines suggest HCV treatment be considered in patients who have HCV RNA values that remain detectable 12 weeks after the suspected date of exposure. In this setting, a shorter course of treatment may be considered (perhaps only 6 weeks) with a cure being achieved in more than 95% cases. This should only be considered in consultation with a specialist in HCV therapy.

Once chronic infection is established, it is generally asymptomatic for many years. Patients remain viremic and at risk of transmitting the infection to susceptible hosts. Compared to uninfected patients, those with chronic HCV infection are more likely to die at a younger age and from liver-related causes. Disease progression rates among substance users have been well studied. On average, cirrhosis occurs 34 years post-infection, with compensated cirrhosis occurring at 6.6 events/1000 PYs and decompensated cirrhosis at 1.8 events/1000 PYs [50]. HCC occurs at a rate of 0.3 events/1000 PYs [50].

Until 10 years ago, treatment of HCV infection was complex and toxic, with marginal efficacy. The regimen was as long as 48 weeks in duration, including weekly interferon injections, and was curative in only 50% of cases for the most common genotype. Highly effective, well tolerated all-oral agents known as direct-acting antivirals (DAAs) are now the treatment of choice for the vast majority of HCV-infected individuals (Table 82.3). Controlled clinical trials have shown

Table 82.3 Currently available all-oral treatment regimens for the management of HCV infection and their reported efficacy among substance users

Drug name	Genotypes	Studies in substance users	SVR12 (cure) rate
Sofosbuvir/velpatasvir	All genotypes	SIMPLIFY (Ref. [24])	94%
Sofosbuvir/velpatasvir/voxilaprevir	All genotypes	None	—
Glecaprevir/pibrentasvir	All genotypes	MISTRAL (Ref. [45])	98%
Elbasvir/grazoprevir	1, 4	C-EDGE CO-STAR (Ref. [15])	91.5–94%
Ledipasvir/sofosbuvir	1, 4, 5, 6	None	—
Ombitasvir/paritaprevir/ritonavir and dasabuvir	1	D3FEAT (Ref. [23])	91%

them to produce a cure of HCV infection (defined as the absence of detectable HCV RNA in the blood 12 or more weeks after the end of therapy, known as a sustained virologic response, or SVR12) in 95% or more of cases. Several studies including C-EDGE CO-STAR, D3FEAT, and SIMPLIFY, as well as subset analyses of other clinical trials, have examined the use of DAAs in substance users and/or those receiving OAT. These studies have demonstrated high completion and SVR12 rates in these populations [26]. There have also been many "real-world" reports of the successful treatment of HCV infection among substance users. A meta-analysis of DAA treatment studies in substance users reported an overall cure rate of 87.7% [28]. There is great concern about the risk of HCV re-infection after a cure has been achieved in this population. A systematic review found that low-risk patients had a re-infection rate of 1.85/1000 person-years of follow-up (PYFU), while high-risk patients including injection drug users and prisoners had a rate of 22.32/1000 PYFU [49]. In some centers such as ours, the re-infection rate in substance users is as low as 1.05/100 PY [30]. If HCV treatment is contemplated, measures should be taken to mitigate the risk of re-infection as much as possible. Part of the approach includes maintenance of the patient in long-term follow-up. This allows for ongoing discussion of how to reduce risk behaviors for HCV acquisition and to perform repeat HCV RNA testing every 6–12 months to diagnose and treat HCV re-infection at the earliest possible time.

The World Health Organization has set a goal of eliminating HCV infection as a part of the Sustainable Development Goals by 2030 [59]. Active substance users who are infected have been prioritized to receive HCV treatment, not only to cure their own infection but to limit onward transmission of infection in this population that is, essentially, sustaining the HCV epidemic in the developed world. To date, less than 1% of people with HCV have been treated [25]. There is an urgent need to develop systems of care to engage and treat this population in the context of a global HCV elimination plan.

82.7 Selected Bacterial Infections in Substance Users

Acute bacterial infections are commonly seen among substance users. Their pathogenesis relates to direct introduction of pathogens into the skin or bloodstream from contaminated needles, syringes, and other drug paraphernalia. They are a frequent cause for a substance user to seek medical attention, due to the symptoms that may occur. Although often treated with oral antibiotics and local drainage, a systemic infection may occur and produce life-threatening sepsis. Seeding of distant structures including bones, joints, and heart valves is not uncommon and adds to the potential morbidity and complexity of treatment of the infection.

82.7.1 Cellulitis and Abscesses

Skin and soft tissue infections (SSTIs), which include cellulitis and abscesses, are the most frequent infectious complication of substance use. In Tehran, Iran, 40% of injection drug users interviewed reported ever having an injection site infection [42], while a study conducted within two American needle exchange programs found 66% of attendees had experienced an SSTI [52]. In England, a study on hospitalizations caused by infections in opioid users from 1997 to 2016 found 35% of injecting-related admissions were due to abscess and 23% were attributed to cellulitis [34]. However, hospitalizations may not reflect the full extent of SSTIs as many individuals attempt self-treatment [21]. In a study of injection drug users in San Francisco, 27% reported lancing their own abscesses and 16% reported using antibiotics without a prescription [5].

Intramuscular or subcutaneous injection, also called "skin-popping," and the injection of a heroin and cocaine mixture (speedball) have both been associated with an increased risk of abscesses [5, 40]. The most frequent causative agent for SSTIs in substance users is *Staphylococcus aureus*, particularly methicillin-resistant *S. aureus* (MRSA) [32]. Other bacteria

commonly found are streptococci, anaerobic bacteria such as *Fusobacterium* spp., and Gram-negative bacilli such as *Pseudomonas aeruginosa* [16, 32]. Many other bacteria, including ones not commonly associated with infections, can be found in SSTIs in injection drug users, and polymicrobial infections are quite common. The oral bacterium *Eikenella corrodens* is a facultative anaerobe and has caused SSTIs after drug users have licked needles or other injection equipment [16]. In some cases, spore-forming bacteria such as *Bacillus anthracis* and *Clostridium* spp. have been injected, leading to cases of tetanus, anthrax, or wound botulism [32].

The diagnosis of cellulitis or an abscess is usually made upon visual inspection, although for abscesses sometimes CT or MRI scans may be required [16]. The infected site is typically painful and displays erythema and tenderness. It is sometimes accompanied by fever. Both cellulitis and abscesses require antibiotic treatment, and abscesses generally must be drained. Complications of cellulitis and abscesses may include ulcer development, necrosis, and sepsis.

82.7.2 Endocarditis

Infective endocarditis is another common infectious complication of substance use, with estimates ranging from 1.5 to 20 cases per 1000 injection drug users annually [19]. Its incidence is also increasing in substance users, with a study on opioid users in the United States showing a significant increase in hospitalizations from 2002 to 2012, likely related to limited availability of sterile injection supplies [47]. At a Swedish hospital, the incidence rate of *S. aureus* endocarditis related to injection drug use doubled over the course of 10 years, from 0.52/100,000 PYs in 2004–2008 to 0.99/100,000 PYS in 2009–2013 for all adults, with an estimated rate of 249/100,000 PYs in injection drug users in Stockholm [3]. In the general population, left-side endocarditis is predominant, while in injection drug users up to 76% of cases are right-side endocarditis [19]. The difference is likely due to intravenously injected substances reaching the right-side valves first, leading to endothelial damage and/or the aggregation of microbes on the right side of the heart.

Cocaine has a stronger association with endocarditis than other drugs, which may be due to its physiological effects on the circulatory system including vasospasm leading to vasoconstriction and ischemia, along with more frequent injections when compared to heroin due to the shorter half-life of cocaine [19, 21]. The major bacterial causes of endocarditis in substance users are *S. aureus*, streptococci, *P. aeruginosa*, and other Gram-negative bacilli and enterococci, although many other species have been isolated. *S. aureus* accounts for half of the cases involving the right-side tricuspid valve in injection drug users [19], although notably most *S. aureus* involved in endocarditis is methicillin-sensitive. Patients with endocarditis often present with a fever, cough, and chest pain [38]. Antibiotic treatment is vital and surgical intervention may be necessary in some cases, although ongoing injection drug use may complicate the long-term viability of prosthetic valves. Mortality from endocarditis ranges from 5% to 30%, although this risk does not seem to increase in substance users, perhaps because of the inherent lower mortality of right-side endocarditis [38].

82.7.3 Osteomyelitis

Osteomyelitis, or infection of the bone, is an emerging concern in substance users, with one study demonstrating a twofold increase in hospitalizations for osteomyelitis among opioid users from 2002 to 2012 in the United States [47]. The majority of infections are located in the appendicular skeleton, while 2–7% of cases occur in the axial skeleton, although there is evidence that the latter is more common among injection drug users [22, 31]. Osteomyelitis may occur from the spread of SSTIs to the bone or by hematogenous dissemination of bacteria.

S. aureus is the major causative agent of osteomyelitis in this population, with other commonly isolated organisms including *P. aeruginosa* and streptococci [31]. As with SSTIs, less common

etiologic agents (such as *E. corrodens* and other oral bacteria) may be isolated [31].

Osteomyelitis may be difficult to diagnose, particularly when the underlying bone has become infected from an abscess or other SSTI that was initially treated with a shorter course of antibiotics not suitable in duration for a deeper-seated infection. Imaging of the affected area by CT or MRI scan may be needed to make a specific diagnosis. Long courses (typically 6 weeks) of antibiotic therapy are required, and in some cases, surgery is required to remove an infected sequestrum.

82.7.4 Epidural Abscesses

Once considered quite rare, epidural abscesses are increasingly recognized as an infectious complication of substance use. For example, at a tertiary care center in Massachusetts, USA, spinal epidural abscesses significantly increased from 2.5/10,000 admissions in 2005 to 8.0/10,000 admissions in 2015 [2]. Another study in the United States found the number of hospitalizations for epidural abscess in opioid users more than doubled from 2002 to 2012 [47].

The vast majority of epidural abscesses are caused by infections that have spread through the blood from distant infected locations, with one risk factor being a history of localized blunt spinal trauma [54]. A limited number are caused by direct injection of contaminated material. As with other bacterial infections among substance users, the major causative agents are *S. aureus*, streptococci, and Gram-negative bacilli [54].

While back pain is extremely common among substance users and usually quite benign, it is important to consider the possibility of an epidural abscess in patients complaining of back pain, as early diagnosis is key for limiting mortality or long-term sequelae. Patients present with localized pain in the vertebrate in 70–100% of cases, often accompanied with back tenderness and sometimes with fever [7]. Surgical drainage is typically required in combination with antibiotics, perhaps as long as 12 weeks' duration. In some patients where surgical drainage is not possible, antibiotic therapy alone may be used, which may include longer-term prophylactic regimens. If the infection progresses, neurological deficits may occur. Despite all appropriate interventions, the mortality rate of an epidural abscess is approximately 10% [22].

82.7.5 Prevention of Bacterial Infections

The sources of bacterial infection relate to the use of non-sterile drugs and diluents, as well as exposure to the substance user's own microflora during drug use. Harm-reduction strategies are key to reducing the occurrence of such infections. Expanding access to OAT and needle and syringe programs can limit needle sharing and needle reuse and therefore the introduction of microbes. Instruction about sterile injection practices as well as the risks associated with polysubstance use, skin popping, and needle licking may also be helpful.

82.8 A Multidisciplinary Approach to the Care of Infections Among Substance Users

The needs of an individual who is using/injecting drugs are complex and go well beyond the substance use itself. These include many medical, psychiatric, and social concerns, in addition to the addiction-related issues. In designing systems of care to optimally manage potentially life-threatening complications of substance use, a multidisciplinary program of engagement is required. If we think of a "four-legged chair" that will define a patient's needs in a rigorous and systematic way, specific plans of intervention must be developed for each relevant condition. In committing to a plan to deal with the imperatives the patient defines as most important, adherence to treatment regimens that could be life-long (as in the case of HIV infection) could be improved. Addiction-related interventions could also be optimized to allow for safer drug use on the one hand and perhaps commitment to recovery on the other (Fig. 82.1).

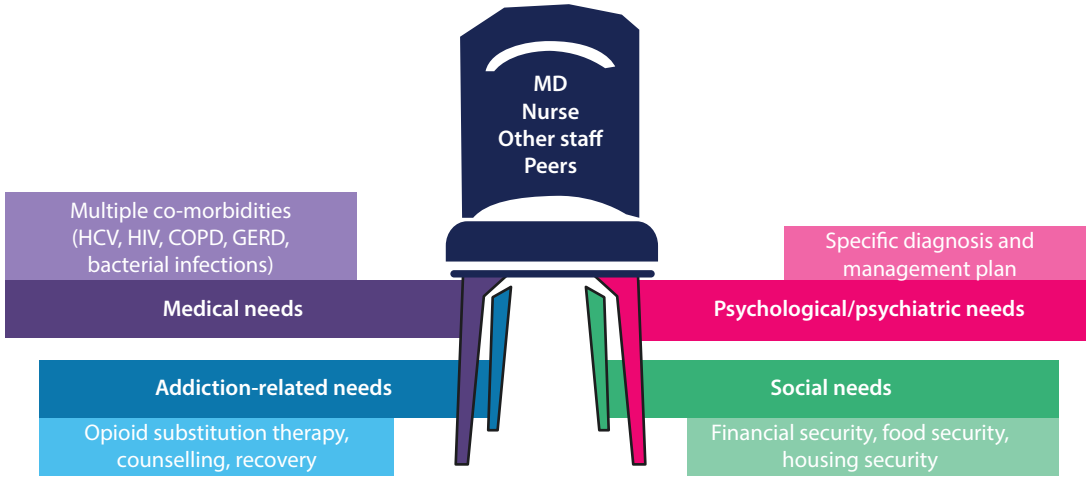

Fig. 82.1 A multidisicplinary program of engagement in care is the key to the long-term management of vulnerable substance users. This can be depicted as a fourlegged chair, to illustrate the need to address medical, psychologic, social, and addiction-related aspects of care [29]

We have designed such a program focused on providing multidisciplinary care. This model aims to address all patient-related needs in an integrated setting. We offer weekly support groups; assistance with housing, income assistance, and nutritional supplement applications; snacks; and education workshops, in addition to medical clinic services with infectious disease specialists. We hold weekly community pop-up outreach events, in which we go to various community sites to provide point-of-care HCV and HIV testing, immediate medical consultation for those who test positive, and linkage to care with incentivized appointment attendance. Our center follows the "three pillars" motto in which we aim to provide engagement, multidisciplinarity, and durability. The engagement pillar entails immediate consultation with a healthcare specialist along with the design of a relevant treatment plan. The second pillar of multidisciplinary ensures that all the patients' needs are addressed in a flexible and accountable manner. Lastly, through the pillar of durability, we strive to ensure a low threshold to care, with incentives for long-term engagement and strategies to mitigate loss to follow-up. Through our program we have been able to provide curative HCV treatment to over 500 substance users as well as lifesaving antiretroviral treatment to over 450 HIV-positive individuals. Our program has had a significant impact on opioid-related deaths. In one analysis, based on local opioid-related deaths, we should have expected over 80 deaths over a period of 18 months in our population, while we have only observed eight. We feel that the engagement we provide leads to safer drug use and a greater commitment to recovery. It is important to note that the initial encounter that led to the design of a durable, multidisciplinary plan of care for a given individual was often an infectious complication of addiction, perhaps something as simple as a bacterial skin infection.

In the practice of addiction medicine, it is essential to individualize and optimize the care plan to manage substance use and the addiction itself. It is equally important to have a systematic program in place for HIV and HCV screening given the prevalence of these two chronic and treatable conditions in this population. In those found to be uninfected (as well as in those who have been cured of HCV infection and exhibit risk behaviors for repeat exposure to the virus), this screening must be incorporated into the long-term management of substance users. In addition to this, an evaluation for the presence of an infectious complication must be incorporated into each clinic visit. Many conditions are easily treated, while some may be life-threatening and may require urgent referral for specialist evaluation.

82.9 Conclusion

Infectious complications of substance use are common and have a significant morbidity and mortality. Addressing them in a systematic manner will be an important part of a worldwide response to the two great pandemics of this era, namely, HIV and HCV infections. Serious bacterial infections are also common in this population. Particular attention must be given to the diagnosis and treatment of these infections when substance users present for medical care. Ultimately, the approach must be a holistic one, based on three pillars: engagement, multidisciplinarity, and durability. If we treat substance users as complex human beings with multiple needs, not only will we treat their infections more effectively, we will also help them become better functioning members of society. This must be our ultimate goal.

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Sleep Disorders in Addiction: An Overview

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Timothy Roehrs, Jelena Verkler, Gail Koshorek, and Thomas Roth

Contents

T. Roehrs (✉) · T. Roth
Sleep Disorder & Research Center, Henry Ford Health System, Detroit, MI, USA

Department of Psychiatry and Behavioral Neuroscience, Wayne State University, SOM, Detroit, MI, USA
e-mail: TROEHRS1@hfhs.org

J. Verkler · G. Koshorek
Sleep Disorder & Research Center, Henry Ford Health System, Detroit, MI, USA

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Abstract

The overall concept and aim of this chapter is to provide a basic sleep medicine "crash course" with a specific goal of describing a practical approach to treating the patient population afflicted with substance dependence and concomitant sleep complaints.

A sleep medicine overview will be provided, with specific emphasis on sleep physiology, nosology, and psychiatric and addictive disorders associated with sleep concerns. Also, an overview of a diagnostic approach in addiction to treatment options will be presented. The treatment of sleep disorders with both pharmacotherapy and cognitive behavioral therapy approaches will be offered.

The often-heard complaint from our patients of "Doctor, I can't sleep" is not a simple problem, but requires a simple yet comprehensive approach. The addicted population is unique and a unique "skill set" is required from clinicians treating this population.

Treatment settings vary, and the question of "who is going to do what" is important and needs to be clarified prior to approaching optimal treatment strategies. Some treatment settings include physicians from various specialties, sleep specialists, psychologists, therapists, program social workers, and other health professionals. Invoking a multidisciplinary team approach to the diagnosis and treatment of sleep disorders and "insomnia" in particular is crucial.

An evidence-based approach is of paramount importance as we move to superior clinical paradigms and one that should be kept in mind throughout this process.

One can utilize a "sleep assessment package" which should include intake questionnaires, sleep diaries, and other structured assessments. Informed choice of medications for "insomnia" when pharmacotherapy is deemed necessary is required, and this chapter offers practical guidelines and describes other available resources.

It is advisable to screen all patients for primary sleep disorders (i.e., obstructive sleep apnea or periodic leg movement/restless legs disorder), first clinically, and then with sleep studies if indicated. And lastly it is important to link with local sleep clinics or specialists when possible to avail yourself and your patients of a specialist perspective when needed.

83.1 Introduction

People who abuse alcohol and other substances are at high risk for sleep disturbances due to the direct effect of the substance and/or its discontinuation on their sleep. Also, their sleep-wake cycle and its effect on their behavior and daily functioning in-turn impact their daily need for subsequent sleep. Those with substance abuse disorder are 5–10 times more likely to have sleep disorders [26].

83.2 Sleep Disorders

83.2.1 Incidence

It is estimated that up to one third of the adult population have occasional sleep problems. Of these, one third has chronic "insomnia" as a presenting complaint. For example, between midnight and 3 a.m., it has been estimated that on any night, two million Canadians from the total population of 35 million are awake watching television. Many professionals in our current society (including doctors, nurses, EMS workers, and police) work irregular sleep-wake schedules or shift work, often leading to sleep disturbance. Compared with the population at the turn of the century, we are now sleeping 1.5 h less per 24-h period. Epidemiological studies show that EDS (excessive daytime sleepiness) in Westerners is between 5% and 36%. The number one cause of excessive daytime sleepiness is insufficient sleep due to reduced opportunity or ability to sleep given adequate opportunity. In any given year, 20–40% of adults complain of difficulty sleeping and 17% consider it serious [29]. The majority remain unrecognized and untreated. It has been estimated that the average family MD asks two questions before offering a prescription medication to deal with "insomnia." In addition it is well known that many medical school curricula do not spend adequate time in educating young doctors in the area of sleep medicine.

83.2.2 Implications and Consequences of Sleep Problems

There are multiple very well publicized examples of the consequences of sleep insufficiency and the resulting fatigue and excessive daytime sleepiness. Excessive sleepiness has been implicated in the following world catastrophes: Exxon Valdez oil spill, Three Mile Island nuclear accident, Chernobyl nuclear plant disaster, Bhopal chemical explosion in India, and the US Space Shuttle Challenger explosion.

Sleep deprivation studies in animals have clearly shown that "sleep is necessary for survival" [34]. In 1965, a 17-year-old college student tried to set a new world record for staying awake. The resulting clinical scenario was one of frequent micro sleeps, visual and auditory hallucinations, tachycardia, hypotension, psychosis, and profound weakness at 264 h and 12 mins (11 day, 12 mins). Interestingly, he fully recovered after sleeping 14 h and 40 min, just as the Rechtschaffen rat studies.

Sleep-deprived people have nearly as many car accidents as drunk drivers and double the rate of car accidents as the general population. Sleep-deprived people have a higher incidence of infection and other illnesses, as sleep acts as a "host defense" against infection and facilitates the healing process. Sleep plays a critical role in memory consolidation. Disturbed or reduced sleep can have an effect on cognitive functions such as learning and decision-making [9].

Sleep disorders medicine, from a historical and international perspective, is a relatively new field and one which many countries have little access to. The field largely began at Stanford University in 1970 and, as an example, is approximately 25 years old in Canada. In 1981 with the introduction of CPAP (continuous positive airway pressure used to treat obstructive sleep apnea), the field grew exponentially. There are currently available fellowship programs and board certification via the American Board of Sleep Medicine.

83.2.3 NPSG and MSLT

Most sleep laboratories in North America deal primarily with respiratory-related sleep disorders, such as obstructive sleep apnea (OSA), with a significant number providing the full range of sleep disorders diagnosis and treatment. Sleep specialists' backgrounds differ widely and range from those whose primary training is in psychology, general medicine, pulmonology, neurology, and psychiatry, and many then become board certified in sleep disorders medicine as well.

The PSG (polysomnogram, sleep study) is complex and labor intensive, often generating volumes of information which would be equal to 1000 pages of data. A typical overnight sleep study monitors EEG (electroencephalogram), EOG, (electrooculogram), chin EMG (electromyogram), EKG, respiratory effort (chest and abdominal movements), oxygen saturation, and leg movements (EMG), all using noninvasive leads. Some centers also perform daytime MSLTs (multiple sleep latency tests) in diagnosing narcolepsy and documenting excessive daytime sleepiness and MWT (maintenance of wakefulness tests) used in documenting treatment efficacy for the excessive daytime sleepiness associated with a number of sleep disorders.

83.3 Sleep Physiology

83.3.1 Normal Human Sleep

The exact function(s) of sleep is still not precisely known. The "normal" amount of sleep that a healthy adult individual needs is 7–8 hrs and that amount may vary with age or when one is ill or stressed [9]. It is estimated that 20% of the population regularly sleeps less than 6 h and 10% sleeps 9 h or more (long sleepers).

Sleep is characterized by different EEG signals that range from active wake patterns of beta waves to relaxed states with eyes closed and alpha waves. Deeper sleep, defined by higher arousal threshold, is associated with slow theta and high amplitude delta waves. There are two types of sleep: REM (rapid eye movement) and NREM (non-REM). Thus, sleep is not a homogeneous state, but rather a combination and cycling of these two separate and distinct states. These distinct states are characterized by specific behavioral and physiologic changes that occur during these phases of sleep.

83.3.2 NREM

NREM sleep is divided into three stages: stage N1 with low-amplitude mixed-frequency waves (predominantly in the 4–7 Hz theta frequency) and slow rolling eye movements, stage N2 typified by theta frequency waves and the presence of EEG features known as "sleep spindles" and "K-complexes," and stage N3 featuring the emergence of slow (0.5–2 Hz) delta frequency waves. Arousal thresholds are generally lowest in stage N1 and highest in stage N3 sleep.

83.3.3 Rem

Even without any instruments, we can tell if someone is in REM sleep by looking at the movements in their eyes, even when closed. In REM, we will often report dreaming when awakened. Alpha motor neuron activity is suppressed through a number of inhibitory pathways, and our skeletal muscles are paralyzed. REM periods typically occur every 90–120 min, with each successive REM phase getting longer in duration: first, 5 min; second, 10 min; and third, 15 min. Blood flow is directed to the brain (active) and the EEG pattern is that of low-amplitude, mixed-frequency waves, often with the presence of distinct waves with a sawtooth appearance. REM sleep accounts for 20–25% of sleep.

NREM sleep accounts for 75–80% in adult humans and is further divided in three stages, based on EEG criteria:

- Stage N1 sleep ➔ 3–10% of total sleep time
- Stage N2 sleep ➔ 45–55%
- Stage N3 sleep ➔ 15–20%

Sleep normally cycles through the various stages as follows: generally stage N1 ➔ stage N2 ➔ stage N3 ➔ stage N2 ➔ REM ➔ stage N1, N2, or N3. A full sleep cycle consists of a sequence of NREM and REM sleep, typically lasting approximately 90–120 min, and there are generally 4–6 cycles per night. The first two cycles are dominated by SWS (slow-wave sleep), and REM sleep increases as the night progresses, dominating the last 3–5 cycles.

Sleep patterns also change throughout our lifespan, with sleep occupying two thirds of a human newborn's time and REM sleep occupying one half

of total sleep time [9]. The percentage of REM declines rapidly in early childhood, and by the age of 1, the adult percentage of REM sleep is achieved. SWS is minimally present in the newborn but rapidly increases to reach maximum by the age of 10, remaining stable into the 20s and then declining. Arousals during sleep also increase with age.

83.4 Classification of Sleep Disorders

83.4.1 ICSD

The International Classification of Sleep Disorders (ICSD) is a "primary diagnostic, epidemiological and coding resource for clinicians and researchers in the field of sleep medicine" [1], now in its third edition.

The ICSD was published with the goal of standardizing definitions of sleep disorders and creating a systematic approach to diagnosis. It is widely used by clinicians and researchers worldwide, improving research efforts throughout the international community by adhering to a recognized set of standards. The ICSD-3 outlines the following goals:

1. To describe all currently recognized sleep and arousal disorders and to base the description on scientific and clinical evidence
2. To present the sleep and arousal disorders in an overall structure that is rational and scientifically valid
3. To render the sleep and arousal disorders as compatible with ICD-9 and ICD-10 as possible

As a result the ICSD-3 includes 60 specific diagnoses within seven major categories:

1. Insomnia disorder
2. Sleep-related breathing disorders
3. Central disorders of hypersomnolence
4. Circadian rhythm sleep-wake disorders
5. Parasomnia
6. Sleep-related movement disorders
7. Other sleep disorders

83.4.2 Insomnia

Studies of insomnia have been hampered by wide-ranging definitions of the disorder, putting the prevalence rate between 4% and 48% depending on the definition used and sample studied.

The ISCD-3 criteria for insomnia disorder include a report of sleep initiation or maintenance problems, despite adequate opportunity and circumstances to sleep, and daytime consequences. Both the ISCD-3 and the DSM-5 specify a 3-month duration of the sleep problem, as well as a minimum frequency of 3 times a week. However the DSM-5 and ISCD-3 differ in how they classify sleep disturbance in substance use disorders. In DSM-5, insomnia is classified as comorbid with SUD if occurring beyond immediate use of the substance (prior to and after the discontinuation of substance use).

In ICSD-3, a subtype of insomnia is "insomnia due to drugs or substances." The ICSD-3 is making a somewhat stronger causal inference regarding the relation between substance use and sleep disturbance.

Insomnia is an expected aspect of many medical and psychiatric conditions and is the most common sleep diagnosis associated with SUD. Treatment for insomnia occurring with SUD will be discussed later in this chapter.

83.4.3 Other Sleep Disorders

83.4.3.1 Sleep-Related Breathing Disorders

1. Sleep-related breathing disorders are divided into four types: obstructive sleep apnea (OSA), central sleep apnea (CSA) syndromes, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder. OSA is one of the most common sleep disorders and is caused by partial or complete obstruction of the upper airway. A diagnosis of OSA is evaluated using a PSG or home sleep test and requires 15 or more obstructive events (hypopneas, respiratory event-related arousals, or obstructive or mixed apneas) per hour for severe OSA or ≥ 5 to ≤ 14 for patients with

mild OSA. Symptoms of OSA include excessive daytime sleepiness, observed episodes of breathing cessation during sleep, abrupt awakenings, and loud snoring.

Specific consequences of OSA include high blood pressure, cardiac arrhythmias, cerebrovascular accidents (stroke), myocardial infarction, erectile dysfunction, and fatalities from driving while excessively sleepy. Psychological consequences of sleep apnea include depression and anxiety.

OSA treatments may include weight loss, positional therapy, PAP (positive airway pressure), or surgery.

83.4.3.2 Circadian Rhythm Sleep-Wake Disorders (CRSWD)

1. According to the ISCD-3, this category of disorders includes conditions in which sleep timing is out of alignment with the light-dark cycle. Criteria for CRSWDs include:
   (a) Chronic or recurrent pattern of sleep-wake rhythm disruption primarily caused by an alteration in the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or require
   (b) A sleep-wake disturbance (i.e., insomnia or excessive sleepiness
   (c) Associated distress or impairment

   CRSW disorders include delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, non-24-h sleep-wake rhythm disorder, jet lag, and shift work disorder. Drug use may affect homeostatic and circadian processes involved in sleep-wake regulation. Research on circadian factors linked to drug use has been neglected largely due to attributing the disorder to lifestyle factors, such as erratic sleep schedules and all-night drug binges. However, some studies suggest alcohol consumption leads to moderate melatonin suppression [12, 43], which may also be true for other drugs of abuse. Treatment of CRSWD may include chronotherapy, light/dark exposure, prescription medications, or melatonin.

83.4.3.3 Sleep-Related Movement Disorders

These conditions are characterized by simple movements during sleep and may be associated with excessive daytime sleepiness or insomnia. Drugs like antidepressants and alcohol may exacerbate sleep-related movement disorders.

Periodic limb movement disorder (PLM) is defined by the AASM (American Academy of Sleep Medicine) scoring manual as >15 events/h and must be accompanied by sleep disturbance or other functional impairment.

Restless leg syndrome (RLS) is a disorder of the dopamine system that causes an urge to move the legs. RLS occurs primarily with rest/inactivity, is partially or totally relieved by movements for as long as the movement occurs, and occurs primarily in the evening or night.

Treatment for RLS and PLM usually involves medication that either reduces the movements or helps the individual sleep through the movements. Medications include benzodiazepines, dopaminergic agents, anticonvulsant agents, opioids, and GABA agonists.

83.5 Psychiatric Disorders and Sleep

Almost all mental disorders, as well as their treatments, can have associated sleep disturbance. Insomnia often sets the stage and is a major risk factor in the development of some psychiatric disorders. If we can treat insomnia, it may protect against significant mental illness.

The following section will aim to provide a brief description of the common sleep disturbance/architecture irregularities seen in those major mental disorders most commonly comorbid with SUD.

Mood Disorders: It has been estimated that 90% of cases of major depression have associated symptoms of insomnia or hypersomnia are among the diagnostic criteria. Patients with major depression complain about difficulty fall-

ing asleep, increased awakening during the night, early morning awakening (a unique characteristic), and un-refreshing sleep. While a PSG is not generally done unless a primary sleep disorder is suspected, the PSG reveals unique features including reduced slow-wave sleep, shortened latency to REM sleep, increased REM sleep especially in the first part of the night, and increased density of eye movements per REM time. These are all markers of increased REM pressure. Antidepressants are virtually all REM suppressants and treatment is associated with normalization of these PSG abnormalities.

Generalized Anxiety Disorder (GAD): Patients with GAD report difficulty falling asleep, maintaining sleep, and restless sleep; again these are among the diagnostic criteria. But, the worry of GAD is nonspecific and differs from insomnia in that it is not focused on sleep. The PSG of GAD is unremarkable with the exceptions that stage 1 may be increased and onset to REM sleep may be delayed, not reduced as in depression.

Posttraumatic Stress Disorder (PTSD): One of the "hallmark" features of PTSD is frequent nightmares and insomnia complaints are also common. The PSG findings are not particularly unique with one exception. Given the prominence of nightmares to PTSD, studies have focused on REM sleep. The findings suggest fragmentation of REM sleep with frequent transitions from REM sleep to stage 1 or wake.

83.6 Role of Sleep Disturbance in Initiation, Maintenance, and Relapse in Substance Use Disorders

In some cases insomnia may precede the presence of drug use. Alcohol and marijuana are frequently used to initiate sleep. New emerging data also suggest that an age-corrected deficiency in slow-wave sleep, possibly premorbid, is associated with the likelihood of use of alcohol as a sleep aid. Alcohol does initially enhance slow-wave sleep in the presence of a deficiency [38, 40]. Tolerance to these "beneficial" drug effects develops leading to increased use.

In those who abuse stimulants, continued stimulant use is reinforced as the alerting effects of the stimulant decreases the sleepiness and fatigue caused by the drug-associated disturbance of sleep, allowing the individual to function on a "normal" level and hence maintaining the stimulant use [5, 6, 37]. In opiate use disorder, based on animal studies, the timing of sleep and wake and NREM-REM cycling is linked to the timing of the opiate self-administration pattern, irrespective of the light-dark cycle [31].

The relationship between sleep and substance use appears to be bidirectional, in that use of drugs or alcohol may directly cause sleep disturbances, and difficulty sleeping may induce relapse to substance use. In alcoholics, disturbed sleep is a significant predictor of relapse and the severity of alcohol dependence and relapse is greater in individuals with insomnia versus those without insomnia at baseline [21]. Higher levels of REM sleep or shortened REM latency predicted relapse within 3 months after hospital discharge in 80% of patients. In other studies, those who eventually relapsed exhibited a higher proportion of REM and a lower proportion of SWS at baseline [37]. The same has been shown in cocaine use disorder; slow-wave sleep deficiency is predictive of relapse.

If sleep problems lead to relapse, then treatment of those problems should improve relapse rates. As yet, behavioral and pharmacological treatments targeting sleep disturbance have not definitively shown that *sleep improvement (treatments are generally associated with sleep improvement)* is associated with relapse reduction.

83.7 Contributing Medications and Substances Causing Sleep Problems

The majority of people with substance abuse or dependence experience some form of sleep disorder. While the effects of alcohol have been most studied, there is sufficient evidence on the direct

Table 83.1 Common medications and substances contributing to sleep problems

Category	
Antidepressants	SSRI (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine), venlafaxine, duloxetine, MAO inhibitors
Stimulants	Caffeine, methylphenidate, amphetamine derivatives, ephedrine and derivatives, cocaine
Decongestants	Pseudoephedrine, phenylephrine, phenylpropanolamine
Narcotic analgesics	Oxycodone, codeine, morphine, propoxyphene, methadone
Cardiovascular	Beta-blockers, alpha agonists and antagonists, diuretics, lipid-lowering agents
Pulmonary	Theophylline, albuterol

effects on sleep continuity and architecture parameters by a great variety of substances (see Table 83.1 below).

83.7.1 Stimulants

Nicotine, caffeine, amphetamines, and cocaine can all cause increased arousal and disruption of sleep acutely and then subsequently cause hypersomnia and fatigue or sleepiness upon discontinuation.

83.7.2 CNS Depressants

Anxiolytic benzodiazepines, alcohol, and opioids may all cause excessive daytime sleepiness and fatigue acutely, while alcohol and opioids cause insomnia upon discontinuation. The effects of these drugs, as well as their discontinuation, require close monitoring and caution in patients with a history of substance dependence [10].

83.7.3 Opiates

Opiates/heroin causes a decrease in stage 3 and 4 sleep and decrease in REM sleep with frequent awakenings. Discontinuation typically has been shown to cause a REM rebound and more frequent nightmares. Individuals receiving treatment for opiate/heroin dependence using methadone or buprenorphine have shown an increased risk of sleep-related breathing disorders [14, 45].

83.7.4 Alcohol

Acute effects of alcohol intake in the evening include increased sleepiness approximately 30 min after ingestion leading to reduced sleep latency, increased SWS (if a deficiency exits), and decrease in awakenings for the first 4 h but increased awakenings for the last 4 h and an increase in REM sleep [4, 7].

Chronic effects of alcohol use include increased sleep fragmentation and shorter SWS (slow-wave sleep) interrupted by brief arousals. An increase in alcohol intake improves the above symptoms, which typically leads to a worsening problem [23].

Insomnia is a common feature for alcoholism with prevalence rates of 36–72%. Alcohol has also been shown to exacerbate or induce OSA in those at risk (obstructive sleep apnea) [19].

83.7.5 Cannabinoids

Short-term marijuana use results in minimal sleep disruption, characterized by a slight decrease in REM sleep. Chronic use of THC is associated with reduced levels of SWS. During marijuana discontinuation, users show lower total sleep times, less slow-wave sleep, worse sleep efficiency, longer sleep onset, and shorter REM latency when compared to healthy controls [3].

83.8 Diagnosis of Sleep Disorders

The goal of this section is to provide a brief overview of the approach to diagnosis of a variety of sleep disorders, with a specific emphasis to substance use disorder patients. This section will cover initial sleep intake history and physical

examination, sleep diary or log, and sleep questionnaires.

83.8.1 Intake History and Physical Examination

Much like with any other medical conditions, it is of paramount importance to obtain a full medical and psychiatric history. Specific to sleep disorders, it is important to include a bed partner or caregiver interview. Discussion about the patient's sleep habits and daytime functioning should be undertaken. Specific and detailed analysis of substance use or abuse is crucial. This should include both licit (e.g., tobacco, caffeine, alcohol) and illicit substances, as these can all have an effect on sleep.

The physical examination should be targeted at ruling out specific diagnosis but should typically include a mental status examination (e.g., mini-mental status), as well as a cardiovascular, respiratory, and neurologic examination.

Specific details on a "typical" night's sleep should be obtained and should include the following:

- Time to bed
- Pre-sleep activitie
- Delay to onset of sleep
- Specific symptoms or behaviors delaying sleep onset
- Awakenings – number, duration, and cause if known
- Time of final awakening
- Time out of bed
- Total estimated duration of sleep (total sleep time (TST))
- Nocturnal behaviors, e.g., eating, smoking, and nocturia
- Napping behavior during daytime
- Sleeping environment, noise, light, and temperature

The details above can be tabulated in detailed notes or by the use of a sleep "diary" or "log."

A variety of standardized sleep questionnaires exist that can be used to provide an objective characterization of specific sleep parameters, depending on the clinical situation at hand. The table below includes the most commonly used questionnaires, and here we provide a brief description of some (Table 83.2).

Table 83.2 Examples of insomnia questionnaires used in baseline and treatment outcome assessment

Questionnaire	Description
Epworth sleepiness scale	ESS is an 8-item self-report questionnaire used to assess subjective sleepiness (score range: 0–24; normal <10)
Insomnia severity index	ISI is a 7-item rating used to assess the patient's perception of insomnia [0–7, no insomnia, 8–14 subthreshold, 15–21 clinical insomnia (moderate), 22–28 clinical insomnia (severe)]
Pittsburgh sleep quality index	PSQI is a 24-item self-report measure of sleep quality (poor sleep: global score >5)
Beck depression inventory	BDI (or BDI-II) is a 21-item self-report inventory used to measure depression (minimal or no depression: BDI <10; moderate to severe: BDI >18)
State-trait anxiety inventory-form Y trait scale	STAI is a 20-item self-report inventory used to measure anxiety (score range: 20–80; minimum anxiety: T score <50; significant anxiety: T score >70)
Fatigue severity scale	FSS is a 9-item patient rating of daytime fatigue
Short form health survey (SF-36)	SF-36 is a 36-item self-report inventory that generically measures quality of life for any disorder (range from 0 (poorest) to 100 (well-being))
Dysfunctional beliefs and attitudes about sleep questionnaire	DBAS is a self-rating of 28 statements that is used to assess negative cognitions about sleep

83.8.2 Sleep Questionnaires

The Epworth Sleepiness Scale is a widely used and accepted questionnaire that a patient can complete in a few minutes and can help assess the patient's subjective sleepiness (excessive daytime sleepiness). This is of particular importance

to assess daytime effects of sleep disorders. The scale is copyright protected but is available for private clinical use free of charge and can be accessed at the following web address: http://epworthsleepinessscale.com.

The Insomnia Severity Index is an index used to document the severity of insomnia on which the patient rates (not at all to very much) their difficulty falling asleep and maintaining sleep and its impact on their daytime function. It also can be used to assess the effect of treatment.

83.9 Treatment of Insomnia

The aim of this section is to provide a brief overview to an approach to deal with insomnia complaints in the substance use population. This is by no means an exhaustive account of each technique used, but rather a "primer" to introduce each modality.

The overall approach is that of identifying and treating the underlying condition, as well as perpetuating factors. One can then utilize a combination of behavioral, psychological, and pharmacological modalities, depending on the specific clinical presentation and patient needs.

Predisposing factors to insomnia typically include varying tendencies toward psychological, emotional, or cognitive arousal that promotes insomnia but are insufficient to cause insomnia without the presence of other factors.

Precipitating factors are often identifiable events that initiate insomnia and can be major (e.g., bereavement) or minor (e.g., sleeping in unfamiliar bed). These also depend on the predisposing arousal level of the individual.

Perpetuating factors include poor sleep habits that develop during episodes of insomnia such as erratic sleep-wake schedules, nocturnal eating, and excessive worry about sleep.

83.10 Treatment of Chronic Insomnia: An Overview

The overall approach is to identify and treat underlying condition(s) and to identify and treat perpetuating factor(s). This is best achieved with a combined approach which includes behavioral, psychological, and pharmacological strategies.

83.10.1 Behavioral/Psychological

83.10.1.1 Sleep Hygiene Therapy

Sleep hygiene therapy typically makes an attempt to educate the patient about healthy sleep habits, exercise, caffeine consumption, eating behaviors, and sleep environment.

These suggestions may be ineffective alone in yielding results; they are usually a part of most behavioral treatments for insomnia. Below is an example of a list of sleep hygiene "rules" that can be utilized for this approach (Table 83.3).

You may choose to focus on two or three of the above recommendations at a time and reeval-

Table 83.3 Sleep hygiene rules: the dos and don'ts of a good night's sleep

1.	Keep a regular schedule. Go to sleep and wake up roughly at the same time each day, even on weekends
2.	Exercise regularly, in the morning or afternoon. Don't exercise in the late evening
3.	Have a comfortable bed in a quiet, dark room. Don't have your bedroom too hot or too col
4.	If hungry before bed, eat a light snack or have a glass of milk. Don't eat a heavy meal before retiring
5.	Schedule a relaxing period before retiring
6.	Keep the bedroom just for sleeping, sickness, and sex (3-S's), not as an all-purpose activity area
7.	Don't use alcoholic beverages or recreational drugs as sedatives.
8.	Don't try too hard to fall asleep. Get out of bed and return to bed only when you feel sleepy (30 min rule)
9.	Don't nap during the day
10.	Don't smoke or drink caffeinated beverages or eat foods for several hours before bedtime
11.	Use an alarm clock to wake you at your regular time, but position it away from you so you don't "clock watch" which can cause unnecessary tension
12.	If worrying keeps you awake or you are awake in the middle of the night and can't return to sleep because of worries, set aside a 15-min "worry" period to occur at the same time, perhaps after dinner, and in the same place every day. Writing down a "problem" list may help to relieve stress associated with worrying about forgetting certain things

uate your sleep habits every few weeks. And remember, a consistent sleep schedule works best.

83.10.1.2 Behavioral Therapy

Behavioral therapies for insomnia that are empirically supported include stimulus control, progressive muscle relaxation, and paradoxical intention, with sleep restriction, biofeedback, and multifaceted cognitive behavioral therapy for insomnia [2].

83.10.1.3 Stimulus Control Therapy

Based on the theory that cues in the bedroom precipitate and perpetuate arousal. The therapy involves instructions such as the following: "go to bed only when sleepy," "establish standard wake up time," "avoid using the bedroom as an all-purpose activity area, restricting behaviors to the 3 S's (sleep, sickness, sex)," leave the bedroom when lying in bed for greater than 20 min," and "refrain from napping during the day."

83.10.1.4 Sleep Restriction Therapy

The therapy restricts time allotted for sleep each night. First a "sleep log or diary" is maintained for 2 weeks and then an initial TIB (time in bed) prescription is set at a minimum of 5 h total bed time. This is followed by an expansion of a 15–30 min sleep at the beginning of the sleep phase (i.e., desired bedtime time), every few days. This is carried out over a few visits, with fine-tuning as needed.

83.10.1.5 Progressive Muscle Relaxation

Based on the theory that mental relaxation will be a natural outcome of physical relaxation leading to sleep, the patient is instructed to tense or tighten muscles, one at a time in a specific order. A greater degree of muscle tension is attempted, and subsequently when muscle tension is released, the patient learns the sensation of relaxation.

83.10.1.6 Paradoxical Intention

Performance anxiety contributes to preventing proper sleep. The patient is encouraged to stay awake (the feared behavior). As the patient stops trying to fall asleep, the performance anxiety related to attempting to fall asleep is reduced.

83.10.1.7 Biofeedback

Teaches patients to facilitate increased slow wave brain activity (and thus facilitate falling asleep) by using electroencephalographic (EEG) monitoring of brain waves. Eventually this skill can be applied without the EEG.

83.10.1.8 Multifaceted Cognitive Behavioral Therapy

The goal is to identify dysfunctional beliefs and attitudes about sleep and replace them with more adaptive substitutes.

The treatment targets the following: unrealistic sleep expectations ("I must get eight hours of sleep per night"), misconceptions regarding causes of insomnia ("My insomnia is due to a chemical imbalance"), amplification of consequences of insomnia ("I can do nothing after a bad night's sleep"), and performance anxiety due to excessive attempts at controlling the sleep process.

This is also referred to as CBT-I (cognitive behavioral therapy for insomnia) and involves a combination of cognitive and behavioral modalities.

Topics commonly addressed are an array of cognitive, circadian, and sleep-inhibitory factors that affect primary insomnia.

The combination of SCT (stimulus control therapy) and SRT (sleep restriction therapy) has proven most efficacious [44].

Cognitive behavioral therapy enhances sleep-related self-efficacy and reduces depressive and anxiety symptoms. It has also been shown to correct dysfunctional beliefs about sleep and to reduce the use of sleep medications, with an overall improvement in insomnia-related sleep-wake symptoms.

CBT-I should be the standard treatment for many insomnia patients, as comparative data suggest that CBT-I is associated with a more durable benefit in patients with insomnia disorder than pharmacologic therapy and may have an indirect effect of preventing drug dependence and relapse

[22], although that has not been shown (see discussion below).

83.10.2 Pharmacotherapy of Insomnia in the Addiction Population

People who abuse alcohol and other substances are at a high risk for sleep disturbances due to the direct effect of the substance or its discontinuation on their sleep continuity and architecture and their sleep-wake cycle. The drug effect on their behavior and daily functioning, which in turn impacts their daily need for sleep, is also paramount [37].

See Table 83.4 for a listing of those sedative/hypnotics approved for sleep by the US FDA. Benzodiazepine receptor agonists are the most commonly used prescription medication with good evidence of their effectiveness in insomnia, both objectively and subjectively. However, in those with a history of substance abuse, the potential for abuse of these substances is heightened.

In this population, alternative indicated medications such as melatonin receptor agonists (for sleep-onset insomnia), histamine-1 antagonists (for sleep maintenance insomnia), or the newly approved orexin antagonist hypnotic for sleep onset and sleep maintenance may be preferred due to their low risk of abuse. Over-the-counter medications and off-label uses of antidepressant medications (unless there is comorbid depression) should *not* be considered because there is limited evidence on efficacy, dosage, and safety.

Table 83.4 US FDA-approved hypnotics

Generic name	Dose (mg)	T max(h)	T ½ (h)
Benzodiazepine receptor agonist			
Flurazepam	15, 30	0.5–1.0	48–120
Triazolam	0.125, 0.25	2	2-4
Temazepam	7.5, 15, 30	1.2–1.6	8-20
Estazolam	1, 2	0.5–6	8-24
Quazepam	7.5, 30	2	48-120
Nonbenzodiazepine benzodiazepine	*Receptor agonist*		
Zolpidem	5, 10	1.6	1.5-2.4
Zaleplon	5, 10, 20	1	1
Eszopiclone	1, 2, 3	1	5-7
Zolpidem ER	6.25, 12.5	1.5	2.8-2.9
Zolpidem (sublingual)	1.75, 3.5	0.5–0.75	2.1-2.4
Zolpidem (oral spray)	5.10	0.8-2.6	1.5-2.4
MT agonist			
Ramelteon	8	0.75	1.0–2.6
Histamine antagonist			
Doxepin	3, 6	3.5	15
Orexin antagonist			
Suvorexant	5, 10, 20	2	8–14

83.10.2.1 OTC

The most commonly used medications in this class are diphenhydramine and dimenhydrinate. The problem with these OTCs is that there is little or no placebo-controlled evidence that they are effective in insomnia, much less the comorbid insomnia of substance abuse.

1. Diphenhydramine

   Some of the more commonly available brand names are sold as Excedrin PM, Benadryl, Tylenol Allergy Sinus, Tylenol Flue Nighttime Max Strength Power, and Tylenol PM.

   These drugs work as antihistaminic agents, to decrease sleep latency (sleep onset). The anticholinergic effect in the morning leads to drowsiness, especially in higher doses [27]. The potential for diphenhydramine-related toxicity and drug-drug interactions is substantial [24], and tolerance to its sleep-inducing effects occurs within a few days [35], suggesting that diphenhydramine and related compounds such as dimenhydrinate should not represent a viable treatment strategy for long-term sleep maintenance in chronic insomnia.
2. Valerian

   This older compound had been used for many years, in a variety of preparations and

forms depending on country of origin. While there is some subjective improvement in the quality of sleep, there is little scientific evidence documented in clinical trials [17] and doses used vary widely from 75 to 3000 mg.

3. Melatonin

   Melatonin is a hormone naturally produced in the pineal gland which regulates the circadian cycle and is thought to promote sleep through its circadian activity. In the early evening at dusk, melatonin levels rise and remain high throughout the night. Some studies have reported a positive effect of OTC melatonin administration, while others have reported little or no effect on sleep parameters [42]. Inconsistency of results may be due to dose and timing of administration.

83.10.2.2 Prescription Drugs

1. Benzodiazepine and Non-benzodiazepine Receptor Agonists (BzRA)

   The BzRAs are the most commonly prescribed class of medications used for insomnia. Some have a benzodiazepine chemical structure (i.e., estazolam, flurazepam, temazepam, triazolam) and some do not (i.e., "z drugs"). They all are GABA-ergic agonists with effects at the benzodiazepine site on the GABA receptor complex. There are subunits on the site which are associated with specific pharmacological/behavioral effects, and the BzRAs do differ in their subunit specificity. Commonly available and prescribed medications are the "z-drugs" zolpidem (Ambien), zolpidem ER (Ambien CR), zaleplon (Sonata), zoplicone (Imovane), and eszopiclone (Lunesta). Eszopiclone and zolpidem ER are BzRA hypnotics that are FDA approved without a specified time limit on the duration of prescription, and clinical trials indicate they remain effective for 1 year of nightly use (Table 83.4). This probably does not reflect differential activity of these medications, but rather the FDA recognition that insomnia is a chronic disorder and hence the need for chronic therapy.

   The hypnotic efficacy of BzRAs has been well documented using objective measures and patient reports of sleep induction, maintenance, and duration in clinical trials, as well as in meta-analyses [18]. Thus, it can be concluded that they are effective.

   Adverse reactions to BzRA hypnotics include residual effects, which can be related to the half-life and dose of the specific hypnotic, falls in the elderly, amnesia, rebound insomnia, amnesic parasomnia episodes, and potential for abuse. The FDA has recently (April 30, 2019) issued a "black box" warning around the "z-drugs" regarding the possibility of amnesic parasomnia episodes and cautioned regarding the need to select the lowest available dose.

   Dependence has been noted in daily and long-term use of anxiolytic BzRAs, as opposed to short-acting hypnotic use (1 dose/24 h). Short-term studies (<2 weeks) [39] and a long-term study (12 months) [41] of hypnotic use did not indicate dose escalation, rebound insomnia, or withdrawal symptoms on discontinuation.

   The FDA has designated BzRA hypnotics as controlled substances, giving them a schedule IV designation, which indicates these drugs have a known abuse liability in at-risk populations, and thus this must be a particular concern when prescribing these hypnotics to a patient with a history of substance abuse.

2. Melatonin Receptor Agonist: Ramelteon

   Ramelteon has an FDA indication for sleep-onset insomnia, supported by patient reports and objective studies showing that sleep onset is hastened along in a dosage range of 4–32 mg [11, 13].

   Adverse events reported include somnolence, fatigue, dizziness, and nausea, all occurring at rate <5%, and based on behavioral assessments of abuse liability, no liability was seen [16].

3. Histamine-1 Antagonist: Low-Dose Doxepin

   Doxepin is a tricyclic antidepressant that is frequently used off-label as a hypnotic in antidepressant doses (26–150 mg). At the doses approved for insomnia (3–6 mg), doxepin is thought to be a relatively pure H1 histaminic receptor antagonist, which, when antago-

nized, produces sedating effects, without anticholinergic, antiserotonergic, and antiadrenergic activity. Doxepin has been shown in both adults and the elderly to maintain sleep, particularly in the last 2 h of the night, unlike the BzRAs, without producing residual effects. Doxepin is not a scheduled drug and is considered not to have an abuse liability; however, more evidence on this is required due to evidence for behavioral dependence of H1 antihistamines. As the clinical trials have all been short and intermediate term (<=3 months), the issue of dependence must be more fully studied before caution of low-dose doxepin is lifted.

4. Suvorexant

Suvorexant is a dual orexin receptor antagonist which acts to block the binding of wake-promoting neuropeptides and promotes sleep. In the treatment of insomnia, suvorexant has been shown to improve subjective and objective total sleep time, wake after sleep onset, and latency to persistent sleep without altering sleep architecture [33]. At doses of 20 mg or less, suvorexant is relatively safe and effective for the treatment of sleep onset and sleep maintenance in insomnia disorder, although it has not been evaluated in the substance abuse population.

Additionally, orexin neurons have an established role in modulating reward pathways. This suggests an antagonist could be a novel treatment for drug addiction by blocking reward signals. Although not explored in humans, animal studies have shown suvorexant can attenuate motivational and hedonic properties of cocaine and decrease alcohol drinking, self-administration, and reinstatement [15, 30].

5. Other Off-Label Drugs

(a) Antidepressants: Trazodone, Amitriptyline, and Mirtazapine

The most commonly used off-label drugs for insomnia are antidepressants used at "lower doses" for insomnia than their standard antidepressant doses. Trazodone, amitriptyline, and mirtazapine are three of the most widely used antidepressants for insomnia. There is limited information regarding the dose range over which these drugs improve sleep and their safety at those doses. No studies of amitriptyline and mirtazapine on primary insomnia were found in literature, and two studies of trazodone gave mixed results with improvements at lower doses giving reduced sleep latency and increased total sleep time; however, these effects lasted for only 1 week.

The dosage generally recommended for sleep is lower than the antidepressant dosage, and it is not known where potential serious side effects documented at higher doses – suicidality, residual effects, anticholinergic effects (i.e., dry mouth, urinary retention, weight gain, and hallucinations) to orthostatic hypotension, priapism, cardiac arrhythmias, and conduction abnormalities – would occur at these low doses. Given that there is no clear understanding in regard to the dose range for the hypnotic efficacy and safety of these drugs, it is recommended they not be used as hypnotics.

There is currently no data available on antidepressants for use in sleep disorders among patients with substance use disorders.

Proper diagnosis of comorbid mood disorder may indicate that a single medication can be helpful to treat both conditions.

(b) Atypical Antipsychotics: Olanzapine and Quetiapine

These medications include "off-label use" of such drugs as olanzapine (Zyprexa) and quetiapine (Seroquel) for their effect on sleep problems.

These agents have shown improvement in self-reported sleep measures [36]; however, the concern for the use of these drugs, as with other off-label drugs, is that there is limited information regarding efficacious and safe doses, and their use as hypnotics is not recommended [32]. There is currently no data available on

olanzapine or quetiapine among patients with substance use disorders.

(c) Off-Label BzRAs: Clonazepam, Alprazolam, and Lorazepam

Anxiolytic BzRAs are also often used as hypnotics, with clonazepam, alprazolam, and lorazepam as the most commonly used off-label BzRAs. These share the same hypnotic mechanism of action of the indicated BzRAs and were used previously due to no limitations on long-term use; however, their hypnotic dose is unknown, and due to the availability of BzRAs approved hypnotics as discussed above, there is no advantage to their use. In fact, there may be increased risk as discussed below.

(d) Gabapentin

Gabapentin is an anticonvulsant used to treat seizures, neuropathic pain, and restless legs syndrome. It has been used off label to treat insomnia with polysomnographic studies showing increased sleep efficiency and slow-wave sleep and decreased wake after sleep onset and spontaneous arousal index [25]. The dose for most patients is 600 mg. In those with alcohol dependence, gabapentin significantly improved rates of abstinence as well as relapse-related symptoms of insomnia [8, 28]. When used alone, there is little abuse potential, but if used in conjunction with muscle relaxants, opioids, or anxiety medications, a euphoric effect (i.e., "high") may be produced and thereby abuse potential is increased.

83.11 Medications and Potential for Abuse

83.11.1 Abuse Liability Signs

There is abuse liability associated with the BzRA hypnotics. The non-BzRAs that are not scheduled have limitations in regard to their indications, ramelteon being only for sleep-onset and doxepin only for sleep maintenance insomnia. The orexin antagonist, suvorexant, carries a schedule IV designation. Therefore, if a scheduled drug is prescribed, the following important signs have been identified regarding potential abuse liability of BzRAs [20]:

1. Dose escalation beyond the indicated clinical hypnotic dose within the first week of treatment
2. Use during daytime outside of the sleep period

These patterns suggest nonhypnotic drug effects that were being sought and guidance to closely monitor the patient during the first week of use, and not allowing patient-initiated dose adjustments is recommended.

83.11.2 Precautions and Contraindications

Patients who have histories of drug or alcohol abuse with difficulty sleeping, particularly sleep maintenance, which is the chief complaint among abstinent alcohol and drug abuse patients, require precautions. These sleep disturbances can continue for a year or more. The non-BzRA, low-dose doxepin or the orexin antagonist, suvorexant, may be options, although further studies are required to fully understand their benefit-risk profile in SUD patients.

If the physician considers the use of a BzRA hypnotic in an outpatient setting, the patient must be monitored closely beyond the initial week of use. Within the alcohol and drug abuse treatment community, stress-induced relapse is a well-recognized phenomenon that can occur after months of successful abstinence. In such cases, the experience of new life stresses can induce a relapse to drug and alcohol abuse. When alcohol is used concurrent with *any* hypnotic, there is potential for additive sedative effects and the occurrence of any of the aforementioned adverse effects.

In prescribing sedative hypnotics in substance use disorder patients, there are specific cautions and guidance that should be followed. We provide these principles in Table 83.5. Several points should be noted. Sedative/hypnotics can potentially have additive effects with other sedative drugs, exacerbate respiratory disturbance, require

Table 83.5 Guidelines for prescribing sedative/hypnotics

Initiate hypnotic use after identifying and addressing specific behaviors, circumstances, and underlying Guidelines disorders contributing to insomnia
Prescribe the lowest effective dose of the hypnoti
Avoid hypnotic use or exercise caution if the patient has a history of substance abuse, myasthenia gravis, respiratory impairment, sleep apnea, or acute cerebrovascular accident
Normally one prescribes for short-term use, but in SUD patients where sleep disturbance is 3 months and longer, long-term use may be required
Watch for requests for escalating doses or use during the daytime
Hypnotics should be discontinued gradually (i.e., tapered); the physician should be alert for adverse effects (especially rebound insomnia) and withdrawal phenomena if higher, super-therapeutic doses are in use
General Comments About Sedatives/Hypnotics
Administration on an empty stomach is advised to maximize effectiveness
Not recommended during pregnancy or when nursing
Caution is advised if signs/symptoms of depression, compromised respiratory function (e.g., asthma, COPD, sleep apnea), or hepatic heart failure are present
Caution and downward dosage adjustment is advised in the elderl
Safety/effectiveness in patients <18 years not established
Additive effect on psychomotor performance with concomitant CNS depressants and/or alcohol use
Certain antidepressants (amitriptyline, doxepin, mirtazapine, paroxetine, trazodone) are employed in lower than antidepressant therapeutic dosages for the treatment of insomnia. These medications are not FDA approved for insomnia and their efficacy for this indication is not well established

lower doses in elderly and women, should be used with caution in patients with liver disease, and should be avoided in pregnant and nursing woman.

83.12 Conclusion

Insomnia is a prevalent symptom in those with chemical dependency, and it may be a predictor of relapse. The key is proper assessment and diagnosis of the underlying cause. Treatment with pharmacotherapy and behavioral therapy is likely the best option. As of this writing, there is still significant need for further research.

It is crucial to remember that not all "insomnias" are the same. The complaint of insomnia is extremely common, with significant implications and with a high rate for concurrent disorders: medical, psychiatric, and substance use disorder. There is a need for a simple yet comprehensive approach for the diagnosis and treatment of sleep disorders in the substance-abusing population, which should involve a multidisciplinary team approach to care.

Sleep disorders medicine is a fascinating and rapidly growing field. Think about sleep disorders when patients complain of fatigue or EDS (excessive daytime sedation). Think about the possibility of OSA (obstructive sleep apnea) if the patient presents with snoring with fatigue, and they are also overweight or have hypertension or diabetes. It is prudent to stay away from benzodiazepines for insomnia as the first "treatment."

Key Points

1. People who abuse alcohol and other substances are at high risk for sleep disturbances due to the direct sleep effects of the substance or its discontinuation.
2. Disturbed and insufficient sleep can have significant behavioral and health consequences including car and industrial accidents, impairment of memory and decision-making, exacerbation of illnesses, and notably for the addiction medicine practitioner is predictive of relapse.
3. The physiology of normal human sleep is firmly established and classification of sleep disorders has been developed, now in its third revision.
4. The most frequently occurring sleep disorders comorbid with addictions are insomnia, sleep apnea, and restless legs/periodic leg movement disorders.
5. Treatment of sleep disorders in addiction includes behavioral/psychological treatments, pharmacotherapy, and mechanical ventilator devices.

Clinical Relevance

Clinicians can potentially improve outcomes and avoid potential risk by appropriately identifying sleep disorders in their patients with substance use disorder. Sleep problems can contribute to the initiation, maintenance, and relapse of substance use disorders. Consultation with a sleep disorders specialist should be sought when help in identifying and treating the sleep disorder is needed. Newer pharmacological treatment options, without the abuse liability of benzodiazepine-acting hypnotics, are now becoming available and availability of specialists in behavioral insomnia treatment is expanding.

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84 Endocrine Manifestations of Alcohol and Other Drug Use Disorders

Anna Quirk and Stephen Twigg

Contents

A. Quirk (✉)
Department of Endocrinology, St Vincent's Hospital, Darlinghurst, NSW, Australia

Department of Endocrinology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

S. Twigg
Department of Endocrinology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Sydney Medical School (Central), Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

Abstract

Endocrine manifestations of substance use disorders can result from the direct effect of the addictive substance, chronic and acute toxicological phenomena, or more indirectly due to long-term disturbances of delicate hormonal feedback loops. Although the existing data is largely based on case reports and ani-

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mal studies, emerging evidence suggests that addiction can result in physiological disturbances to multiple hormonal pathways. This can result in overt or subtle clinical syndromes and may often be overlooked in addiction patients who frequently have other biopsychosocial factors at play. Chronic opioid use may lead to hypothalamic-pituitary suppression with resultant hypoadrenalism and hypogonadism. Alcohol-induced hypercortisolaemia (previously termed pseudo-Cushing's syndrome) remains under-recognised, with alcohol-related hepatic dysfunction further compounding metabolic risk factors in dependent patients. Human studies of tobacco and cannabis smoking on hormone homeostasis have yielded incongruous results in human studies but remain important modifiable risk factors for osteoporosis and metabolic syndrome. This chapter aims to highlight the clinically important endocrine disturbances associated with drugs of addiction, as well as touching on related metabolic considerations that are vital in holistic patient management.

Keywords

Endocrinopathy · Opioid dependence
Alcohol dependence · Hormonal disturbance
Hypothalamic-pituitary-adrenal axis
Glucocorticoids · Stress · Adrenal insufficiency · Hypogonadism · Fertility
Thyroid dysfunction · Glucose homeostasis
Metabolism · Weight · Reward pathways
Skeletal metabolism · Bone health

84.1 Introduction

Endocrinopathies and hormonal disturbances associated with addiction are widespread and can manifest in a diverse spectrum of clinical syndromes. They can mimic intoxication or withdrawal and if left undetected can result in significant morbidity or mortality from disruption of hormonal axes. Drugs of addiction may be overlooked as potential causes of endocrinopathies, just as hormonal disturbances can be omitted from the differential diagnoses of patients who appear to present with a toxidrome. Comorbid endocrinopathy may also have the potential to lead to exacerbation of a substance use disorder typically via disturbance of mood or quality of life. Clinical questions emerge regarding the treatment of these disturbances and whether hormone replacement may be required above and beyond treatment of the addiction. This chapter primarily addresses hormonal disturbance associated with alcohol and opioid dependence and also touches on the effects of other substances of abuse.

84.2 Hormones and Addiction

Often termed the 'master' gland, the pituitary gland sits in the bony sella turcica and is connected to the hypothalamus by a stalk called the infundibulum. The hypothalamus receives messages from the cortex and signals the pituitary to secrete or inhibit hormones in response to several biochemical, psychological and environmental stimuli. Via this tightly regulated system, the hypothalamic-pituitary axis signals the thyroid, gonads and adrenal glands, with other pituitary hormones and neuropeptides acting on a variety of target tissues. Drugs of addiction, as well as the cycles of intoxication and withdrawal, can alter the biochemical and psychological homeostasis of hormones, both directly and indirectly. Hypothalamic-pituitary dysfunction may result in times of critical illness, with acute and chronic effects of addictive substances becoming increasingly recognised.

84.2.1 Hypothalamic-Pituitary-Adrenal Axis

The effect of addictive substances on the physiological stress response system can be seen at the level of the hypothalamus (corticotrophin-releasing factor), the anterior pituitary (adrenocorticotropic hormone or ACTH) and the adrenal gland. Psychological or physiological stress from

intoxication may contribute to addictive behaviours and ultimately lead to disrupted stress response in chronic use. The effects of exogenous opioids, alcohol and other addictive substances on the hypothalamic-pituitary-adrenal (HPA) axis are discussed here.

84.2.1.1 Action of Opioids

Beta-endorphin is an endogenous opioid which is produced upon the cleavage of proopiomelanocortin (POMC) to ACTH and beta-lipotropin, working on μ-opioid receptors to modulate pain and stress response in normal subjects [67]. Exogenous opioids, both prescription and illicit, are increasingly recognised as contributing to the dysfunction of the hypothalamic-pituitary-adrenal axis with potentially life-threatening adverse effects. G-coupled opioid receptors exist in the hypothalamus and pituitary gland [35] and may be subject to suppression with administration of exogenous opioids.

It is thought that endogenous opioids have a physiological *inhibitory* effect on the HPA axis, with studies of healthy volunteers demonstrating augmented corticotrophin release and increased cortisol levels in response to opioid receptor antagonism with intravenous naloxone [22]. These data suggested opioid receptor agonists should have the opposite effect, but human results of studies have been conflicting. Chronic opioid use in human studies has demonstrated varying degrees of hypothalamic/pituitary suppression [1, 25]. One recent cross-sectional study comparing pituitary function, quality of life and sexual function in chronic opioid users suggested a dose-dependent effect with secondary adrenal insufficiency identified in 22.5% of chronic opioid users versus normal controls [87]. In addition opioids may exert direct toxic effects on the adrenal glands mediated via μ- and κ-opioid receptors leading to a diminished adrenal response to ACTH [87]. The clinical significance of the latter remains unclear.

84.2.1.2 Adrenal Insufficiency

The prevalence of opioid-induced adrenal insufficiency is estimated to range from 9% to 29% of chronic users [25], although epidemiological studies to date have been small in numbers. Postulated risk factors include a higher dose of opioid and long-acting formulations [12] although this has yet to be studied prospectively. Clinical implications including possible adrenal crisis are becoming increasingly recognised in long-term opioid-dependent patients and rarely may result in a frank hypoadrenalism in times of increased physiological stress [23]. Signs of adrenal insufficiency may be non-specific and include fatigue, weight loss, vomiting, dizziness and myalgia, as well as hypoglycaemia. Hyperpigmentation as seen in primary adrenal pathology is absent. In the acutely unwell opioid-using patient, high suspicion for adrenal insufficiency and appropriate steroid replacement are crucial to avoid an adrenal crisis.

A diagnosis of adrenal insufficiency should be made by measuring baseline ACTH and serum cortisol levels, with an early morning serum cortisol of <300 nmol/L raising suspicion for the diagnosis [13]. A corresponding low serum ACTH is suggestive of secondary (pituitary) or tertiary (hypothalamic) adrenal insufficiency. Confirmation via dynamic testing is then necessary. The insulin tolerance test remains the gold standard for the diagnosis of adrenal insufficiency, although it is contraindicated in patients with a history of seizures, ischaemic heart disease or severe panhypopituitarism [31]. Short synthetic ACTH stimulation test may be performed with subsequent assessment of adrenal response via serum cortisol. Limitations to these tests in this population should be expected particularly in patients with abnormalities of albumin or cortisol-binding globulin (CBG), such as cirrhosis or nephrotic syndrome. In addition, short synthetic ACTH stimulation test will not detect acute hypoadrenalism developing across 1–2 weeks, including that due to opioids.

Once the diagnosis of hypoadrenalism is established, glucocorticoid replacement therapy should be commenced in affected patients; mineralocorticoid replacement is not required in secondary adrenal insufficiency. Replacement dosage of 15–25 mg per day of oral hydrocortisone in adults is recommended in divided doses, titrating to patient symptoms. A recent double-blinded randomised control

trial assessing low-dose glucocorticoid therapy in chronic pain patients with hypoadrenalism taking opioids suggested an improvement in pain scores and vitality compared with placebo [74]. The role of replacement and role in prevention of relapse warrant further studies. Education regarding sick day management and stress dosing of hydrocortisone in times of increased physiological stress is necessary. Cessation of opioids should also be considered, as case reports indicate the pathology may be reversible [61, 78].

84.2.2 Alcohol-Related Hypercortisolaemia

Hypercortisolaemia associated with both acute and chronic alcohol use has been well documented. The proposed mechanisms include increased ACTH release [93], decreased cortisol binding to albumin and cortisol binding globulin and impaired hepatic metabolism of cortisol due to liver dysfunction. Patients with hypercortisolaemia secondary to alcohol use may be less likely to exhibit the classic cutaneous and muscular signs of Cushing's syndrome [6], and clinicians should be vigilant and refer for screening tests (midnight salivary cortisol and 24-hour urinary free cortisol) in all suspected cases. Signs of hypercortisolaemia can be non-specific and include central adiposity, glucose intolerance, moon-like facies, proximal myopathy, skin thickening, hypertension and hirsutism in women. Initial screening tests may result in false positives and differentiating between causes of hypercortisolaemia can be difficult. Furthermore, a low-dose overnight dexamethasone suppression test may yield inconsistent results in the alcohol-dependent population, with alterations in cortisol binding globulins leading to false negatives, and thus the dexamethasone/CRH suppression test may be more specific. Abstinence from alcohol will result in normalisation of serum cortisol levels [75].

84.2.3 Other Drugs and the HPA Axis

Repetitive exposure to methamphetamine may also lead to chronic activation of the HPA axis resulting in increased release of cortisol. Persistent activation of the HPA axis in this manner may be partially responsible for changes in the reward pathway, making abstinence more difficult to achieve [99]. Similarly, over-activation of the HPA axis is seen in both animals and humans who chronically use cocaine, although the clinical relevance of this remains unclear [68].

Cannabis has been postulated to affect HPA axis function as the endocannabinoid signalling pathway is involved in regulation via hypothalamic CB1 receptors. Again, the real-life effect of THC use on this pathway is unknown and remains an area for further study [72].

84.2.4 Gonadal, Sexual and Reproductive Function

Male hypogonadism secondary to both chronic alcohol and opioid use is well documented, with studies among female subjects yielding heterogeneous results. Hypogonadism can present as low energy, depression, poor libido and erectile dysfunction (or menstrual disturbance in women) with long-term complications, such as osteoporosis discussed later in this chapter. Gonadotropic-releasing hormone (GnRH) from the hypothalamus acts on the anterior pituitary to produce luteinising hormone (LH) and follicle-stimulating hormone (FSH). FSH and LH in turn act on the gonads to produce oestrogen and testosterone. A recent meta-analysis demonstrated low serum testosterone is associated with an increase in all-cause mortality although this association is unlikely causal and is more a reflection of overall health status [46]. Acquired hypogonadotropic hypogonadism has been documented in both alcohol- and opioid-dependent patients [37]. Elevated prolactin may further contribute, as hyperprolactinemia suppresses GnRH and FSH/LH release. Sex hormone replacement therapy may be prescribed following careful consideration of symptoms, quality of life, complications of prolonged hypogonadism and contraindications.

84.2.5 Alcohol and Hypogonadism

Alcohol can impact circulating gonadotropins both directly and indirectly. Numerous animal and human studies describe direct toxic effects on the testes with histological, anatomical and biochemical disturbances. A recent rodent study showed that abstinence did not reverse alcohol-induced testicular damage as measured by sperm count and testicular weight [27], yet there was some biochemical recovery in testosterone level with alcohol abstinence. Secondary hypogonadism indicated by low serum testosterone without corresponding elevation of LH or FSH is seen following acute ethanol ingestion.

Chronic alcohol use, with or without cirrhosis, can lead to feminisation including gynaecomastia and may be a cosmetic concern to male patients. This appears to be multifactorial, with elevated oestradiol, androstenedione and serum hormone-binding globulin (SHBG), but reduced DHEAS, free and total testosterone concentrations. These changes appear to be related to the stage of cirrhosis and hypogonadism and appear to be of hypothalamic origin [76]. Alcohol-induced hypogonadism has been reported to resolve after withdrawal of alcohol use.

The relationship between hypothalamic-pituitary-gonadal function and alcohol use in females is less clear. Following acute ingestion of alcohol, oestradiol levels have shown a positive relationship compared to placebo [69]. Moreover chronic heavy alcohol consumers, compared to occasional or social drinkers, appear to have a higher incidence of menstrual disturbances [70]. In long-term use, elevated FSH and decreased ovarian reserve have been shown [66]. No conclusive evidence regarding progesterone levels and alcohol use has been observed to date, although decreased catabolism of circulating sex hormones has been hypothesised [85].

Higher levels of alcohol consumption appear to adversely impact fertility in both men and women. However, a safe level of consumption has yet to be established with studies thus far yielding heterogeneous results. In men, abnormalities in gonadal function, testosterone levels and spermatogenesis in heavy alcohol use may further hinder any desired conception. Semen quality and decreased spermatogenesis appear to be associated with alcohol use; one large systematic review showed decreased semen volume and impaired morphology in daily drinkers compared to non-drinkers, but no conclusive results regarding overall sperm quality [82]. Furthermore, daily drinkers appeared to have more marked alterations than occasional consumers. This finding was echoed in the cannabis-using population, with a study of 1215 Danish men demonstrating 28% reduction in sperm concentration and 29% reduction in sperm count. A recent meta-analysis and systematic review evaluating daily alcohol dose and chance of conception in women suggested a linear association between decreased fecundity and each additional 12.5 gram of alcohol per day compared to non-drinkers [32]. Alcohol use may also lead to hyperprolactinemia [21] that may further suppress gonadotropin secretion and impaired testicular or ovarian function.

84.2.6 Opioids and Hypogonadism

First recognised among heroin-addicted patients and later among methadone maintenance patients, opioid-induced hypogonadism remains an under-recognised phenomenon [71]. In chronic pain patients receiving intrathecal morphine, hypogonadism was found in both men and women [34]. Chronic administration of opioids may cause hypogonadotropic hypogonadism with reduced pulsatile secretion of GnRH [1] resulting in lower circulating levels of oestrogen and androgens. The increased sex hormone-binding globulin (SHBG) production seen in chronic opiate users leads to a further reduction in testosterone levels. In one large retrospective cohort study, men on long-acting opioids were over three times more likely to develop hypogonadism than men taking short-acting opioids [84]. Interestingly not all opioids appear to have the same effect; with buprenorphine [11] and more recently tapentadol [29] appearing to have less significant effects than pure opioid analgesics on testosterone levels in men. The same effects have not been consis-

tently replicated in female chronic opioid users with one cross-sectional study demonstrating much lower rates of opioid-related hypogonadism in female subjects [38].

84.2.6.1 Clinical Considerations

The role of sex hormone replacement in opioid- or alcohol-related hypogonadism is not clearly established in guidelines. Hormone replacement may be indicated where opioid therapy is required in long term, symptoms of hypogonadism are onerous and complications of hypogonadism have developed or are affecting treatment adherence.

In men, a diagnosis of hypogonadism may be made with consistently low serum total testosterone concentrations, on two separate occasions measured on early morning fasting biochemistry. Clinicians should also be aware that recent opioid use may result in low testosterone levels [10]. Important differentials for hypogonadism (particularly primary pituitary pathology) must be excluded prior to commencing replacement therapy. Although a recognised complication of long-term opioid therapy, prescribing guidelines for testosterone replacement vary internationally. In Australia, androgen deficiency caused by drugs is an exclusion criterion for federal subsidy, which limits access to testosterone replacement in many cases.

Testosterone therapy in a hypogonadal man has been shown to improve mood, sexual function, areal bone mineral density, fat-free mass and muscle strength [36]. Contraindications to therapy include prostate or breast cancer, elevated haematocrit, poorly controlled congestive cardiac failure or desire for fertility. Common adverse effects include mood or behaviour disturbance, erythrocytosis, acne, reduced spermatogenesis and prostatism. One recent retrospective analysis of 27 men demonstrated that with opioid-induced hypogonadism, testosterone replacement therapy reduced opioid requirement in patients with chronic pain [81]. Studies to date have been underpowered to establish definitive data regarding cardiovascular risk or prostate events in the testosterone replacement population [7]. A frank discussion with patients outlining possible risks and benefits, as well as routine monitoring while on therapy, is necessary. Diagnosis of hypogonadism in premenopausal women may be suspected with a clinical history of menstrual disturbance but may go undetected for some time. Biochemical evaluation of FSH, LH, oestradiol and prolactin may be useful; however, there is no current consensus for diagnosis. Treatment with oestrogen and progesterone replacement may be warranted. Oral and transdermal preparations are widely available, including the oral contraceptive pill.

84.2.7 Thyroid Function and Addiction

The hypothalamic-pituitary-thyroid (HPT) axis is responsible for maintaining normal levels of circulating thyroid hormones: thyroxine (T4) and its active form, triiodothyronine (T3). T4 and T3 circulate in both a protein-bound inactive form and a free, readily available active form. When the hypothalamus detects reduced circulating levels of thyroid hormones, it responds by releasing thyrotropin-releasing hormone (TRH), which in turn stimulates the anterior pituitary to secrete thyroid-stimulating hormone (TSH). Thyroid hormones are responsible for setting the basal metabolic rate, growth and protein synthesis, among other functions [24].

Thyroid dysfunction is an important differential in the addiction population. Disturbance to thyroid hormone levels can be seen in any cause of acute illness, the so-called sick euthyroid state. True hyper- or hypothyroid states can mimic conditions of both intoxication and withdrawal with symptoms ranging from non-specific fatigue or mood changes to rare life-threatening thyroid emergencies. Overt clinical thyroid syndromes associated with addictive substances are rare; however, both animal and human studies have shown that acute intoxication, withdrawal and abstinence periods may affect the thyroid hormone axis. This may occur at the level of the pituitary and thyroid gland or affect the peripheral conversion of T4.

84.2.8 Thyroid and Alcohol

The relationship between alcohol use and thyroid disturbance remains unclear. Acute alcohol exposure appears to have little effect on the HPT axis. In contrast, chronic alcohol use appears to have several effects. Chronic exposure of adult male rats to ethanol for 40 days induced a significant decrease in total T4 and T3, free T4 and T3 as well as basal TSH levels [80]. In human studies a blunted TSH response to TRH can be seen that may persist into abstinence [88]. Inconsistent data exists regarding levels of circulating thyroid hormone in the alcohol-dependent patient; however, levels of both T4 and T3 are observed to be lower in people with alcohol use disorder during withdrawal and early abstinence than in healthy control subjects [47]. Following long-term abstinence, thyroid dysfunction has been reported to recover [79] although dysfunction may recur if alcohol use is recommenced [48]. A positive correlation between higher free T3 levels and increased alcohol cravings has been demonstrated in a small study, generating some interest that this may demonstrate a link between thyroid dysfunction and alcohol dependence [3].

84.2.9 Thyroid and Tobacco

Tobacco smoking is unambiguously associated with an increased risk of Graves' disease [19]. The association between Graves' ophthalmopathy and smoking is even stronger. In a meta-analysis investigating the association between thyroid disorders and smoking, the odds ratio for developing Graves' ophthalmopathy was 4.40 (95% CI: 2.88–6.73) in patients who had ever smoked compared to never smokers [92]. Furthermore, Graves' ophthalmopathy severity is positively related to smoking amount in tobacco smokers [16]. Interestingly, there appears to be a lower prevalence of thyroid autoantibodies and subclinical hypothyroidism among smokers, although the clinical significance of this is unclear [58].

84.2.9.1 Thyroid Function and Other Drugs

Opioid use and thyroid dysfunction have yet to be conclusively studied. In general opioids do not appear to alter primary thyroid function [56] but may interfere with levels due to changes in thyroid-binding globulin and hypothalamic action via K-receptors [44]. Early studies examining clinically euthyroid methadone-maintained patients revealed elevations of *total* T3 and T4 and thyroxine-binding globulin compared with normal controls; however, *free* T3 and T4 and thyroid-stimulating hormone (TSH) were normal [30]. Neither cannabis nor psychostimulants have been associated with increased prevalence of thyroid disorders. Acute methamphetamine intoxication is an important differential diagnosis in cases of thyroid storm, as both present with agitation, tachycardia, fever and symptoms of catecholamine excess.

It may be reasonable to assess for other causes of thyroid dysfunction, prior to attributing causality to substance use exclusively. Screening for dysfunction via thyroid function tests (TSH, free T4 and free T3 levels) may be prudent where there is any clinical suspicion, proceeding to antithyroid autoantibody testing and imaging where appropriate.

84.3 Weight, Glucose Metabolism and Appetite in Addiction

Although addictive disorders are most frequently associated with malnutrition [83], metabolic complications and labile blood glucose levels are not uncommon. Substance-related sympathomimetic effects may result in elevated serum cortisol and catecholamines, with a subsequent increase in hepatic gluconeogenesis and glycogenolysis [62]. Prolonged malnutrition may deplete hepatic glycogen stores further altering energy homeostasis. Maladaptive eating patterns and neurobiochemical similarities to addiction have become areas of increasing interest for developing therapies in addiction, eating disorders and obesity.

84.3.1 Opioids

Chronic opioid use is associated with weight gain, hyperglycaemia and worsening glycaemic control in people with diabetes, postulated to be due to a central action via the sympathetic nervous system and impaired insulin secretion [14]. Data also suggests that opioids play a role in regulating food intake and food choice as well as the reward system associated with good-tasting foods. Interestingly, there appears to be an association between opioid use and taste preference for sweet foods over and above increased caloric intake [42]. It is likely that there is significant overlap between reward pathways associated with food consumption and addiction. The observed weight gain in opioid users may also be related to decreased gastric motility and slowed absorption of glucose, resulting in a delayed release of insulin. Furthermore, the suppression of growth hormone during hyperglycaemia appears to be impaired in the opioid-using population compared to controls [40] with other studies postulating opioids may stimulate hypothalamic GH secretion via the mu-opioid receptor [97]. Abnormalities in growth hormone secretion may further contribute to body composition changes.

84.3.2 Alcohol

The relationship among alcohol use, weight gain and cardiometabolic complications including diabetes mellitus is complex and appears to be dose dependent [59]. Frequent but low-level daily use of alcohol may have a protective metabolic effect [73]. A study in nondiabetic postmenopausal women demonstrated lower serum insulin and triglyceride levels in those who drank 30 g of alcohol daily than in those who were abstinent [20]. This effect has been hypothesised to explain the lower frequency of type 2 diabetes mellitus in moderate users of alcohol. The protective effect of moderate alcohol use (<30 g daily) against type 2 diabetes is obviated in those who drink above 48 g daily [50]. Moderate alcohol use in known patients with diabetes is associated with a reduction in cardiac disease although further studies are needed to clarify this effect.

Data detailing the relationship between weight gain and alcohol use is conflicting. While alcohol may account for a large proportion of caloric intake, this has not been consistently observed to correlate with weight gain ([86], p.). Men and those drinking primarily beer as opposed to other forms of alcohol may be more susceptible to gaining central adiposity [98]. Alcohol use disorder, particularly with variable levels of consumption, complicates the management of established diabetes due to the impact on carbohydrate metabolism and treatment adherence. Alcohol-related pancreatitis leading to insulin deficiency, non-adherence to prescribed diabetic therapies and high risk of hypoglycaemia should all factor into the holistic management of patients with comorbid diabetes and substance disorder. Acute alcohol-induced ketosis and lactic acidosis are common acute entities and may lead to acid-base disturbances in the critically unwell patient. In addition, alcohol excess may contribute to euglycaemic diabetic ketoacidosis in patients prescribed the newer SGLT2 inhibitor agents.

There is anecdotal evidence that alcohol may cause increased post-prandial hypoglycaemia, which has been inconsistently replicated in small studies [77]. Hepatic impairment due to alcohol use will also impair gluconeogenesis and therefore patients with liver disease are at risk of hypoglycaemia if inadequate caloric intake occurs. This is especially important clinically in people with type 1 diabetes, where alcohol binges can contribute to the precipitation of severe nocturnal hypoglycaemia. In a different setting, malnutrition is frequently observed in heavy alcohol users and may contribute to this effect.

84.3.3 Tobacco

Tobacco smoking is associated with an increased risk of developing type 2 diabetes, thought to be due to nicotine impairing glucose sensitivity [95]. Both tobacco smoking and nicotine replacement therapy are associated with increased insulin resistance [17]. Smoking reduces body weight

by multiple potential mechanisms including via uncoupling protein-1 induction in subcutaneous fat. The association between smoking cessation and weight gain is well known and remains a barrier to quitting for many patients (Filozof 2004 Obes rev). The average weight gain following cessation of smoking is 3–5 kg, although some patients may gain considerably more [96]. This effect may be attenuated by the use of bupropion, nicotine replacement therapy, fluoxetine or varenicline; however, only exercise interventions have shown convincing benefit [33].

84.3.4 Cannabis

The metabolic role of the endocannabinoid system remains an ongoing area of interest, with both peripheral and central cannabinoid receptors likely playing some role in appetite, weight and energy homeostasis. CB1 receptors in the hypothalamus may mediate food intake, with peripheral CB1 expression on adipocytes and skeletal muscle demonstrated [8]. In trials of cannabinoid receptor-1 antagonist, promising metabolic benefits such as decreased waist circumference, insulin resistance and triglyceride levels raised particular interest as a target for weight loss. However increased suicidality and mood disturbances halted further development and use [39].

84.3.5 Appetite Factors

Regulation of hunger involves multiple neurobiochemical signals stimulated by the gastrointestinal tract, incretins and serum glucose levels. Current evidence suggests that gut hormones responsible for the regulation of food intake also affect dopaminergic neurotransmission in the mesolimbic reward pathways in the brain. Hunger is regulated by several gastric peptide hormones, including ghrelin, amylin, leptin and GLP-1.

During fasting the appetite-stimulating peptide ghrelin is secreted producing hunger signals as well as reward centre activation following food and alcohol intake. It is therefore relevant in alcohol abstinence, as increased ghrelin has been shown to correlate with cravings in early abstinence in alcoholic men [63], making this hormone a potential target for intervention.

Leptin regulates satiety, with leptin resistance developing in obesity. Despite high levels of circulating leptin and high-energy stores, patients with leptin resistance are unable to feel satiated (Pan H 2004 Physiology and behaviour). In animal models, leptin appears important in mediating dopaminergic reward pathways in alcohol, cocaine and amphetamine use [53]. Female, but not male, tobacco smokers with pathological eating behaviours also had evidence of raised leptin levels [64].

Glucagon-like peptide-1 is an incretin and is released in response to food intake, acting to enhance glucose-dependent secretion of insulin shortly after meals. GLP-1 agonist therapies have proven successful in the treatment of obesity. Emerging animal studies suggest central GLP-1 activation may attenuate addictive behaviours via inhibition of the mesolimbic dopamine reward system [91]. Commandeering the mesolimbic dopaminergic reward pathways may potentially lead to targeted treatment for substance addiction in the future, but warrants further prospective studies. The opioid receptor antagonist naltrexone combined with the dopamine and norepinephrine reuptake inhibitor bupropion has demonstrated positive weight loss effects in post-marketing data. In combination, the agents are thought to act on hypothalamic hunger centres and modulate food cravings through an effect on reward pathways [5].

Interestingly, there appears to be a significant overlap between the eating disorder population and substance use population, with 27% of anorexia nervosa patients having comorbid substance use [51]. Chronic starvation, leading to hypothalamic-pituitary suppression, profound electrolyte disturbances, hypogonadism, osteoporosis and cardiac arrhythmias are common in the terminal stage of the condition. Neurobiochemical, genetic and environmental factors appear to all contribute to maladaptive eating behaviours, although precise aetiology warrants further investigation. In addition, patients with schizophrenia have high rates of

tobacco smoking well over 50% and multiple-fold the general population; the cause of this high-frequency relationship may be both behavioural and physiologically based.

84.4 Bone and Skeletal Metabolism

Skeletal homeostasis results from a continuous process of bone turnover, mediated by osteoclasts resorbing bone and osteoblasts forming new bone. This does not occur only as a response to injury but is a continual process mediated by multiple hormonal regulatory pathways. Bone pathology, including osteoporosis and osteopenia, results from an imbalance between the activity of osteoclasts and osteoblasts. In addition, calcium hydroxyapatite is the primary building block of the bone matrix laid down by osteoblasts, and therefore normal calcium homeostasis is essential to this process. Adequate vitamin D is critical to allow bone mineralisation, maintain dietary calcium absorption, promote bone resorption, maintain calcium and phosphate levels and allow adequate parathyroid hormone function. These pathways are all susceptible both to the disturbance by the direct toxicological effect of substances and to lifestyle changes.

84.4.1 Alcohol and Bone

Alcohol is a risk factor for fracture independent of bone density which may be in part attributable to increased fall risk [55]. In addition to fall risk, alcohol produces changes in bone homeostasis resulting in net bone loss. Animal studies have demonstrated that the effect of alcohol on bone homeostasis is mediated via action on osteoblasts [41]. Osteoblast function and numbers are reduced in chronic alcohol ingestion disrupting osteoblast gene expression and bone matrix synthesis. Rodent studies suggest that even moderate levels of alcohol consumption may reduce bone turnover and have detrimental effects on the skeleton. The results from human observational studies in this area have been heterogeneous due to extensive confounding factors; however an increased risk of fractures was seen in patients with an intake of greater than two units of alcohol daily [55]. Part of the mechanism may be related to alcohol-induced hypercortisolaemia, described earlier in this review. A large meta-analysis observed a definitive increase in fracture risk in men consuming alcohol daily or greater than ten drinks per week [28]. Interestingly, another study demonstrated those consuming 0.5–1 unit of alcohol daily had a lower risk of fractures than abstinent patients [9].

As previously discussed, chronic alcohol ingestion may cause pituitary suppression, hypercortisolaemia and hypogonadism further contributing to low bone mineral density. Nutritional considerations, exocrine pancreatic dysfunction and malabsorption of fat-soluble vitamin D may lead to further bone loss.

84.4.1.1 Tobacco Smoking and Bone

Many mechanisms have been proposed for the effect of tobacco smoking on bone health. Nicotine has a direct inhibitory effect on osteogenesis and decreases osteoblast cell production, with cigarette smokers having lower serum concentrations of RANK ligand and osteoprotegerin than non-smokers ([60], p.). In one in vivo study, bone healing was impaired in nicotine-exposed rabbits, leading to an upregulation of vascular endothelial growth factor and hypoxia-inducible factor 1-alpha, yet decreased levels of bone healing factors [26].

Tobacco smoking is a well-recognised risk factor for osteoporosis. This effect appears to remain even after adjustment for confounders such as weight, age and level of physical activity, involves all skeletal sites and appears to be dose dependent [94]. One large meta-analysis demonstrated increased risk of fracture in smokers compared with non-smokers [54]. A twin study of discordant tobacco use demonstrated that smoking one pack per day of cigarettes throughout adulthood resulted in approximately 5–10% reduction in bone mass [49]. The risk of osteoporosis remains elevated even after cessation of smoking, although not as high as in current smokers, suggesting that bone health can improve with

smoking cessation. Anti-oestrogenic effects caused by smoking may also contribute to accelerated bone loss. This effect may be particularly important in postmenopausal women on hormone replacement therapy, as tobacco smoking may increase the metabolism of exogenous oestrogen, further contributing to bone loss in this high-risk population [2].

84.4.1.2 Opioids and Bone

Accelerated bone loss and increased fracture risk have long been observed in the chronic opioid-using population. The net bone loss seen in this population is likely a cumulative effect of disturbed systemic hormone levels and direct opioid inhibition of bone formation via opioid receptors on osteoblasts [18]. Interestingly, in one recent in vivo study, increased bone density was seen in mice administered with opioid receptor antagonist naltrexone [89]. Bone mineral density is lower than normal at all sites in men but not women on methadone maintenance therapy [45]. In one cross-sectional study of men on long-term opioid maintenance therapy, BMD was significantly lower in the lumbar spine but not at the hip compared with age and BMI-matched controls. This appeared to correlate directly with lower serum free testosterone [43]. Moreover, the decreased bone mineral density correlates with an increase in fracture risk as demonstrated in a large case-control study of over 100,000 patients [65, 66]. The purported mechanisms of increased fracture risk in this study are twofold and relate primarily to increased fall risk and the aforementioned hypogonadism.

84.4.1.3 Other Drugs and Bone

The relationship between bone health and other drugs of addiction is less well defined. Endocannabinoids and their associated receptors have been shown to be involved in signalling pathways relating to bone development and remodelling. This suggests THC use may have an effect on skeletal homeostasis, but further study is required [4]. There is little literature relating to the effect of methamphetamine and cocaine use on bone mineral density. A small study of 46 hospitalised methamphetamine users demonstrated lower BMD than in matched controls although the differences were not statistically significant in all age groups [57].

84.4.1.4 Clinical Management

All patients who are at risk of osteoporosis should be screened and commenced on therapy if warranted. Classical risk factors for osteoporosis include hypogonadal states, low body weight, chronic illness and malabsorption syndromes. In the addiction population, one should be especially vigilant and have a low threshold to screen for poor bone health. Patients who use alcohol, tobacco or opioids should be carefully assessed given that these substances may be associated with increased risk. Minimising fracture risk in this cohort should be prioritised even in the context of continuing substance use.

If there is suspicion of poor bone health, a dual-energy X-ray absorptiometry (DXA) bone mineral density scan should be performed. A diagnosis of osteoporosis can be made with a T-score of less than −2.5 or following a minimal trauma fracture with a T-score less than −1.5. If osteoporosis is confirmed, screening for secondary causes should be undertaken. If hypogonadism is suspected, screening via measurement of gonadotropins (FSH, LH, SHBG and testosterone) should be performed. Calculation of fracture risk via fracture calculation tools may be useful in stratifying patients at risk, with WHO estimates showing cost-benefit for treatment when ten-year major osteoporotic fracture risk exceeds 3% [90].

Ensuring adequate dietary calcium (1200 mg of calcium) is paramount to good bone health, with supplementation necessary if dietary intake cannot be maintained. Vitamin D3 (approximately 800 IU daily) is essential for calcium absorption and bone mineralisation [52]. A low threshold should be maintained for vitamin D deficiency in this at-risk population who may not have adequate UVB exposure. A 25-hydroxyvitamin D level equal to or greater than 50 nmol/L is considered sufficient. If levels fail to rise with adequate supplementation, screening for malabsorption syndromes is warranted.

Once a diagnosis of osteoporosis is made, referral to a specialist physician may be prudent in patients with addiction, with advantages and disadvantages of all the available treatment options to be considered. In the hypogonadal cohort, testosterone replacement therapy can be considered in those who are deficient. Combined oestrogen/progesterone or oestrogen monotherapy reduces fractures in postmenopausal women with efficacy equivalent to that of other specific antiresorptive therapies [15]. The minimal effective dose for bone protection has yet to be established and assessment of cancer, cardiovascular and thrombotic risk should be considered prior to commencing these agents.

Antiresorptive therapies (bisphosphonates, denosumab) are beneficial in reducing fracture risk and bone loss in the addiction patient with confirmed poor bone health. Bisphosphonates have proven efficacious for fracture reduction and are available in oral and parenteral forms. Denosumab, a monoclonal antibody that targets RANK-L, is given via subcutaneous injection and has also proven efficacious for fracture reduction. Teriparatide, a PTH analogue given daily, leads to an increase in bone mineral density as well as significant decrease in fracture risk and may also be considered in those with severe osteoporosis or ongoing fractures despite antiresorptive therapy.

84.5 Key Points and Conclusions

- Chronic alcohol use can lead to hypercortisolaemia, hypogonadism and poor bone health. Comorbid hepatic dysfunction may contribute to altered hormone-binding globulins and disrupted glucose homeostasis.
- Opioids are increasingly recognised as having an inhibitory effect on the hypothalamic-pituitary axes, with resultant hypogonadism and hypoadrenalism.
- Tobacco smoking increases the risk of Graves' disease and associated ophthalmopathy and remains an important modifiable risk factor in the management of metabolic syndrome and osteoporosis.
- Disruption of hormonal homeostasis is less well understood in the stimulant-using population and warrants further studies.
- Endocannabinoid antagonists have demonstrated promising metabolic effects, with cannabinoid receptors in the hypothalamus and peripheral tissues an ongoing target of therapeutic development. Cannabis use leads to impaired spermatogenesis compared to non-users.

Disturbances of delicate hormonal balances in the addiction population are becoming increasingly recognised phenomena. Delicate biochemical and hormonal homeostasis may be altered by numerous stimuli including addictive substances and cycles of addiction and withdrawal. An index of suspicion linked to careful assessment of comorbid endocrinopathy in these patients is crucial. Although overt clinical syndromes remain uncommon, subtle disturbances appear to be common. Furthermore, complications of prolonged disturbances may persist in abstinence and should be carefully evaluated in chronic care. Whether these disturbances could perpetuate addictive behaviours requires further study, with guidelines for screening and treatment yet to reach consensus. Nevertheless, any neurohormonal process that may lead to relapse or chronic comorbidity warrants consideration in this population.

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Sexual Function and Alcohol and Other Drug Use

85

Richard Hallinan

Contents

Abstract

Alcohol and other drugs have actions in limbic-hypothalamic hedonic motivational pathways that subserve basic biological functions including sexual behaviors. They may also have a range of other physiological and psychological effects on sexual function.

Psychoactive drugs are often used to facilitate or enhance sexual behaviors, but they can also cause sexual dysfunction. Their use can be associated with risky or harmful sexual behaviors.

Pharmacotherapies commonly used in addiction treatment, including opioid pharmacotherapies, sedative/hypnotics, antidepressants, and antipsychotics, can negatively affect sexual function, with implications for treatment adherence and effectiveness. Further, common psychological and physical comor-

R. Hallinan (✉)
Drug Health Services, Liverpool Hospital, South Western Sydney Local Health District, Liverpool, NSW, Australia

The Byrne Surgery, Redfern, NSW, Australia

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bidities in people with substance use disorders may cause sexual dysfunction.

An understanding of these issues can help clinicians working in the field of addiction better to appreciate motivations for continuing or reducing drug use, can inform motivational and harm reduction interventions, and can improve understanding of issues around treatment adherence. While there are challenges for clinicians in speaking about sexuality with their patients, this may be an important part of comprehensive assessment and treatment planning. The clinical benefits of addressing these issues, ranging from reducing sexual risk behavior to improving the quality of life of people receiving pharmacotherapies, can be substantial.

Keywords

Sexual function · Erectile dysfunction
Arousal · Libido · Drugs · Alcohol
Hypogonadism · Chemsex

85.1 Introduction

The impact of alcohol and other drugs (AODs) on human sexuality can be considered across three domains: (1) the deliberate use of alcohol and drugs to facilitate or enhance sexual behaviors, (2) their association with risky or harmful sexual behaviors, and (3) their association with sexual dysfunction [85].

Human sexuality and its disorders are complex and there are uncertainties even in the definitions of normality and dysfunction in human sexuality, differing between males and females, across the human lifespan, within and across cultures. One must distinguish between acute effects and chronic effects in heavy or dependent users of alcohol and other drugs. Epidemiologically, moreover, there are three distinct types of study populations for AOD-related sexual dysfunctions:

1. Populations with sexual dysfunctions
2. Clinical populations with substance use disorders
3. Population studies, which generally shed light only on commonly used substances

85.2 Substances and Sexual Dysfunction

85.2.1 Models and Neurochemical Substrates of Normal Sexual Function

In order to understand the effects of alcohol and other drugs on sexual function and to identify and manage sexual dysfunction where it occurs, it is important to have an idea of what is normal.

Since Masters and Johnson in the 1960s and with various amendments (Kaplan, Lief, and Levine, among others), the human sexual response has been described as proceeding in linear fashion through phases of desire, excitement, orgasm, and resolution. Progressive editions of DSM and ICD correspondingly defined disorders of reduced or impaired desire, arousal, and orgasm, adding premature ejaculation (PE) in the case of men and dyspareunia and vaginismus in women.

The linear model has been challenged for women and a cyclic model proposed instead, with overlap between phases, especially desire and arousal, reflecting the complexity of sexual motivation, the importance of intimacy, and a broader view of sexual satisfaction [13]. In DSM-V, desire and arousal disorders are merged for women but not men, while they remain distinct for both sexes in ICD-11 [96]. Hypersexual disorder was rejected for DSM-V but compulsive sexual disorder was included in ICD-11 under impulse control disorders.

A model for sexual responsiveness in mammals including humans posits a dynamic balance of excitatory and inhibitory forces, across all domains of sexual function [57, 87]. There are commonalities among the neurochemical substrates of reward and reinforcement of the essential biological functions of feeding and sexual activity, and those of drugs and alcohol, which most clearly increased dopamine activity in the nucleus accumbens [66, 82].

Sexual excitatory factors include dopaminergic pathways which control attention to incentive stimuli, behavioral responses, and parasympathetic outflow to genital areas, melanocortin, the "bonding hormone" oxytocin, and noradrenaline, which has an "inverted U"-shaped relationship with sexual behavior, whereby states of fear or anxiety reduce excitation. There are complex interplays among these factors, and their tone is influenced hormonally by estradiol and testosterone and also by gonadotropins directly. Testosterone is important for sexual desire and arousal in both men and women, and estrogen for arousal in women, including genital swelling and lubrication. Peripherally these hormones modulate mechanisms involving nitric oxide synthase, vasoactive peptides, prostaglandins, and serotonin, which act to increase genital blood supply [87].

The evolutionary value of the inhibition of mammalian sexual function is likely dual: to allow refractory periods and to avoid conflict within the species. Inhibition can be divided into two aspects, satiety and executive (prefrontal) inhibition. Evidence from the feeding literature suggested serotonergic mediation of satiety. Opioids may have a dose-related rewarding function, inducing satiety at higher doses. Endocannabinoids also appear to have a role in sedation after orgasm. Sedation in itself is likely to play a role in sexual responsiveness.

The central role of dopaminergic, serotonergic, and opioid-mediated processes in normal human sexuality points to the potential effects of prescribed and nonprescribed psychoactive substances in human sexuality.

85.2.2 How Common Is Sexual Dysfunction? Evidence from Population Studies

Population studies show high prevalence of sexual difficulties in women and men. Approximately two thirds of women report difficulty with sexual desire, one third difficulty with orgasm, one third difficulty with arousal, and a quarter of sexual pain [53]. However, only a proportion of the women were distressed by these difficulties, and symptoms were often not persistent [102]. Difficulties with erection are reported by 30–40% of men, with premature ejaculation by 10–20% and delayed orgasm being less common. In general, while the prevalence of sexual difficulties increases with age in both men and women, associated distress declines with age [33].

85.2.3 Deliberate Use of Psychoactive Substances in Sexual Behavior

Population studies show that drugs and alcohol are often used for sex-related purposes. There are differences among drugs in their perceived effects and uses: cocaine to prolong sex, alcohol to facilitate encounters, and MDMA to increase desire, closeness, and satisfaction but which may reduce erection and delay orgasm [7, 71, 122]. Opiate users are less likely than other drug users to attribute positive sexual effects to their drug [95]. Amphetamines and cocaine are most commonly reported to be pro-sexual, but some people report the opposite.

It should be borne in mind that childhood abuse, especially sexual abuse, is a risk factor for the development of substance use disorders and also for risky sexual behaviors [5, 11].

Both perceived effects and expectancies about drug use vary by demographics, gender, and context; women may believe or perceive the effects of drugs in men to be different from their own [38, 95]. Some evidence suggests the use of drugs as self-medication for sexual difficulties, which may be an important factor in the initiation of drug use [67, 75].

The term sexualized drug use "refers to the use of drugs in a sexual context…." "Chemsex" has been defined as "the use of drugs…before or during planned sexual activity to sustain, enhance, disinhibit or facilitate the experience" [37]. These include methamphetamine, GHB/GBL, mephedrone, phosphodiesterase type 5 inhibitors (PDE5-I), ketamine, and alkyl nitrites (such as amyl nitrate or "poppers") [47].

Recreational drug use and binge drinking have been associated with risky sexual behaviors including condomless sex and having partners of unknown HIV serostatus [71, 97]. People using stimulants, including nonmedical users of prescription stimulants, are reported as having higher numbers of sexual partners, higher rates of providing sex for money or drugs, and higher rates of sexual risk behavior [49, 68, 76, 116]. Risky sexual behaviors among people who use drugs and alcohol may reflect impulsivity, disinhibition, and impaired judgement and capacity for consent. While sedative/hypnotics and GBH are sometimes implicated in "date rape" cases, the most commonly identified substance is alcohol [85].

Oral erectile dysfunction (ED) agents are commonly used by recreational and dependent users of alcohol [90]. Among men who have sex with men, the use of sildenafil is associated with increased HIV risk; the combined use of methamphetamine and sildenafil is especially of high risk [42]. People who inject drugs reporting same-sex activity had substantially higher odds of chemsex use than those reporting heterosexual activity [54]. Higher sexual risk is not limited to sexual minorities, as suggested by increasing heterosexual syphilis transmission among persons who use methamphetamine in the USA [61]. In Africa and the Middle East, numerous groups are identified at higher risk of HIV, including people who use drugs, especially people who inject them, women in general, and female sex workers and their clients [77, 86].

85.2.4 Understanding the Etiology of Sexual Dysfunction in General

Assessment and management of sexual dysfunction in any clinical context require a consideration of its numerous possible causes.

85.2.4.1 Hormonal Factors

In women, testosterone and DHEAS peak in early adulthood and decline rapidly and progressively after such that levels are halved by age 40 [31]. By contrast, decline of testosterone in men is progressive from about age 40. Men have 10–16 times the level of testosterone compared to women, so the slow decline with age does not impact on hormonal drive and libido until older ages.

Androgen deficiency is common in men presenting with erectile dysfunction (ED) [62] and androgen replacement is beneficial for sexual function in hypogonadal men [8, 9], though not for the normal testosterone decline of aging. A large population-based cohort of older men showed no association of testosterone with ED, except in men with increased luteinizing hormone (LH) levels suggesting primary testicular disease [64].

Although androgen deficiency has not been unequivocally associated with female sexual dysfunction, several studies have shown the benefit of testosterone therapy on sexual desire, arousal, orgasm, and satisfaction in naturally or surgically menopausal women [31]. There is a challenge in understanding changes with menopause as distinct from aging itself: declining estrogen after menopause is a cause of vaginal dryness and dyspareunia [32]. Postmenopausal status increased the risk of sexual dysfunction in middle-aged women, while postmenopausal hormone replacement use was protective [17].

Hyperprolactinemia and hypothyroidism are also potential causes of sexual dysfunction in both men and women. While hyperprolactinemia commonly manifests with sexual dysfunction, hyperprolactinemia is an uncommon cause of male sexual dysfunction, which is not necessarily mediated by reduced testosterone [8, 16].

85.2.4.2 Vascular and Neural Factors

Normal sexual function requires intact vascular and neural function to the genital areas. Neuropathy may include autonomic or reduced tactile sensation, especially in genital areas. Endothelial disease is a common cause of erectile dysfunction in men [8]. Sexual dysfunction in diabetes is probably mediated by both vascular disease and neuropathy and multiple sclerosis through neuropathy.

85.2.4.3 Bodyweight, Obesity, Sleep Apnea, and Exercise

Overweight and obesity are increasingly implicated as risk factors for male sexual dysfunction, principally erectile dysfunction [106]. ED has a U-shaped relationship with weight (i.e., underweight is also a risk factor) and abdominal obesity and physical inactivity were associated with ED independent of body mass index, while physical activity itself appears protective against ED and female sexual dysfunction [2, 20, 56].

Obstructive sleep apnea is also independently associated with ED [15] as it disturbs REM sleep, which is the time during sleep when most nocturnal erections occur. Fewer nocturnal erections are a factor in the development of chronic diffuse corporeal fibrosis, leading to ED. This is preventable with early CPAP.

85.2.4.4 Other Medical Illnesses

Numerous other medical illnesses can cause sexual dysfunction, especially those affecting general constitution and fitness, such as chronic heart disease and lung disease. Chronic liver disease, especially liver failure, is related to sexual dysfunction independent of alcohol use [36].

85.2.4.5 Psychological Factors

Distress from sexual dysfunction appears to be dependent not only on age but also on relationship. Postmenopausal status and presence of sexual dysfunction in the male partner increased the risk of sexual dysfunction in middle-aged women, while partner faithfulness and menopausal hormone replacement use were protective [17]. In men, self-esteem and depression mediate the effect of erectile dysfunction on quality of life [89]. Continued alcohol use by alcohol-dependent men had negative impacts on sexual intimacy in the relationship which improved with abstinence [80]. Marital conflict may be an important factor in reported sexual dysfunction in male alcoholics [81].

85.2.4.6 Psychiatric Disorders and Their Treatment

A key issue is distinguishing between *preexisting and treatment-emergent* sexual dysfunction in people with mood, anxiety, and psychotic disorders, who may be prescribed with psychotropic medications. In each of these groups of disorders, there are high rates of sexual dysfunction, generally in the direction of hypofunction [25]. Anxiety and depression are also associated with premature ejaculation in men [92]. As with opioid pharmacotherapies (see below), sexual emergent side effects can affect psychiatric treatment adherence [104].

While SSRIs appear mainly to affect orgasm and antipsychotics primarily desire, all phases of sexual function can be affected by psychotropic medications. There appears to be a hierarchy among antidepressants regarding treatment-emergent sexual dysfunction with prevalence ranging from 25% to 80%. Among SSRI/SNRIs, sertraline, venlafaxine, and citalopram have higher prevalence of sexual dysfunction than escitalopram and fluvoxamine. Several other types of, primarily non-serotonergic, antidepressants (including agomelatine, bupropion, moclobemide, mirtazapine, and nefazodone) do not significantly differ from placebo [50, 103].

Sexual dysfunction is also common in people treated with antipsychotic agents, with no significant difference found among risperidone, quetiapine, and olanzapine [78]; these drugs are commonly associated with hyperprolactinemia, but hyperprolactinemia and sexual dysfunction were not correlated with each other [59].

For benzodiazepines and mood stabilizers, evidence of effect on sexual function is relatively lacking [25, 65]. Diazepam, clonazepam, and alprazolam have been associated with treatment-emergent male sexual dysfunction [44].

85.2.5 Sexual Dysfunction Related to Substance Use and Dependence

85.2.5.1 Tobacco and Cannabis

In men, tobacco smoking is a clear risk for vasculogenic ED, cumulative with packet years of smoking and persisting in former smokers [22, 72, 112]. Evidence is lacking for specific effects of tobacco smoking on arousal in women, though

other risks/indicators of endothelial disease (metabolic syndrome, obesity, diabetes, and coronary heart disease) are associated with female sexual dysfunction [74].

Daily cannabis use was associated in one study with difficulty achieving orgasm in men, but not sexual dysfunction in women [108], in another study with inhibited orgasm and dyspareunia [60], and in other studies with the beneficial effects of cannabis for erectile function [105]. The effects of cannabis use on sexual function are hard to disentangle from those of tobacco, as tobacco is often mixed with cannabis when the latter is smoked, and where cannabis is used in other ways than smoking, tobacco smoking is typically also common.

85.2.5.2 Alcohol

Low to moderate alcohol use in men may confer protection from erectile dysfunction [2, 22, 72].

Heavy alcohol use and alcohol dependence are common in clinical populations with sexual dysfunction, and alcohol-dependent men have been reported in studies in a range of countries to have sexual dysfunction including premature ejaculation, ED, and reduced desire [3, 35, 39]. Sexual dysfunction is also reported for alcoholic women, though evidence is less [58].

Pach et al. [83] found high prevalence of ED in alcohol-dependent men, which was not associated with testosterone or prolactin concentrations, but to higher gonadotropin levels, consistent with a toxic effect of ethanol on the testes. In the absence of severe liver disease or hypogonadism, male sexual dysfunction improves with abstinence [114].

Autonomic neuropathy commonly goes unrecognized in alcoholics and appears to be dose related and potentially reversible on abstinence; in heavy male alcohol users, erectile dysfunction may be the only symptom of parasympathetic neuropathy [94].

85.2.5.3 Opioids

Chronic users of opioids including heroin, and opioid pharmacotherapies for dependence and for chronic pain, have high prevalence of sexual dysfunction, consisting in hypoactive sexual desire and arousal difficulties in both genders, and increased ejaculatory latency in men [29, 88].

There is strong evidence of sexual dysfunction in both treated and untreated opioid-dependent men, including numerous studies in heroin users from a range of countries and cultures and several studies of opioid substitution treatment [6, 10, 52, 79, 91, 115]. Erectile dysfunction may be less common in men on buprenorphine than on methadone for the treatment of opioid dependence [119]. The smaller published evidence for women suggests reduced libido, emotional arousal, and orgasm satisfaction in women using opioids [12, 115, 101].

Early studies of methadone maintenance treatment (MMT) found either improvement or little change in sexual function in opioid-dependent women and men compared with their prior heroin use [45, 117]. Garbutt and Goldstein [45] prospectively studied 120 entrants into MMT, and while average "climax" and "impotence" scores improved at 27 weeks, compared with baseline, the majority of the 30% who dropped out of treatment reported loss of sexual function as a major reason. More recent studies of men on MMT and buprenorphine maintenance treatment (BMT) have given mixed results for erectile dysfunction with opioid pharmacotherapy showing improvement [4, 24], deterioration [123], or no change [19] compared with prior heroin use. By contrast with heroin users entering opioid pharmacotherapy, where prior sexual dysfunction is common, sexual dysfunction in men treated with opioids for chronic pain is more clearly treatment emergent [29].

Cross-sectional studies of the relationship between methadone dose and sexual dysfunction have given mixed results [21, 52, 79]. This may reflect the large interindividual variation in the pharmacokinetic and pharmacodynamics of methadone. Clinical experience is that methadone dose reductions may improve sexual dysfunction. The relationship between testosterone levels and erectile dysfunction has not consistently been shown in cross-sectional studies of opioid users [23, 46, 120].

Numerous other correlates of sexual dysfunction in opioid users have been variously, if inconstantly, identified. These include marriage status, depression, MMT duration, age, sleep quality, unemployment, education level, and tobacco smoking [21, 34, 70, 113, 119].

Most reported studies identifying orgasmic difficulties in men do not distinguish between premature ejaculation and delayed orgasm. Where it has been studied, premature ejaculation is found to be more common in men using heroin and on methadone treatment than in general community studies, and opioids may be used deliberately by some men to manage this problem [1, 18]. Although opioid antagonists have been trialed as treatment for erectile dysfunction, the only study available of sexual dysfunction in men on naltrexone maintenance treatment found high prevalence of erectile dysfunction, comparable with buprenorphine maintenance. However, premature ejaculation was the most common dysfunction in these men [93].

Increasing literature in recent times points to significant impacts of sexual dysfunction in patients injecting opioids or receiving opioid pharmacotherapy on quality of life and psychological distress [21, 70, 113]. Gerra et al. [46] found evidence suggesting psychiatric symptom load and neglect history may actually mediate opioid effects on sexual function.

85.2.5.4 Stimulants

In contrast to population studies finding the use of stimulants to improve sexual function, in clinical populations with substance use disorders, cocaine use was commonly associated with impaired desire and sexual, especially orgasmic, function [63, 95, 116]. Amphetamine users had high rates of sexual dysfunction, though less than those of dependent opiate, mostly injecting, users [48, 6] reporting IIEF scores of men shortly after their entry into a compulsory drug treatment facility, found odds ratios for erectile dysfunction were significantly higher relative to controls for heroin (4.8) and amphetamines (3.2), but not for MDMA users. While 23% of amphetamine users reported increased sexual desire, the sexual desire scores of this subgroup were still significantly lower than those of controls. The heterogeneous nature of actual or perceived drug effects is further reflected in the fact that about half of the men in this study reported increased, while about 15% decreased, ejaculatory latency.

85.2.6 Sexual Function and Alcohol and Other Drug Use: Clinical Assessment and Management

Assessment of sexual dysfunction in people with substance use disorders is based on the understanding that there may be multiple contributing factors:

1. The actions of the substances themselves
2. Psychiatric and medical comorbidities, as described above
3. The psychosocial context including partner status, self-esteem, and relationship issues
4. The effects of treatments, especially with dopamine antagonists, serotonergic agents, and opioids, but also non-psychotropic medications such as beta-blockers, antihistamines, NSAIDs, and thiazide diuretics

Few patients may volunteer information about the impact of substance-related sexual disturbance on their lives, and few clinicians may ask [19, 101, 118]. Low sexual desire may not constitute a symptom – if anyone complains, it may be the partners. Clinical presentation can be indirect, with depression, relationship problems, underdosing of or poor treatment adherence with opioids and other medications, and even dropping out of treatment.

Clinicians can develop skills to incorporate inquiry about sexual matters as part of comprehensive assessment and ongoing assessment in a way that puts patients at their ease. For example, it may be helpful to inquire about sexual dysfunction as one of other common medication-associated symptoms: in the case of opioids, these include sweating, constipation, and disturbances of menstruation.

It should be clarified which phases of sexual response are involved, desire, arousal, and orgasm, as this may determine the focus of management. Also important in assessment are the effect that sexual dysfunction is having on their lives and whether it is affecting their attitude to treatment in any way. Unless there is distress, sexual dysfunction may not need specific management.

Drug treatment services and other settings where brief interventions can be carried out provide opportunities for discussing drug-related sexual risks and promoting safe sex. For people continuing to use drugs or alcohol, discussion of sexual function may be important in motivational interventions. Abstinence may come at a perceived or actual cost to one's sex life. Equally, sexual dysfunction resulting from alcohol or drug use may be a salient motivation toward abstinence [84]. Sexual contexts, cues, and triggers may be important, for the risk of relapse, to be considered in relapse prevention strategies [95].

Where "self-medication" of premature ejaculation with alcohol or other drugs is causing problems, discussion of alternatives might reduce harms and risk of dependence or relapse. The SSRIs fluoxetine, paroxetine, and citalopram, and also tramadol have shown benefit for the treatment of premature ejaculation, and the short-acting SSRI dapoxetine has been approved in a number of countries specifically for the indication on premature ejaculation. Other treatments include local anesthetics such as topical lignocaine and the Masters and Johnson "squeeze technique."

Small open-label studies reported the benefit of the serotonin antagonist and reuptake inhibitor trazodone for erectile dysfunction in men on MMT [111] and of the dopamine agonist bromocriptine to treat sexual dysfunction in MMT on the hypothesis of possible hyperprolactinemia [107] – however hyperprolactinemia is uncommon in men on MMT and unrelated to sexual dysfunction [52, 119]. Small randomized controlled trials have shown promise for Damascus rose oil for sexual dysfunction in both men and women on MMT [40, 41] and for bupropion for erectile dysfunction in men on MMT [99, 121]. There are a few reports of improvement in sexual function with androgen replacement in men receiving opioid treatment for chronic pain (see [27] for a review) and buprenorphine for opioid dependence [26].

Otherwise there is limited specific evidence to guide the treatment of sexual dysfunctions arising out of substance use and its disorders. In the absence of such evidence, the clinician must integrate more general evidence into clinical practice.

85.2.7 Treating Sexual Dysfunction

85.2.7.1 The Example of Opioid Pharmacotherapy

Where sexual dysfunction is identified in the setting of opioid pharmacotherapy, management is likely to be multifaceted, with consideration of:

- Mood, anxiety, and psychotic disorders and related psychotropic medication use including antipsychotics, "antidepressants," and sedative/hypnotics
- Other potentially treatable or reversible risk factors for sexual dysfunction including tobacco smoking, alcohol and other drug use, sleep apnea, and obesity (noting that exercise may be protective against sexual dysfunction)
- Issues related to poor self-esteem, including obesity and poor dentition
- Hormonal status, especially hypogonadism
- Partner status and relationship issues

Sexual dysfunction attributed to methadone treatment may cause patients to drop out of treatment [45, 101]. Set within the larger issue of treatment planning, people may be prepared to tolerate the side effects of pharmacotherapies if these are discussed, and their identification may provide a rational and structured context for goals in treatment.

Pharmacological strategies for hypoactive sexual desire include hormone replacement where there is hypogonadism. The centrally acting dopaminergic agent apomorphine is limited by side effects especially nausea [73]. Centrally

acting pro-dopaminergic and anti-serotonergic medications are the foci of ongoing research [109]; see also Sect. 85.2.7.2. Such treatments usually involve consultation with an endocrinologist or sexual health physician.

In both men and women with sexual dysfunction emergent with opioid, antidepressant, or antipsychotic therapy, dose reduction, changing medications to alternatives with lower reported rates of sexual side effects, timing of medication in relation to planned sexual activity, and addition of phosphodiesterase type 5 inhibitors (PDE5-I) are all plausible strategies, though studies of these approaches are lacking [98, 100]. As well as having favorable profiles for sexual side effects in monotherapy, the antidepressants bupropion, trazodone, and mirtazapine have shown benefit as add-on treatment to SSRIs for depression.

Despite the lack of a consistent dose relationship of sexual dysfunction to methadone dose in cross-sectional studies, it is likely that sexual dysfunction is dose related in any one individual and that dose reductions can help, provided this does not lead to relapse into other opioid use. With the same caveats, cross-sectional studies showing less prevalent sexual dysfunction in men on buprenorphine than methadone suggest possible benefit of switching medication.

How is the clinician to understand the inconsistencies in the epidemiological literature as to the role of opioid medication, dose, other drug use, and demographic and clinical correlates in sexual dysfunction? They may reflect the complexity of human sexuality, the large number of factors involved, and interindividual variation in these factors. It may be that a correspondingly individual approach is the most practicable clinical approach. In practical terms, that means considering all of the potentially relevant issues and seeking pragmatic individual solutions.

85.2.7.2 Some Specific Issues for Women

Systemic testosterone may have a role for hypoactive sexual desire in surgically and naturally postmenopausal women. It is only approved for limited indications in a few European countries, although off-label use is common [30, 43]. Side effects include hirsutism, deepening of the voice (the latter can be irreversible), male pattern alopecia, and clitoromegaly, and longer-term concerns include possible increase in cardiovascular disease and breast cancer.

Systemic estrogens with or without progestins can improve menopause-related symptoms, including reduced genital arousal and lack of vaginal lubrication. Topical estrogens may be preferred for equal efficacy and the absence of systemic side effects and lower risk of breast cancer. Evidence does not support benefit for estrogen treatment to increase sexual desire [30]; indeed, estrogens might reduce sexual desire.

The PDE5-I sildenafil, in lower doses than are used in men, shows benefit for female sexual dysfunction related to multiple sclerosis, spinal cord injury, and diabetes, secondary to antidepressant use [14].

Two medications have now been approved in the USA for treatment of hypoactive sexual desire disorder, both showing significant but modest effects. Flibanserin is functionally characterized as a noradrenaline and dopamine disinhibitor [110] and is marketed for daily use. It has had a small market uptake so far, possibly owing to its side effect profile and interactions with alcohol and medications. Bremelanotide, a melanocortin receptor agonist, is marketed as an injection for on-demand use by injection. Limited study populations led to corresponding limitations in drug labeling and drug subsidy. The need for research in "additional study in diverse populations" [69] and the redefinition of arousal and sexual desire disorders add to the uncertainty in the use of these medications.

85.2.7.3 Some Specific Issues for Men

PDE5-I are effective for erectile dysfunction of a broad range of etiologies. They may be beneficial where erectile dysfunction is a side effect of opioid pharmacotherapy and where opioid dose reductions are likely to be counterproductive. They have advantages including on-demand effectiveness and absence of long-term side effects. However, some men who have erectile dysfunction do not respond at all, or if so not longer term, to PDE-5 inhibitors, and for some, these

drugs are contraindicated. Currently available alternatives include intracavernosal injections.

In counseling, one should bear in mind that orgasmic dysfunction itself may contribute to erectile dysfunction in men, and loss of confidence and relationship stress can play a large role in perpetuating erectile dysfunction. Involvement of the partner in counseling may be helpful, and nondrug aids such as penile rings and vacuum devices are cheap and easily available or can be improvised, though not without their risks.

Opioid-induced androgen deficiency can be managed by dose reduction, medication switch, or androgen replacement [55] and weight loss where there is obesity. It is questionable whether androgen replacement should be considered where heavy alcohol use or unprescribed opioid use continues. The decision for androgen replacement should be informed by the possibility of placebo response and the possibility that initial benefit for sexual symptoms may not be sustained [28]. Concerns about excessive or otherwise inappropriate use of androgens can be minimized by prescribing transdermal formulations or limited supply and supervised administration of injected formulations.

85.2.7.4 Setting the Management of Sexual Dysfunction Within the Social Context

Relationship conflict can be a contributing factor in sexual dysfunction. In management, it can be helpful to place the sexual problem within the context of the relationship rather than the individual. At the same time, it must be recognized that people with AOD problems often have high levels of social dislocation, including disrupted or lacking intimate relationships. Economic factors, low self-esteem, poor dentition, tobacco smoking, and obesity are all factors to which the social context is relevant; none can simply be solved with a prescription.

85.2.8 International and Public Health Perspectives

Research into the nexus of sexuality and AOD use is increasing. Where research was previously mostly from Western societies, the increasing published literature from Asia, the Middle East, and South America indicates that issues of sexuality are important across a range of societies and cultures.

Numerous screening and research instruments for sexual dysfunction are available for both men and women, of which some are widely validated in different cultures/languages. That single question instrument have shown utility in identifying sexual problems in research settings suggests that simple methods of enquiry may also have clinical utility. For clinicians, the challenge in any setting is to develop sensitive and culturally appropriate techniques of inquiry. Eliciting information about sexual experiences other than heterosexual intercourse, "self-pleasure" (masturbation), and sexualized drug use may be challenging in all cultures.

Given the public health concerns related to AOD and sexually transmitted diseases, it may be that addiction medicine clinicians should pay attention to their patients' sexual lives no less than do sexual health clinicians. There is a need for interventions to reduce health risks related to sexual behaviors, including sexualized drug use, which are informed by understanding social and cultural contexts. These may include the impact of gender/sex identity, sexual orientation, sexual venue, relationship dynamics, and socioeconomic factors such as poverty, stigma, and marginalization.

85.3 Clinical Relevance

This chapter encompasses three main theses relevant to the clinical practice of addiction medicine, namely:

1. Human sexuality can be a major motivational factor in the initiation and continuation of alcohol and other drug use and may entail high-risk sexual behaviors.
2. Alcohol and other drug use might have both adverse and positive (whether actual or perceived) effects on people's sexual lives.

3. Pharmacological treatments used in addiction treatment may (mostly adversely) affect people's sexual function, and this has implications for treatment acceptability and adherence.

The overarching proposition is that awareness of these issues can inform both clinical practice and public health policy. The clinical implication is that enquiry about sexual experience and function can be an important element of assessment in AOD contexts, from general practice to the specialist addiction treatment facility, providing opportunities for informed counseling around risky sexual behaviors and improving access to and adherence to treatments.

At face value it seems no more remarkable to propose that clinicians should ask about matters of human sexuality than that they should ask about the clinically important matter of bowel function (which can have considerable health impacts; [51]). This proposal comes with some caveats: that enquiry about sexual matters ought to be culturally appropriate, that it be sensitive to the high prevalence of abuse including childhood sexual abuse in AOD clinical populations [5, 11], and that examination of genitalia be considered in the light of a possible abuse history and where necessary referred to another clinician.

85.4 Conclusion

Human sexuality and its disorders are complex, involving a wide range of physiological, pathological, psychological, and societal factors. The benefits of addressing these issues in AOD settings, from reducing sexual risk behavior to improving the quality of life of people receiving pharmacotherapies, can be substantial. Better understanding of the relationship between sexuality and AOD use might enable more effective prevention, treatment, and harm reduction for AOD use and is the focus of ongoing diverse research endeavors.

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86 Patients with Substance Use Disorder and Addiction: Acute Pain Including Perioperative Issues

Stephen Gilbert and Kai Yeng Chan

Contents

S. Gilbert (✉)
Anaesthesia and Pain Medicine, Townsville Hospital, Douglas, QLD, Australia

K. Y. Chan
Consultation Liaison and Addictions Psychiatry Medicine, Townsville Hospital, Douglas, QLD, Australia

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Abstract

This chapter outlines the problems that may arise when patients with a substance use disorder present for surgery, including the social, psychological and biomedical aspects. The assessment and management of patients and the factors that may affect anaesthesia and perioperative pain management are covered.

Keywords

Substance use disorder · Anaesthesia
Acute pain

86.1 Introduction

Much of the literature on the effect of substance use disorder (SUD) and perioperative care focus on the biomedical effect of any substances used on the patient's physiology and on interactions with pharmacological agents. Social and psychological factors may cause more difficulty in providing the best medical care to people with substance use disorders and addiction. The patient has a different focus when presenting for surgery than when attending addiction services. Having surgery and anaesthesia carries a set of meanings: fear of pain, complications or death, worry about diagnosis and prognosis, being in the alien environment of the hospital, among others. For the patient with SUD, there is also the anxiety of being unable to access their substance and the value judgements that they feel may be made about them. The perioperative setting is an opportunity for brief intervention. An open, empathic approach is essential to avoid triggering an antagonistic confrontation. The priority is to ensure quality and safety in perioperative care and a successful outcome from surgery.

86.2 Social and Psychological Factors

When patients with SUD or addiction are admitted to hospital for surgery or when acute pain management is required, there can be problems with establishing a good therapeutic relationship between the patient and healthcare professionals (HCPs). There may be a perception by the HCP that SUD or addiction is a character defect or a lifestyle decision, rather than a neurobiological condition, with complex predisposing and perpetuating factors. HCPs involved in perioperative care may have limited knowledge or understanding of the underlying causes and treatment of the condition.

Societal and cultural differences between the HCP and patient may make establishing a trusting relationship more challenging.

From the patient's perspective, there may be lack of trust in HCPs due to previous negative experiences, feeling judged and not believed in, when reporting pain and other symptoms. The perceived stigma of addiction and feelings of guilt or shame may lead patients to withhold information. Sometimes, symptoms can be exaggerated by the patient, in an attempt to ensure that

they are taken seriously by the HCP. The social circumstances of the patient may foster feelings of alienation from the HCP and there may be attempts to mislead, deceive or manipulate, which can lead to further loss of trust. Intoxication, withdrawal symptoms or mental health problems, such as personality disorders, can deter the establishment of therapeutic alliance. Patients may be anxious or fearful of undertreatment of pain or of withdrawal symptoms if they are not able to access tobacco, alcohol or other substances. Those on opioid substitution therapy (OST) may worry that they will not be able to access it. Illicit drugs can be taken in addition to prescribed treatment, or the patient can take discharge against medical advice, due to anxiety, among many other factors.

Frequently, these factors can lead to a perpetuation of the cycle of negative experience on the part of the patient and the perception of patients with SUD as difficult to help or not deserving of care from the perspective of HCPs.

The development of an open, empathic and non-judgemental approach, as well as being able to understand more of the underlying issues for the patient, is key to ensuring a more humane and patient-centred care in the perioperative period, as well as contributing to more effective and safe management of acute pain.

Reassurance that pain and withdrawal will be managed as well as can be is the first step while recognising that pain cannot be completely eliminated and is sometimes more difficult to manage, due to factors such as tolerance and opioid-induced hyperalgesia. The development of a realistic agreement with the patient and emphasising that mutual respect and honesty are expected are important in ensuring safe and effective medical care.

86.3 General Assessment of SUD

Gaining the patient's confidence is important in the assessment of what substances may have been abused and whether intoxication, withdrawal or social, psychological and behavioural problems might affect their care in the perioperative period.

In many countries, particularly in more prosperous nations, substances that are liable to cause dependence or to be abused are more likely to be prescribed medication, such as opioids, benzodiazepines and gabapentinoids, than illicit drugs [1]. When taking a history, problematic or aberrant drug use can be elicited by asking about the quantity prescribed at a time, whether the prescription has run out before it was due for renewal and whether the patient has taken more than was prescribed or has overdosed. Corroborating information with the prescriber, pharmacist and prescribing monitoring schemes can construct a more accurate picture of whether to expect tolerance, withdrawal or problematic behaviour.

Over the recent years, the demographics of persistent opioid use has changed, with more liberal prescription of strong opioids for persistent or chronic pain. This increase in prescribing has resulted in rising rates of harm [2]. The numbers of patients coming to harm from prescribed opioids has exceeded those taking illicit drugs. The initial medical enthusiasm, in the 1990s and 2000s for using the principles of the analgesic ladder in chronic non-cancer pain, was based on the experience of success in being able to manage 85% of patients with cancer pain with oral opioids [3]. There was a widespread belief that patients with pain are unlikely to develop addiction. Unfortunately, the evidence that has emerged subsequently failed to show improved pain relief, quality of life or likelihood of recovery from chronic non-cancer pain. At the same time, there is increasing evidence of harms associated with prescribed opioids [4].

There is a complex interplay of pharmacological, biomedical, social and psychological factors in patients taking prescribed opioids as well as in healthcare practitioners caring for them. Often patients will be presenting for orthopaedic or neurosurgical treatment for the condition which has led to them being prescribed with opioids. In the case of back and neck pain, this can be especially problematic, with little evidence that either opioids or surgery are helpful in managing the

patients' pain [5, 6]. When assessing patients for care in the perioperative period, those taking prescribed opioids will outnumber those taking illicit drugs.

86.4 Societal Factors

Opioids have been the mainstay of pain management for thousands of years. Widespread use and misuse among veterans following the American Civil War led to an international treaty to restrict the availability of opioids in 1914. There followed many years of "opiophobia", with the belief that the use of opioids for treatment, even of terminal cancer pain, would lead to the rapid development of tolerance and addiction. As a result, it was advised not to prescribe opioids even in terminal cancer until the last few days of life. The introduction of the World Health Organisation "Analgesic Ladder" in 1986 [3] led to the establishment of the principle of treating the patient's pain based on their subjective rating of severity and relief with treatment. The publication of an observational letter and a small trial in patients with back pain led to an advocacy for the use of the analgesic ladder in patients with non-cancer pain in 1990 [7]. These influential publications in combination with promotion of better pain management, in which the pharmaceutical industry was involved, led to a marked rise in opioid prescribing, particularly in North America, the UK and Australia.

When considering the DSM criteria for substance use disorder, many patients taking opioids for persistent pain fulfil the criteria for mild SUD at least [8] (Table 86.1).

Illicit drug use or aberrant use of prescription medication can be explored after enquiring about alcohol and smoking, which are more socially acceptable for patients [9]. It can help to know about the local drug scene (e.g. gabapentinoids are much more commonly abused in prisoners); information can be gathered from addiction services, law enforcement and drug intelligence networks. The features that may affect the HCP involved in perioperative care are as follows (Table 86.2):

Table 86.1 DSM-5 criteria for SUD: mild, 2–3; moderate, 4–5; severe, 6 and greater

1.	Taking the substance in larger amounts or for longer than you're meant to
2.	Wanting to cut down or stop using the substance but not managing to
3.	Spending a lot of time getting, using or recovering from use of the substance
4.	Cravings and urges to use the substance
5.	Not managing to do what you should at work, home or school because of substance use
6.	Continuing to use, even when it causes problems in relationships
7.	Giving up important social, occupational or recreational activities because of substance use
8.	Using substances again and again, even when it puts you in danger
9.	Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the substance
10.	Needing more of the substance to get the effect you want (tolerance)
11.	Development of withdrawal symptoms, which can be relieved by taking more of the substance

Table 86.2 Assessment of SUD and common problems

Cannabis Party drugs Synthetic cannabinoids – spice, etc.	Whether under the influence History of psychosis or other behavioural problems Vascular disease (myocardial ischaemia, cerebrovascular disease) Respiratory disease, COPD, cough and liability to laryngospasm
Stimulants – cocaine, methamphetamine, ice	Liable to cardiovascular depression with anaesthetic agents when wearing off – cautious dosing Hypertension, MI and CVA
Heroin or other opioids	Whether opioids – interaction with perioperative analgesics causing depression of respiration and conscious level How much and how often? Whether injected How long can they be without? Are there unpleasant withdrawal symptoms? Opioid substitution therapy; methadone or buprenorphine
Other problems associated with drug or alcohol use	Infections Malnutrition, vitamin deficiencies, hepatic dysfunction and coagulation abnormalities Problems with venous access Blood-borne viruses and associated immunosuppression or liver disease Mental health problems Involvement with police or prisons Social work and child welfare

86.5 Alcohol

86.5.1 Alcohol's Impact on Operative Outcomes

Around 20% of surgical patients have alcohol use disorder (AUD) [10]. Alcohol misuse has an impact on virtually every organ system. Uncontrolled use may lead to severe complications summarised in Fig. 86.1; Table 86.3.

Patients with AUD have up to 2–5 times increased risk of post-operative morbidity [11] and increased hospital stay [12]. Many of ethanol's effects contribute to increased adverse outcomes such as modulation of immune function [13], delayed wound healing [14], reduced cardiac function and altered haemostatic balance. The increased risk applies across all types of surgeries [15].

Post-operative alcohol withdrawal can be difficult to manage and be confused with delirium of other causes. Untreated withdrawal may lead to confusion, hallucinations or seizures. Other alcohol withdrawal symptoms include anxiety, tremors, headaches, sweating, nausea, vomiting, increased heart rate and blood pressure. Alcohol withdrawal symptoms may appear as soon as blood ethanol starts falling. Most severe withdrawal symptoms typically appear on day 3 of alcohol cessation and may worsen over the course of 5–7 days.

Wernicke's encephalopathy from thiamine (vitamin B1) deficiency may result from malabsorption and malnutrition in patients with chronic alcohol issues. All three of the classic Wernicke's triad (see Table 86.4) might only be present in 10–16% of patients with Wernicke's encephalopathy [16]. Caine suggested the addition of dietary deficiencies to the triad and requiring only two out of four criteria to diagnose Wernicke's encephalopathy. This increased the sensitivity to 58% and specificity to 100% [17]. Untreated thiamine deficiency may lead to irreversible Korsakoff's syndrome. This is characterised by long-term memory impairment. A key characteristic of patients with Korsakoff's syndrome is confabulation (Table 86.4).

Despite these known complications and impact on surgical outcomes, screening and intervention for AUD are often neglected [18]. A short duration of abstinence may have significant benefits. Two weeks of abstinence improves delayed-type hypersensitivity (DTH) and haemostatic balance [19]. Four weeks of abstinence reduces stress response.

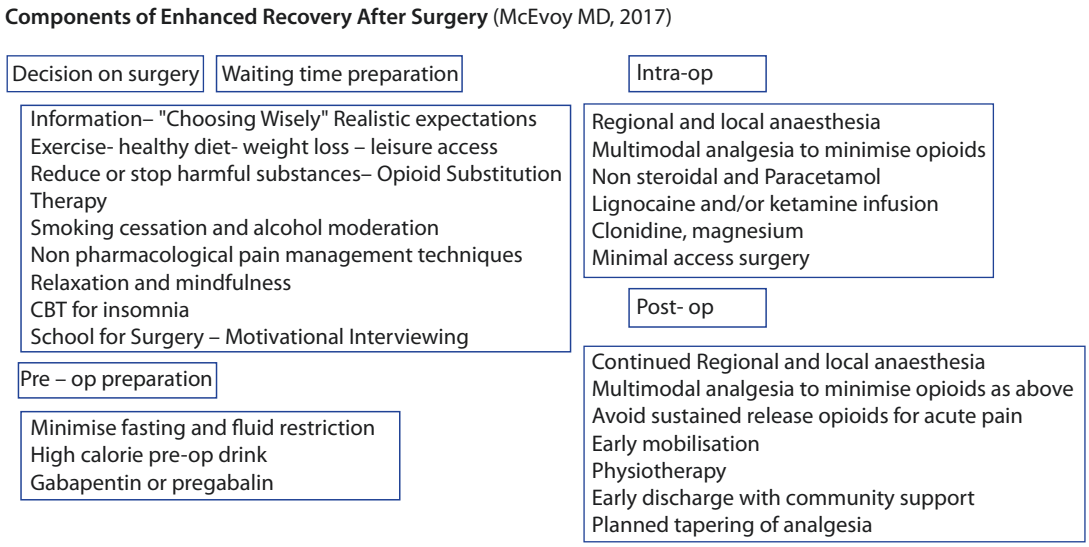

Fig. 86.1 Components of an ERAS programme. The waiting time preparation opportunities are not widely utilised. Many of these measures would benefit people with SUD

Table 86.3 Complications associated with chronic alcohol use

Cardiovascular	Dysrhythmias Cardiomyopathy Hypertension
Gastrointestinal	Esophagitis Gastritis Hepatic cirrhosis and fibrosis Alcoholic hepatitis Pancreatitis
Endocrine	Decreased testosterone Decreased gluconeogenesis Hypalbuminaemia Hypomagnesemia
Haematologic	Thrombocytopenia Leukopenia Anaemia
Neurologic	Peripheral neuropathy Cerebellar degeneration Cerebral atrophy Cognitive impairment including confusion and amnesia (Wernicke-Korsakoff's syndrome)
Psychiatric	Depression Anxiety Hallucinations Insomnia

Table 86.4 Signs of Wernicke's encephalopathy

Ophthalmoplegia	Nystagmus, papilledema, gaze palsies
Cerebellar dysfunction	Dysdiadochokinesia, ataxia, motor skill impairment
Mental state changes	Confusion, agitated delirium, decreased consciousness, memory impairment

86.5.2 Preoperative Considerations and Management

Routine screening using questionnaires is recommended. The ten-item Alcohol Use Disorder Identification Test (AUDIT) [20] can be used and takes less than 5 minutes to complete. History regarding alcohol use should be mandatory preoperatively. End-organ damage from chronic alcohol use should be evaluated via physical examinations.

Investigations such as mean corpuscular red cell volume (MCV), gamma-glutamyl transpeptidase (GGT), aspartate transaminases (AST) or alanine aminotransferase (ALT) and carbohydrate-deficient transferrin (CDT) may be useful in confirming suspicions of AUD. Blood alcohol level (BAL) may be considered in trauma situations.

A 2018 Cochrane review of perioperative alcohol cessation revealed that intensive preoperative alcohol cessation interventions reduced the number of post-operative complications [21]. These interventions lasted from four to eight weeks and incorporated pharmacotherapy such as thiamine, disulfiram and chlordiazepoxide. The intense interventions often included motivational counselling, as well as phone support. The high levels of resources required for these intensive preoperative interventions aimed at abstinence may not be easily available to most hospital systems.

Two other Cochrane reviews have confirmed that brief intervention, with or without pharmacotherapy in primary care [22] and hospital wards [23], is effective in reducing alcohol consumption. It is recommended that brief psychoeducation, as well as motivational counselling, should be attempted for all patients with AUD.

86.5.3 Management of Perioperative Alcohol Withdrawal

Recognition of AUD and withdrawal symptoms allows early treatment. Delay or inadequate treatment will result in worse prognosis. Severity of alcohol withdrawal should be assessed regularly using an objective scale such as the Alcohol Withdrawal Scale (AWS) or Clinical Institute of Withdrawal Assessment for Alcohol (CIWA-Ar) [24]. Any other causes of delirium such as infections or metabolic dysfunction should be ruled out. Basic pathology monitoring full blood count, electrolytes (including potassium and magnesium), liver function and coagulation function should be mandatory.

Main treatment consists of long-acting benzodiazepines (e.g. diazepam, lorazepam) with special consideration for any liver dysfunction. Benzodiazepines should be given aggressively at the recognition of withdrawal symptoms.

Symptom triggered as per-required regime should be used along with regular doses of benzodiazepines. Dosage should be adjusted according to the severity of alcohol use and withdrawal symptoms.

Symptomatic treatment should be considered, such as antipsychotics for hallucinations and agitation (e.g. haloperidol), antiemetics for vomiting (e.g. metoclopramide) and fluids for dehydration. Common non-pharmacotherapy for managing confused or agitated patients such as a low-stimulus environment and increased nursing care may help.

Thiamine replacement is vital to preventing Korsakoff's syndrome. Parenteral thiamine is preferred, as oral absorption is impaired in those with severe alcohol use disorder. A total of 300–500 mg IV three times daily should be considered and be given until improvement of cognition.

86.6 Nicotine

86.6.1 Tobacco's Impact on Operative Outcome

Tobacco users are more likely to suffer from perioperative complications [25]. Tobacco inhalation produces carbon monoxide, which binds strongly to haemoglobin and reduces its capability to carry oxygen. This decreases the tissue oxygen availability by 3–12% [26]. Nicotine also activates sympathetic activity and increases heart rate, blood pressure and vascular resistance. The combination of reduced oxygen supply and increased oxygen demand results in escalated risk of perioperative complications.

Current smokers are 1.38 times more like to die perioperatively than non-smokers [27]. Tobacco users also have increased risks of pulmonary complications (pneumonia, unplanned intubation, mechanical intubation) and cardiovascular complications (cardiac arrests, myocardial infarctions and stroke), as well as increased likelihood of wound healing and infections [28]. As a result, tobacco smokers tend to have longer hospital stays and be more likely to require intensive care [29].

86.6.2 Management of Preoperative Tobacco Use

There is expert consensus to support smoking cessation before surgery. Longer duration of quitting is associated with increased benefits. Cessation for one day can improve tissue oxygen delivery [30]. Abstinence of at least three weeks can improve wound healing [31]. Six to eight weeks of stopping improves pulmonary function [32] and decreases cardiovascular and wound complications [33]. Six months of abstinence restores immune functions [34].

Surgical patients may be more receptive to cessation advice. Patients' odds of quitting increases by 30% if undergoing minor surgical procedure. When faced with major surgery, patients might be twice as likely to quit [35]. This suggests possible intervention points at times of health crisis. Despite increased rates of success, provision of preoperative cessation advice is often low from both surgeons and anaesthetists in general [36, 37]. Brief interventions such as offering a quit advice before surgery may double the chance of smoking cessation [38]. Intensive interventions (dedicated consultation with follow-up in 4 weeks and nicotine replacement) reduce post-operative complications by 60% and improve abstinence rates by ten times [39].

Nicotine replacement should be a first-line treatment, followed by nicotine partial agonist such as varenicline and bupropion. Transdermal nicotine substitution does not increase opioid use or post-operative pain [40].

86.7 Opioids

Patients on chronic opioids will have developed tolerance to their effects and be liable to withdrawal symptoms if they are ceased. Autonomic disturbances associated with withdrawal can be treated with clonidine either given orally, transdermally or intravenously.

Patients on preoperative opioids are at higher risk of more severe post-operative pain. It is unclear whether this is a result of tolerance or the development of opioid-induced hyperalgesia

[41]. Both tolerance and hyperalgesia are thought to result from the internalisation of opioid receptors and alterations in intracellular processes. Tolerance can be overcome by increasing the dose of opioid, except in the case of buprenorphine, where other opioids have less affinity for the μ-receptor. Hyperalgesia also seems to involve mechanisms in the spinal cord, where NMDA receptors lead to wind-up. In the central nervous system, alteration in the balance between endorphin and dynorphin may play a role. Opioid-induced hyperalgesia can occur acutely. It was hoped that pre-emptive analgesia, with opioids given before surgical incision, would reduce post-operative pain, but the opposite has been found [42]. A clear demonstration of opioid-induced hyperalgesia is seen in patients who receive remifentanil, an ultra-short-acting opioid, as part of their anaesthetic. There is a higher incidence of pain post-operatively and increasing doses of opiates seem to lead to greater hyperalgesia and pain experience.There is some evidence that this phenomenon can be reduced by ketamine, in low doses of 0.2–0.4 mg/kg [43].

Those on higher doses of opiates may be at risk of opioid-induced ventilatory impairment, especially with doses of opiates above 100 mg oral morphine equivalent daily dose (OMEDD), in combination with benzodiazepines, gabapentinoids and quetiapine. Other factors that increase the risk are obesity, obstructive sleep apnoea, smoking, chronic lung disease and other sedatives such as alcohol. Patients who have been on opioid substitution treatment (OST) or long-acting opioids should be monitored closely in the post-operative period, where the residual effects of their normal medication can combine with post-operative opioids, anaesthetics and the negative effects of surgery on respiration, particularly in the case of thoracic and abdominal surgery.

86.7.1 Illicit Opioids

Those taking illicit opioids may be liable to be treated more judgementally by healthcare professionals than those on prescribed opioids. The actual opioid content of illicit drugs is more variable [44]. The opioid may be adulterated, "cut" with inactive substances, which may contribute to tissue damage and infection if they are injected. More recently, the adulteration of heroin with fentanyl and carfentanil has led to an increase in overdoses, especially in North America.

86.7.2 Prescribed Opioids

The dose of prescribed medication should be verified with the patient's normal prescriber or dispensing pharmacist. Prescribing monitoring schemes can identify patients who have multiple prescribers or dispensing pharmacies, which may indicate aberrant drug use. The possibility of patients having diverted their prescribed medication should be borne in mind if they become sedated when given their normal stated dose. In some situations, urine drug screening is a low-cost and rapid method of confirming the presence or absence of expected opioids. Urine drug screen may also reveal additional substances such as benzodiazepines. To obtain a more accurate screen, chromatography may be considered.

86.8 Opioid Substitution Therapy (OST)

There are different considerations for patients on methadone or buprenorphine (usually prescribed in combination with naloxone sublingually), and there is some debate about the recommendations for buprenorphine. Buprenorphine is a partial μ- and κ-agonist and it has a higher affinity for the μ-receptor than other opioids. This prevents patients from obtaining any euphoric effects, but may also prevent any analgesic benefit from additional opioids. It has a long duration of effect; 24–72 hours can make post-operative pain management particularly problematic [45].

Patients on buprenorphine have been found to be hyperalgesic in response to the cold pressor test and to not respond to morphine [46]. Recommendations are based on case reports, ret-

Table 86.5 Recommendation on buprenorphine OST

Recommendations on pain management in patients on buprenorphine OST	
Recommendation	Benefits and limitations
Use higher doses of short-acting opioids + OST [47]	Single case report, risk of respiratory depression and poorly controlled pain
Continue OST with PCA [48]	Retrospective study
Increase OST dose [49]	Ceiling effect at 32 mg buprenorphine daily
Reduce OST dose by 2 mg every 2–3 days to completely discontinue 3 days before surgery	Risk of relapse in use of illicit opioids, expert consensus
Substitute methadone 30–40 mg, can be increased to manage withdrawal symptoms	Expert consensus
Divide OST to 3 daily doses	Expert consensus

rospective case series and expert opinion (Table 86.5).

Patients on methadone can continue their normal maintenance treatment. This can be split into three times a day, although this is not supported by any evidence, and the rationale is unclear in view of its long durations of action. Patients on methadone may have prolongation of the QT interval, which should be screened for with an ECG. Other drugs affecting the QT interval, such as ondansetron and droperidol, should be avoided or used with caution. In common with patients on buprenorphine, there may be opioid-induced hyperalgesia and an increased risk of respiratory depression.

86.9 Intoxication

The main features of acute intoxication are respiratory depression and reduced conscious level, which respond to the administration of naloxone. Initial administration of small amounts, incrementally, such as 20–40 micrograms at a time, is usually sufficient to restore adequate respiratory drive and improve conscious level, without precipitating withdrawal. Of course, naloxone has a short duration of 30–60 minutes, so an infusion should be started and the patient cared for in a high-dependency environment, where their condition can be closely monitored. The infusion rate will normally be between 0.5 and 0.75 of the initial effective bolus per hour. It might be necessary to admit the patient to an intensive care unit for airway and ventilation management.

86.10 Withdrawal

Opiate withdrawal is uncomfortable but has not been documented to be fatal. Reassurance and an empathic non-judgemental approach can help the patient settle. Clonidine, hyoscine, loperamide and benzodiazepines can be helpful.

86.11 Assessment of the Patient for Anaesthesia

86.11.1 Physical

Venous access may be difficult and the patient may be the best guide of where to find a patent vein. The use of ultrasound to locate vessels can be very helpful. If a general anaesthetic is planned, an inhalational induction with volatile anaesthetic can be used.

Patients may have coexisting cardiorespiratory disease and often have an irritable airway, due to smoking. Dentition may be poor, with broken or fragile teeth.

86.11.2 Infections

Universal precautions should be used, where there is a possibility of previous intravenous drug use, in case of hepatitis, HIV or other bloodborne viruses. Assessment should include the consideration of the possibility of endocarditis, heart valve damage, immunosuppression and opportunistic infections. Osteomyelitis is not uncommon and vertebral osteomyelitis can spread to abscess formation in the epidural space which may compromise the spinal cord and inter-

fere with spinal or epidural anaesthesia. In the cervical spine, there may be an increase in pressure on the spinal cord with positioning for laryngoscopy.

86.11.3 Perioperative Pain Management

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of tissue damage. The management of pain has evolved to recognise that the distress and suffering as well as social and psychological factors are at least, if not more, important than biomedical ones [50].

Wherever possible, the use of regional and local anaesthetic techniques can avoid most of the problems associated with these patients. Single-injection local anaesthetics have a limited duration of action to a maximum of 24 hours, and there can be difficulty controlling pain when the block wears off, often in the middle of the night. For this reason, the use of a nerve catheter and local anaesthetic infusion for 3 days postoperatively is advisable.

Multimodal analgesia with paracetamol and nonsteroidal anti-inflammatory drugs reduces opioid requirements. NSAIDs have better analgesic effect for dental and musculoskeletal pain than opioids.

The use of adjuvants such as ketamine, clonidine and lignocaine has evidence for improving perioperative pain management [51, 52]. Gabapentin and pregabalin have shown some evidence of benefit in acute pain management [53].

86.12 Prediction of Poorly Controlled Post-operative Pain

Studies of the relative risk factors have used heterogenous study design and methods of determining risk. The following table is derived from a recent systematic review and meta-analysis [54] (Table 86.6).

Table 86.6 Risk factors for poorly controlled post-operative pain

Predictive factor	Increase in risk
Sleep difficulties	OR 2.32 [95% CI 1.46 to 3.69]
History of depressive symptoms	OR 1.71 [95% CI 1.32 to 2.22]
Use of preoperative analgesia	OR 1.54 [95% CI 1.18 to 2.03]
Smoking	OR 1.33 [95% CI 1.09 to 1.61]
Female sex	OR 1.29 [95% CI 1.17 to 1.43]
History of anxiety symptoms	OR 1.22 [95% CI 1.09 to 1.36]
Presence of preoperative pain	OR 1.21 [95% CI 1.10 to 1.32]
Young age	OR 1.18 [95% CI 1.05 to 1.32]
Higher BMI	OR 1.02 [95% CI 1.01 to 1.03]

86.13 Other Substances Cannabis

Legalisation and increasing social acceptability have led cannabis to be widely used. Often patients have a tachycardia, and drugs which might exacerbate this, such as ephedrine and ketamine, should be used cautiously [55]. The airway may be irritable with an increased risk of coughing and laryngeal spasm and patients are liable to have COPD and other smoking-related diseases. There has been inconclusive evidence of any benefit in the use of cannabis or cannabinoids in the treatment of pain. In a recent review of chronic pain, the number needed to treat for obtaining 30% relief of pain was 24 and the number needed to harm was 6 [56].

The selective breeding of cannabis plants with a higher concentration of THC (skunk) has led to an increase in dysphoric and psychotic symptoms.

86.14 Synthetic Cannabinoids

These compounds are a diverse group of chemicals which act to the CB1 and anandamide receptors. They can cause negative symptoms such as nausea, vomiting, palpitations, anxiety, confu-

sion, coordination problems and convulsions. Deaths have occurred directly and also due to adulteration with brodifacoum, rat poison, thought to extend the duration of effect.

86.15 Cocaine, Amphetamines and Methamphetamine

The main problems in the perioperative period are due to sympathetic overactivity, caused by inhibition of the presynaptic reuptake of dopamine, noradrenaline and serotonin. Hypertension and tachycardia can cause myocardial ischaemia. Use of β-blockers can lead to unopposed α-effects causing coronary vasoconstriction. Propranolol is not recommended and there is debate about the safety of esmolol and labetalol. Nitroglycerine, phentolamine, verapamil, benzodiazepines and aspirin have been used. Dexmedetomidate may be useful in reducing the risk of cocaine-induced seizure.

Thrombocytopaenia can occur due to vasoconstriction and increased platelet aggregation. Renal failure has been reported, possibly due to vasoconstriction or to rhabdomyolysis.

Patients should be advised to abstain from cocaine for at least one week before an elective operation.

86.16 Hallucinogens, Ecstasy and Other Club Drugs

Psilocybin, mescaline, lysergic acid diethylamide (LSD) and phencyclidine (PCP) are hallucinogens, inducing hallucinations, distortion of perception and anxiety. They can cause sympathetic overactivity with hypertension and tachycardia. PCP can induce coma with muscle rigidity and nystagmus.

3,4-Methylenedioxymethamphetamine (MDMA) is also known as ecstasy. Sympathetic overactivity, with dehydration, hyperthermia, renal, hepatic and cardiac problems, can ensue.

γ-hydroxybutyrate (GHB) was used as an anaesthetic in the past, but was abandoned due to side effects. It produces ecstasy-like symptoms.

Ketamine is derived from PCP. The main features that are seen are sympathetic activation and reduction in conscious level, which will interact with anaesthetic actions.

86.17 Factors That May Improve Post-operative Care for Individuals with Substance Use Disorder

The evidence for a particular approach to the perioperative management of people with substance use disorder seems to be based on consensus and expert opinion, rather than research evidence. The main consideration should be safety and minimising the risk of exacerbating substance use. For all patients, a multimodal analgesic technique with the use of non-pharmacological strategies has the best results [54]. Preoperative preparation of patients, improving physical fitness and addressing psychosocial factors, is showing promising results, but instituting this takes a cultural shift in attitudes which has been difficult to achieve [57].

86.18 Components of Enhanced Recovery After Surgery [58]

86.19 Conclusion

The focus in managing patients with substance use disorder, presenting for anaesthesia and acute pain management should be on how to provide the safest and best care for patients who are in a vulnerable and fearful situation.

Addiction specialists have a clear understanding of the role that traumatic experiences, social circumstances, mental health issues and genetic predisposition have in leading to the complex neurobiological condition of SUD or addiction. HCPs involved in anaesthesiology and acute care may see the patient with SUD in a less favourable light than patients with other mental health conditions. We hope that this brief overview of the

subject will inspire clinicians to learn more and to know what to do to improve the patient's experience [59].

Key Points

- Substance use disorders may have biomedical and pharmacological implications for patient care in the perioperative period.
- Social and psychological factors may also affect care.
- The priorities should be to ensure patient safety and a successful outcome from surgery.

Clinical Relevance

Having an understanding of substance use will help clinicians provide more humane and patient-centred care. For more in-depth details of post-operative pain management, we would refer the reader to *Acute Pain Management: A Practical Guide*, Macintyre P and Schug S. Fourth Edition, 2014.

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Chronic Pain and Dependence

87

Stephen Gilbert

Contents

S. Gilbert (✉)
North Queensland Persistent Pain Management Service, Townsville Hospital, Townsville, QLD, Australia

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Abstract

Chronic or persistent pain is a common problem, affecting around 20% of the population. It can be complex; social, psychological and biological factors are entwined in its causes and effects. The societal factors leading to the increased recognition and demands for treatment of chronic pain have focused on the biomedical aspects and the use of the WHO analgesic ladder, which was intended for treatment of cancer pain. Despite initial optimism, the treatment of chronic non-malignant pain, in the same way as cancer pain, has been found to be ineffective for pain management or improvement in quality of life. Indeed, the opposite effects of increasing disability and dependence seem to be the result, with the epidemic of opioid-related deaths being the tip of the iceberg.

This chapter briefly outlines the underlying mechanisms of pain and dependence, but the main focus is on possible strategies to reduce the potential harms arising from the pharmacological treatment of chronic pain.

Keywords

Chronic · Persistent · Pain · Opioids Dependence

87.1 Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or expressed in terms of such damage' [1]. Chronic or persistent pain has been defined as pain that has been present for more than 12 weeks or 3 months. This is a largely pragmatic definition as, when conducting research on treatments for pain, we might expect tissue healing and natural resolution of pain within 6–8 weeks. Hence, the natural course of events, where pain resolves due to healing of the tissues, might confound whether improvement was due to a treatment. Another perspective is to define pain as chronic, when it has persisted after we would normally have expected tissue healing to be complete. There is debate about whether to use chronic or persistent as a description. ICD 11 has used chronic in its classification [2].

Epidemiological studies have found that 20% of the population lives with chronic pain and it is severe and disabling in around 8% [3]. In the Lancet Global Burden of Disease survey, back pain and headache were the two leading causes of years lived with disability. It was noted that there was a 38% increase in opioid use disorder from 1990 to the 2017 survey [4].

Over the last 60 years, there have been great advances in the understanding of the underlying neurobiology which contributes to the experience of pain. The biological causes of pain, are entwined with social and psychological factors, which have a strong influence on the experience, suffering, disability and the persistence of chronic pain. This understanding has been expressed as the biopsychosocial or sociopsychobiomedical model of pain [5].

87.2 Nature of Chronic Pain

Pain can be classified as nociceptive, neuropathic or nociplastic (see Table 87.1).

87.3 Nociceptive Pain

Healthcare training and the general societal understanding of pain have focused on nociceptive pain, with the perception that pain is usually the symptom of tissue damage or an underlying disease. Advances in medical science have enabled diagnosis and treatment, but at the same time have led to increased detection of incidental findings on investigations. One of the areas where this is most problematic is in imaging for back and neck pain. Changes in MRI scans are found in the majority of the population as they age; for instance, 'disc degeneration' is found in 80% of

Table 87.1 Pain classification

Nociceptive	Neuropathic	Nociplastic
Due to activation of nociceptors Signals tissue damage or protects from potential tissue damage	Due to a lesion or a disease of the somatosensory nervous system Continues due to abnormal nerve function Not protective	Due to altered activity in an intact nervous system – formerly called *central sensitisation* Non-noxious stimulation causes pain due to gain of function Overprotective
Tissue damage Noxious heat or cold Noxious pressure Noxious chemical stimulation Inflammatory mediators	Neurological symptoms Plausible cause of nerve damage Abnormal neurological examination Findings on investigations such as nerve conduction tests, MRI and nerve biopsy	Allodynia and hyperalgesia No evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain

asymptomatic people in their 50s [6]. This can lead to attribution of a condition such as back pain to underlying tissue damage, although there is conclusive evidence that biomedical treatment is often useless or even harmful [7]. In the case of true nociceptive pain, due to tissue damage, such as a fractured bone, cancer [8] or post-operative pain [9], analgesic drugs are reasonably effective in the majority of patients. Of course, detection and treatment of treatable pathology are important. The use of 'Red Flags' in back pain can help to avoid masking of a treatable disease, but it is most important to maintain an open and unbiased mindset, rather than a checklist or screening approach [10, 11].

87.4 Neuropathic Pain

Pain due to a lesion or disease of the somatosensory nervous system accounts for a minority of all chronic pain. A systematic review found a wide range of estimates of prevalence from 1% to 17% of the general population [12]. This variability may be due to a change in the definition of neuropathic pain from dysfunction to damage, and the diagnosis may be overestimated by relying solely on questionnaires. It can be classified as possible, probable or definite, by assessing the history, examination and investigations as illustrated in Fig. 87.1.

Most back pain is musculoskeletal – Red flags are to make us think "is there something else I should consider or investigate?"
May not need immediate action – Look for improvement with low back pain MSK treatment or evolution of symptoms with time
Previous history malignancy (however long ago)
Age < 16 or > 50 with new-onset pain
Weight loss (unexplained)
Previous longstanding steroid use
Recent serious illness
Recent significant infection – IV drug use, HIV, TB
Nonmechanical pain – Worse at rest or lying down
Thoracic pain
Fever, rigors or night sweats
General malaise
CAUDA EQUINA SYNDROME IS A SURGICAL EMERGENCY REQUIRING URGENT IMAGING AND SURGICAL OPINION.

87.5 Nociplastic Pain

The majority of chronic pain is nociplastic in nature. Stimuli that would not normally be painful (non-noxious), such as light pressure, changes in temperature and sitting or standing for too long, cause pain. Previously this was termed central sensitisation, and the IASP adopted the new terminology, nociplastic, in 2017 [14].

The details of the mechanism behind this phenomenon have been elucidated to an extent. There is increased activity in the nervous system, descending facilitation and wind-up of pain mechanisms. Biological, psychological and social factors are all important in the development and maintenance of this chronic pain condition. Unfortunately, although pharmacological treatment has limited effect, this has been found to be the first strategy employed in several studies [15].

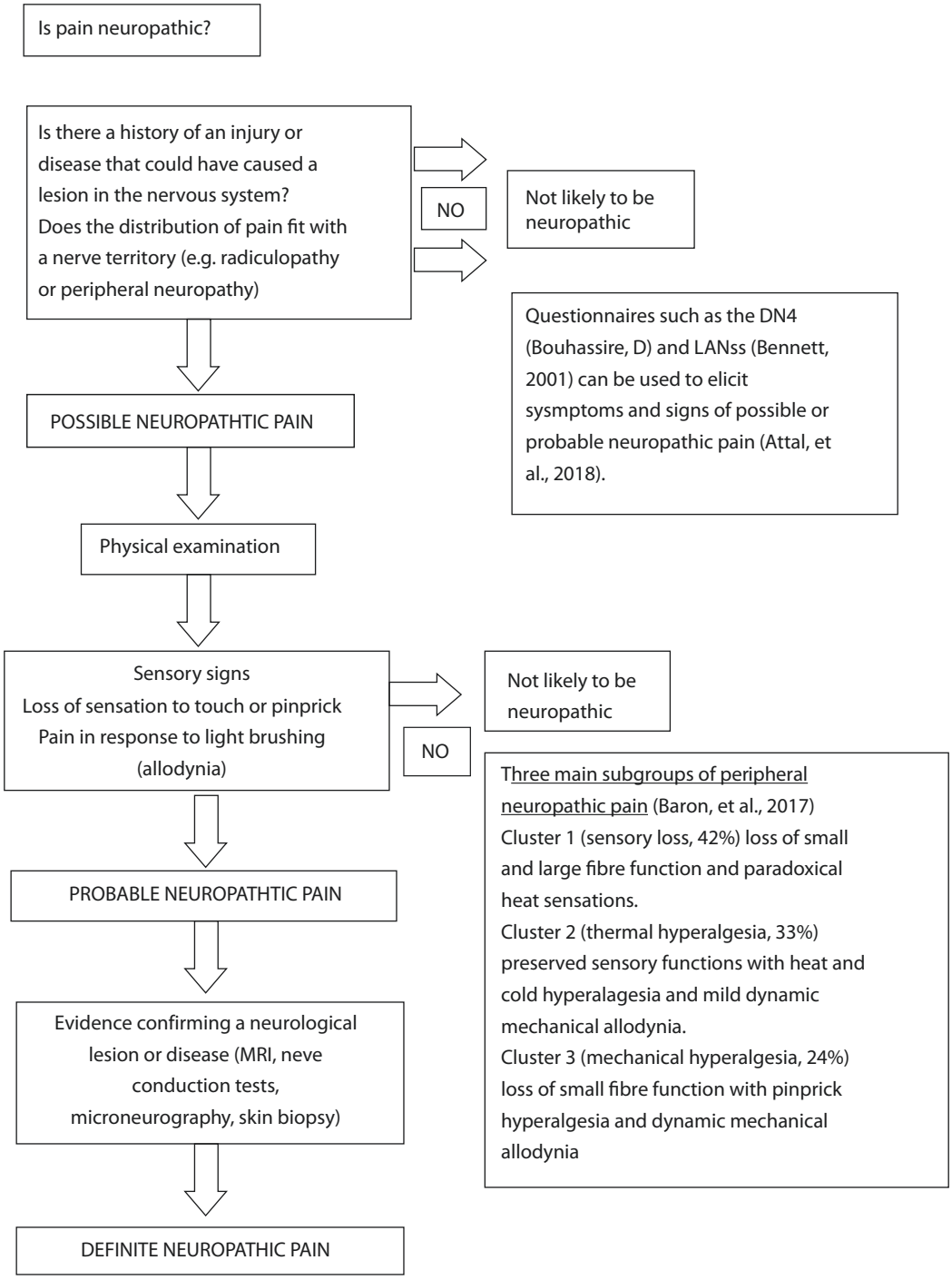

Fig. 87.1 Diagnosis of neuropathic pain [13]

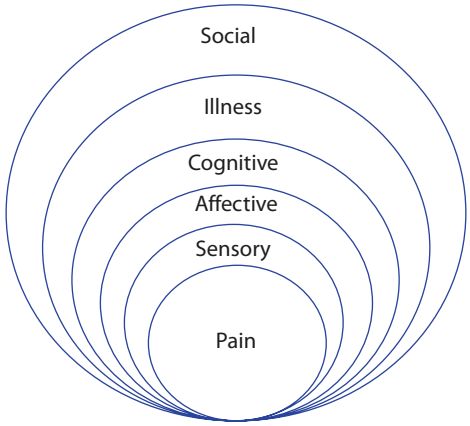

Fig. 87.2 The biopsychosocial model of pain

87.6 Biopsychosocial or Sociopsychobiomedical Model

The onion diagram of the biopsychosocial model was introduced by Engel in 1977. The main factors in the development of persistent and disabling pain seem to be psychosocial. This research was formulated into the "Yellow Flags" approach to identify the psychosocial risk factors for chronicity, which was revised in 2011 to incorporate orange, blue and black flags [16].

The aim of the flags system is to address psychosocial factors early; however, the Lancet Back Pain papers of 2018 identified that the majority of healthcare professionals preferentially take a biomedical approach [7].

The flags can be assessed in primary care and risk factors, which are amenable to modification, and are identified and addressed. The flags can be remembered by the mnemonic 'ABCDEFW' (Fig. 87.2).

- *Attitudes and Beliefs:* feeling they have something serious causing their problem. Thinking the pain has to be completely gone before they can start getting back to normal activities. These beliefs can lead to catastrophisation, a negative mental set, comprising magnification, rumination and helplessness.
- *Behaviours:* development of disability role, rest and passive rather than active treatments, with external locus of control, use and abuse of medication, continually seeking medical opinions and treatments.
- *Compensation**: work-related accidents, compensation and perceived injustice can create a conflicted mindset, where there is an adversarial system in which the person has to prove how much suffering and disability the pain has caused. Multiple medical and legal opinions are often confusing, not necessarily taking the patients' long-term interest as the first priority.
- *Diagnosis:* often healthcare professionals can give confusing and conflicting information about the likely cause of the pain. There is widespread belief that tissue damage or 'degenerative' changes are the cause of musculoskeletal pain, such as low back pain. Imaging reports are often worrying for patients and poorly understood by healthcare professionals.
- *Emotions**: patients with other emotional difficulties such as ongoing depression and/or anxiety states are at a high risk of developing chronic pain. It is natural that isolation from normal social contact leads to mood changes.
- *Family**: those close to the patient may be fearful or catastrophising, being overprotective and solicitous. Often people with pain feel they are not believed, leading to breakdown in relationships and compassion fatigue in the family and friends.
- *Work**: if there are difficulties, people are more likely to develop chronic problems.

*In the revised flag system.

- *Black Flags*: compensation, family, legislation restricting return to work and heavy work or duties that cannot be modified.
- *Blue Flags*: Work which is perceived to be too onerous or likely to cause further injury; belief that supervisors or colleagues are unsupportive or unsympathetic.
- *Orange Flags*: psychiatric conditions such as clinical depression or personality disorders.

Identification of significant psychosocial factors has been simplified to detect those at higher risk with the STarT Back questionnaire [17] (Fig. 87.3).

Low Risk: one-off consultation, examination and reassurance to promote self-management. Avoid unhelpful language, provide written information.

Medium Risk: building on the above, with the aim to restore function, including work. Course of physiotherapy. Some patients may need specialist referral.

High Risk: builds on the above, with the aims to reduce pain and improve functioning. More skilled physio, with additional training enabling them to elicit and address more complex psychosocial issues.

The Keele Start Back Screening Tool		
Thinking about the **last 2 weeks** tick your responses to the following questions	Disagree 0	Agree 1
1. My back pain has spread down my legs at some time in the last 2 weeks.		
2. I have had pain in the shoulder or neck at some time in the last 2 weeks.		
3. I have only walked short distances because of my back pain.		
4. In the past 2 weeks I have dressed more slowly because of back pain.		
5. It's not really safe for a person with a condition like mine to be physically active.		
6. Worrying thoughts have been going through my mind a lot of the time.		
7. I feel my back pain is terrible and it's never going to get better.		
8. In general I have not enjoyed all the things I used to enjoy.		

Overall, how bothersome has your back pain been **in the last 2 weeks?**

Not at all	Slightly	Moderately	Very much	Extremely
☐	☐	☐	☐	☐
0	1	2	3	4

Total score (all9) _____ Sub Score (Q5-9) _____

Fig. 87.3 The STarT Back Screening Tool. (© Keele University 01/08/07 Funded by Arthritis Research)

The use of this approach was found to allow the identification of higher-risk patients and more effective and economical treatment.

87.7 Elements of the Problems Leading to Increased Prescribing and Dependence in Chronic Pain

As outlined in the chapter on perioperative issues and acute pain, there was a societal change in attitudes towards the treatment of chronic non-cancer pain following some influential publications in the 1980s and 1990s [18, 19]. There was increased awareness of the prevalence of chronic pain and the development of campaigns to recognise chronic pain as a vital sign or a disease as well as the perception of pain relief (i.e. the analgesic ladder) as a human right [20]. The resulting increase in prescription of opioid and other pain medications was augmented by influence from the pharmaceutical industry, which claimed that addiction or dependence occurred in less than 1% of people treated for pain. Unfortunately, this has escalated to the point where opioid use and related harms have been considered a crisis, with opioid overdose becoming the leading cause of death in Americans under 50 [21]. Less dramatic, but still significant and worrying, increases in opioid-related harm have been found in the UK, Australia and Europe [22, 23].

At the same time, the hopes for improved pain relief and reduced disability have not been realised. An early publication, showing improvement in back pain, which was widely cited, studied only 38 patients, finding a moderate improvement in pain, but not in employment or ability. Pain management became 'problematic in two patients, both with a prior history of drug abuse'. The conclusion was 'opioid maintenance therapy can be a safe, salutary and more humane alternative to the options of surgery or no treatment in those patients with intractable non-malignant pain and no history of drug abuse' [24]. In 2004, a systematic review found moderate efficacy, but poor tolerability, for opioids, with only 44% of patients continuing with opioids for between 7 and 24 months. The main problems were constipation, nausea and somnolence, with insufficient data to define the risk of addiction [25]. A large Danish cross-sectional study showed worse pain and poorer quality of life in those prescribed with opioids for chronic pain [26].

More recent studies have found that opioids are not superior to non-opioid analgesic drugs even for acute pain, due to a limb injury [27]. In an episode of back pain, their use may increase disability and reduce the likelihood of recovery [28, 29] while not achieving the aim of reducing pain when compared to non-opioids [30].

While the focus has been on opioids, there has also been increasing prescription of benzodiazepines, gabapentinoids, antidepressants and quetiapine, which are synergistic in causing sedation and adverse events with the opioids [31].

87.8 Neurobiology of Dependence and Pain

Opioids have been used for medicinal purposes and for their psychotropic properties since ancient times, with documentation of the use of opium on a Sumerian tablet before 2000 BC [32]. The synthesis of diamorphine in the nineteenth century, by Bayer, was advertised as a breakthrough in maintaining the beneficial analgesic effects of opiates while overcoming the drawback of addiction [33]. Unfortunately, subsequent efforts to synthesise the ideal analgesic, free of undesired side effects or risks, have been similarly ill fated.

The opioid receptors have been classified into three subtypes: μ, κ and δ (mu, kappa and delta), which are G protein-coupled receptors with their endogenous ligands being the endorphins and enkephalins. Activation of the receptor presynaptically inhibits Ca^{2+} channels and postsynaptically hyperpolarises K^{+} channels. Opioid receptors are widespread, throughout the nervous system, with their activation in the spinal cord, periaqueductal gray matter and raphe magnus being most important for analgesic effect. There is inhibition of GABAergic activity in the ventral tegmental area, which was thought to be associated with reward, due to dopaminergic receptors. More recent evidence

points to the rostromedial tegmental nucleus as well as input from the nucleus accumbens. Effects in the hippocampus may be associated with memory of drug effects. Norepinephrine in the locus coeruleus and CCK and NK1 in brainstem mechanisms may also be associated with unwanted or adverse effects. How the endogenous ligands act within the nervous system to modulate many behavioural and physiological phenomena, such as attraction, bonding, learning, sleep, immunity and hormone production, is still incompletely understood. The complexity of these systems and their importance in our experience perhaps make the prospect of discovering an agent that acts as an analgesic, while not having other psychological and behavioural effects, unlikely [34].

Research has focused on differentiation of the analgesic effect of the opioids, which is thought to be mediated through the G protein complex (GαI/O unit) on the cell membrane, while side effects may be caused by activity on β-arrestin2, an intracellular moderator of G protein activity.

β-arrestin2 leads to endocytosis of opioid and also dopamine and cannabinoid receptors. The discovery that β-arrestin2 knock-out mice had preserved the analgesic efficacy of opioids, with less side effects and development of tolerance, has led to the synthesis of ligands with no activity at β-arrestin2, but these are at an early stage of development. The complexity of intracellular actions of the arrestins may lead to other effects on immunity, apoptosis and autonomic and hormonal activity [35].

It has been hoped that drugs, such as tramadol (with μ-opioid, noradrenaline and serotonin reuptake activity) and tapentadol (with weak μ-opioid and noradrenaline reuptake activity), might be less liable to lead to dependence, but the literature does not seem to support this hope [36, 37] (Fig. 87.4 and Table 87.2).

The majority of research has focused on the problem of addiction to opioids, but there is increasing epidemiological evidence for dependence on other classes of drugs, substances and behaviours in people with chronic pain. There is overlap in the brain areas involved in pain and addiction, with aversion, craving, reward, conditioning and withdrawal common to both conditions [38]. Many people with chronic pain will meet the DSM-5 criteria for substance use disorder.

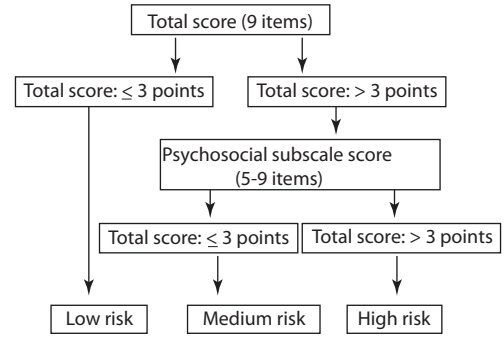

Fig. 87.4 The STarT Back Screening Tool scoring system

Table 87.2 DSM-5 criteria for substance use disorder – Mild 2–3, Moderate 4–5, Severe 6 and Greater

1.	Taking the substance in larger amounts or for longer than you're meant to.
2.	Wanting to cut down or stop using the substance but not managing to.
3.	Spending a lot of time getting, using or recovering from use of the substance.
4.	Cravings and urges to use the substance.
5.	Not managing to do what you should at work, home or school because of substance use.
6.	Continuing to use, even when it causes problems in relationships.
7.	Giving up important social, occupational or recreational activities because of substance use.
8.	Using substances again and again, even when it puts you in danger.
9.	Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the substance.
10.	Needing more of the substance to get the effect you want (tolerance).
11.	Development of withdrawal symptoms, which can be relieved by taking more of the substance disorder.

87.9 Strategies to Reduce Opioid Dependence and Harm in Chronic Pain

The history of the evolution of the opioid prescribing crisis and the measures taken to attempt to counter it are well covered in the literature [21].

87.9.1 Reducing Supply

The Center for Disease Control (CDC) in the USA drew up guidelines intended to reduce over-prescription [39]. These have been taken as a model for moderating opioid use in other countries.

There are 12 main recommendations of the CDC guidelines.

The aims of the guidelines are to improve the assessment and evidence-based treatment of chronic pain and encourage clinicians to evaluate the effectiveness, adverse effects and risks: in other words, good medical care.

Since their introduction in 2016, there has been a fall in opioid prescription in the USA [40], but there has been controversy that patients have been forced to taper their opioids, that they have been denied the right to pain relief and that doctors who have been identified as high prescribers have been targeted by regulatory authorities. A letter to Pain Medicine in 2019, with 104 signatories, called for a moderation of forced opioid tapering, especially where psychosocial support was not available [41]. Some clinicians have refused to prescribe opioids and pharmacies have refused to issue prescriptions. Perhaps as an unintended result, there has been an increase in the consumption of illicit heroin and fentanyl as well as of diverted drugs [42] (Table 87.3).

87.9.2 Monitoring Opioid Use

Prescription monitoring schemes have aimed to detect variation in prescribing and prevent multiple prescribers to the same patient [43]. This has been linked to a reduction in overdose mortality in Tasmania, but there is still concern that this approach will lead to a reduction in supply and an increase in illicit drug use. Urine drug testing to monitor compliance with treatment, limiting diversion and detecting illicit drug use, is still rarely carried out [44], due to lack of clinician education, expense and perceived or actual patient resistance to testing.

87.9.3 Reducing Risk

Providing naloxone and education to patients on high-dose opioids has been found to prevent overdose deaths, but there is limited prescribing due to lack of knowledge and expense [45]. There have

Table 87.3 CDC guideline for prescribing opioids for chronic pain — United States, 2016 | MMWR

Determining when to initiate or continue opioids for chronic pain	
1.	Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2.	Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3.	Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.
Opioid selection, dosage, duration, follow-up and discontinuation	
4.	When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5.	When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to =50 morphine milligram equivalents (MME)/day and should avoid increasing dosage to =90 MME/day or carefully justify a decision to titrate dosage to =90 MME/day.
6.	Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed.

Table 87.4 (continued)

7.	Clinicians should evaluate benefits and harms with patients within 1–4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimise other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.
Assessing risk and addressing harms of opioid use	
8.	Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (=50 MME/day) or concurrent benzodiazepine use, are present.
9.	Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring programme (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10.	When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11.	Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12.	Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioural therapies) for patients with opioid use disorder.

also been concerns that naloxone prescribing may lead to more risk. Opioid substitution with buprenorphine/naloxone has been found to prevent relapse and reduce the risk of opioid-induced respiratory depression, but in common with methadone opioid substitution, patients with chronic pain are reluctant to attend addiction services, and there is a lack of funded provision in any case, with less than 10% of patients with addiction being able to access an addiction service [21].

87.9.4 Substituting Other Medications or Therapies

It had been hoped that the introduction of access to medical cannabinoids would reduce opioid use and harms, but despite the legalisation of medicinal prescription in 2001 and recreational use in 2017 in Canada, there continues to be a high level of opioid prescription and harms [22]. Surgeries and interventions for back pain do not have convincing evidence of improving pain management or reducing medication use [7].

87.9.5 Opioid Reduction Programmes

There has been success with helping patients to reduce their opioids using motivational interviewing, psychological therapies and mindfulness [46]. Patients attending multidisciplinary pain management services may be better able to manage their pain and to reduce medication, but there is very limited access to specialised services; more than 90% of patients with chronic pain are seen in primary care.

87.9.6 Education

Many studies have found that there is very little undergraduate teaching on chronic pain [47]. The hope would be that improving knowledge would lead to better care; however increasing evidence, guidelines and resources seem to have made very little difference to the practice of prescribing medication, rather than good advice to patients. It is possible that engaging public health advice

could have more effectiveness than trying to educate healthcare professionals [7].

87.10 Relevance

Chronic pain is a common condition, affecting 20% of the population and chronic back pain is the leading cause of disability worldwide.

Patients with chronic pain may become dependent on medications, primarily opioids, but also other medications with psychotropic effects.

Helping patients to understand their pain better, to utilise pain management techniques and to reduce their medication can improve their quality of life and reduce the pain they experience.

87.11 Conclusion

The co-occurrence of chronic pain and dependence seems to have some foundations in neurophysiological mechanisms but is also strongly influenced by societal and cultural factors. The attempts to limit prescribing have led to antagonism between pro- and anti-opioid camps, with seemingly little understanding of the scientific evidence. There is a risk of a return to the days of opioiphobia, when adequate pain relief was denied, even to patients with cancer pain. Nevertheless, the improved understanding of chronic pain mechanisms and treatment, particularly non-pharmacological treatments with a sound evidence base, must hold out some hope for the future.

Societal factors have led to an increased recognition of chronic pain and its treatment using the analgesic ladder approach, which was intended for the relief of cancer pain.

There is an overlap of brain regions involved in chronic pain and addiction. People with chronic pain may resent being stigmatised as addicts and there is very limited access to addiction services.

Improved healthcare and public understanding of the non-pharmacological management of chronic pain and the importance of a mind-body approach, rather than a biomedical focus, may lead to a long-term change, but over the last 20 years, the trend has been in the opposite direction.

Key Resources for Patients and Professionals

New South Wales Pain Network http://www.aci.health.nsw.gov.au/chronic-pain

The Pain Toolkit https://www.paintoolkit.org/

International Association for the Study of Pain https://www.iasp-pain.org

American Pain Society http://americanpainsociety.org/

Key Points

– Opioids do not have good evidence for benefit for chronic or persistent non-malignant pain. Rather, they can increase disability and reduce the chance of recovery.

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COVID-19 and Substance Use Disorders: Syndemic Responses to a Global Pandemic

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Contents

Abstract

As this chapter is being written, the COVID-19 pandemic is having enormous impact upon the world. This is not only from direct mortality and morbidity due to the infection itself but also from its impact upon existing health services capacity which has been reoriented to cope. Worldwide infection control measures are causing socioeconomic upheaval. Deep emotional trauma and prolonged anxiety over facing the unseen and unknown are predicted to have lasting effects on individuals and communities. This includes an increase in drug and alcohol use, mental health conditions such as posttraumatic stress disorder, depression, somatisation and anxiety, lowered perceived health and reduced resilience to adversity.

Alongside this however are also huge advancements in medical science and unprecedented access to information and methods of communication through an ever-expanding digital infrastructure. Furthermore, there has been an increased understanding of the interrelatedness of various aspects of life, the so-

J. T. W. Teck (✉)
University of Glasgow, Scotland, Glasgow, UK
e-mail: j.tay-wee-teck.1@research.gla.ac.uk

A. M. Baldacchino
Population and Behavioural Science Division (Psychiatry and Addictions), University of St Andrews and NHS Fife, St Andrews, UK

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called determinants of health, and an explosion of multidisciplinary research approaches.

This chapter proffers to the reader a framework to understand the complexities of the COVID-19 pandemic in relation to the field of addiction medicine. The proposed syndemic response requires us to see addictions and substance use disorders as existing within multiple synergistic systems of social, economic, political and cultural contexts. It opens up opportunities for more effective and responsive multidisciplinary research, interventions and programmatic evaluations. Indeed, it is a good fit for current calls for research and programmes that enable society to prepare for the psychosocial and physiological challenges that lie ahead.

Keywords

Syndemic theory · COVID-19 pandemic
Complex systems · Substance use disorder
Addictions

88.1 Introduction

Few would argue that the COVID-19 pandemic is likely to be the worst public health emergency for a generation. COVID-19 has a high mortality rate (3–30 times that of seasonal influenza) and a high transmission rate (10 times more contagious than SARS). There is therefore a very real possibility of millions dying if the pandemic is not successfully contained [12]. The COVID-19 pandemic is also an economic crisis. The measures required to contain the spread of this disease, such as social distancing, lock-down measures and shielding, all involve a sharp reduction in economic activity. The direct impact of this unprecedented cessation of productivity is a predicted global recession, mass unemployment and debt crises [49].

Health and social services, already under strain from a decade or more of austerity following the last global financial crisis, have been overwhelmed in many countries. A redistribution of resources to manage the pandemic has resulted in the cessation of many services including those for the assessment and treatment or management of addictions [24]. Critically, in poorer, developing countries, or those without adequate investment in a social safety net, the COVID-19 pandemic will be a humanitarian crisis. The World Bank estimates that 49 million people will be pushed into extreme poverty, and the UN food agency has warned of multiple concurrent famines, with an additional 130 million pushed to the brink of starvation by the end of 2020 [67]. Basic social services such as education, health and policing will decline, with consequent increases in conflict, violence and crime.

The world is responding to the pandemic with relief measures to increase health services capacity, support those affected by public health measures and align incentives to comply with social distancing [23]. The duration of this crisis and containment phase is as yet unknown. It will however be followed by many countries undertaking recovery measures to transition out of significant socioeconomic upheaval.

What are the implications of these unprecedented events for people who use drugs and alcohol and people in need of addiction services? As with past global events resulting in socioeconomic upheaval, what are the opportunities and innovations that become possible? How do we understand, adapt, plan, design, implement and evaluate complex services and policies in the rapidly changing landscape the COVID-19 pandemic has brought to us? These are complex questions requiring us to factor in the pathogenic social contexts that people who use drugs and alcohol often experience which include socioeconomic disadvantages with low resilience and increased stigma, discrimination, homelessness and other inequalities in the upstream determinants of health [5, 6, 25, 58].

88.2 Syndemic Theory and Substance Use Disorders

The terms “syndemic”, a portmanteau of “synergy” and “epidemic”, “pandemic” and “endemic” have been used to explain the synergistic interaction of two or more conditions and

the social contexts in which these conditions develop [66] – synergistic in the sense that two or more agents or factors interact to produce a combined effect which is larger than the sum of their separate effects. A syndemics framework has been used most frequently in understanding human immunodeficiency virus (HIV) transmission, one of the leading causes of morbidity and mortality globally as a result of a communicable disease [7, 22, 54, 63]. Closely related with HIV transmission is injecting drug use, and so, unsurprisingly, a number of syndemics which include substance misuse disorder have been described in the literature (Table 88.1).

A key point about syndemics, and its relevance to populations suffering from addiction or substance misuse disorder, is that they include both disease and social epidemics. With reference to Table 88.1, we see that violence, unresolved family conflict, internalised oppression (referred to as homonegativity when in relation to the lesbian, gay, bisexual and transgender (LGBT) community), loss, trauma and homelessness are as much part of a defined syndemic as HIV, substance misuse disorder, and mental and physical ill health [43, 64, 66]. Epidemics within a syndemic framework is both psychosociological (social, structural and behavioural) and physiological [54, 66].

Ultimately, syndemics describe a heightened vulnerability to morbidity and mortality due to a variety of synergistically correlated systems. Syndemic theory is particularly useful at this time as we grapple with the challenges of the COVID-19 pandemic. For example, does the so-called "opioid epidemic" seen in Australia, North America and Scotland constitute an additional syndemic alongside the COVID-19 pandemic? Certainly, there are a number of ways in which this combination fits the syndemic definition. People with opioid dependence may have increased vulnerability to COVID-19 exposure due to the need to source their drug of choice or attend a pharmacy daily to access substitute treatment. They are vulnerable to disruptions in the drug markets which can result in experimentation with unfamiliar or more highly potent drugs. Social isolation, a necessary protective mechanism against COVID-19, increases the risk of a person who injects drugs as there is no one to help if the person experiences an overdose. The impact of COVID-19 in terms of the loss of social

Table 88.1 Examples of syndemics involving substance use

Components of syndemic	Acronym	Country	Reference
Substance abuse including injecting drug use, violence including childhood sexual abuse, intimate partner violence, non-partner sexual assault and trafficking and HIV/AIDS. Special emphasis is placed on the challenges that sufferers have to negotiate condom use or to avoid needle sharing	SAVA	USA, Malaysia, Kazakhstan, Sub-Saharan Africa	[26, 32, 39, 64]
Substance use which often co-occurs with mental illnesses such as depression, schizophrenia, manic depressive disorder mental illness, and overt familial conflicts which are acute or chronic all of which impact upon HIV outcomes	SUMIC	USA	[60]
Substance use during condomless intercourse, adolescent sexual abuse, violence, internalised homonegativity, and depression	SAVID	Tanzania	[1]
Physical health problems, abuse, mental illness, loss, instability, and substance use	PHAMILIS	USA	[42, 43]
Syndemic of lifetime mental illness, substance use disorders, and trauma and adverse perinatal outcomes	–	USA	[45]
Depression, alcohol and violence	DAV	India	[19]
Depression, substance use, violence, sexual stigma and homelessness, unprotected anal intercourse and HIV infection	–	151 countries	[61]

SAVA substance abuse, violence and HIV/AIDS, *SUMIC* substance use, mental illness and familial conflict non-negotiation, *PHAMILIS* physical health problems, abuse, mental illness, loss, instability and substance use, *DAV* depression, alcohol and violence

networks, heightened stress from news stories, and bereavement from the loss of loved ones may result in increased drug consumption. Overall, there is a heightened risk of drug-related deaths as a consequence of the pandemic [3].

As mentioned earlier, there are a number of syndemics involving both substance use and HIV. COVID-19 here would add a further burden of disease and social disadvantage [63] exacerbating the challenges people living with HIV face which often include social and economic inequalities, stigma and homelessness [2, 11, 21]. A further consideration is the syndemic we are observing between communicable (e.g., COVID-19) and non-communicable diseases (NCDs). One strategy of many countries to protect from COVID-19-related mortality was to advise those with preexisting conditions to remain shielded or cocooned at home. Generally, this has meant remaining indoors in their own home for up to 3 months, with essential needs such as food or medication delivered to them. These preexisting conditions are primarily NCDs such as diabetes, chronic obstructive pulmonary disease (COPD) and cardiovascular conditions [47]. Unfortunately, as Volkow [70] identifies, people with addictions are over-represented in the numbers with NCDs. For example, long-term smokers and people who smoke crack cocaine or heroin have higher rates of both pulmonary and cardiovascular disease, both of which increase the mortality rate from coronavirus-related severe respiratory syndrome.

88.3 Syndemics and Complex Systems Thinking

A fundamental problem with a theory of disease, which emphasises social contexts as much as it does physiological pathology, is that it does not easily lend itself to compartmentalised approaches. Complex systems thinking is an approach which supports the understanding of syndemics by examining its elements (the physiological and contextual constituents), the interconnections between them (policies, legislation, social networks and norms and individual-level risk factors) and the true purpose or function of the examined system. To clarify this last point, one would hope that systems are not intentionally designed to perpetuate a syndemic. Yet, a complex systems analysis can uncover the dynamic of a social context and reveal that in fulfilling one function, for example, the lockdown strategy to minimise public exposure to COVID-19, the unintended consequence could be the creation of a system that may perpetuate or contribute to a syndemic (for example by increasing incidences of domestic abuse and violence) [53].

Systems approaches use tools and frameworks to develop a shared understanding of the interconnected and interdependent components of a problem or situation [17]. From this shared understanding, causal relationships and leverage points within them can be identified. Examples of this are provided in Fig. 88.1 through causal loop diagram. With systems-wide leadership and cross-sectoral cooperation, coordinated action can then be carried out, targeting these leverage points to manage the problem.

A complex system has several defining characteristics including emergence, feedback and adaptation. *Emergence* describes properties or phenomena that develop from a particular combination of systems elements that cannot be predicted simply by adding all these elements together [44]. *Feedback* is a situation whereby an intervention on an element within a system reinforces or balances a (usually) desired change within that system [44]. *Adaptation* refers to behavioural changes that come about as a result of an intervention [44]. These terms are explored in more detail in a later section.

88.4 Empirical Methods to Study Syndemics

A critique of the application of syndemic theory is that insufficient attention is paid to the actual mechanisms of interaction between epidemics to form a syndemic. The issue here is that some so-called social epidemics are simply a constellation of risk factors which are added up to create a composite variable which is then

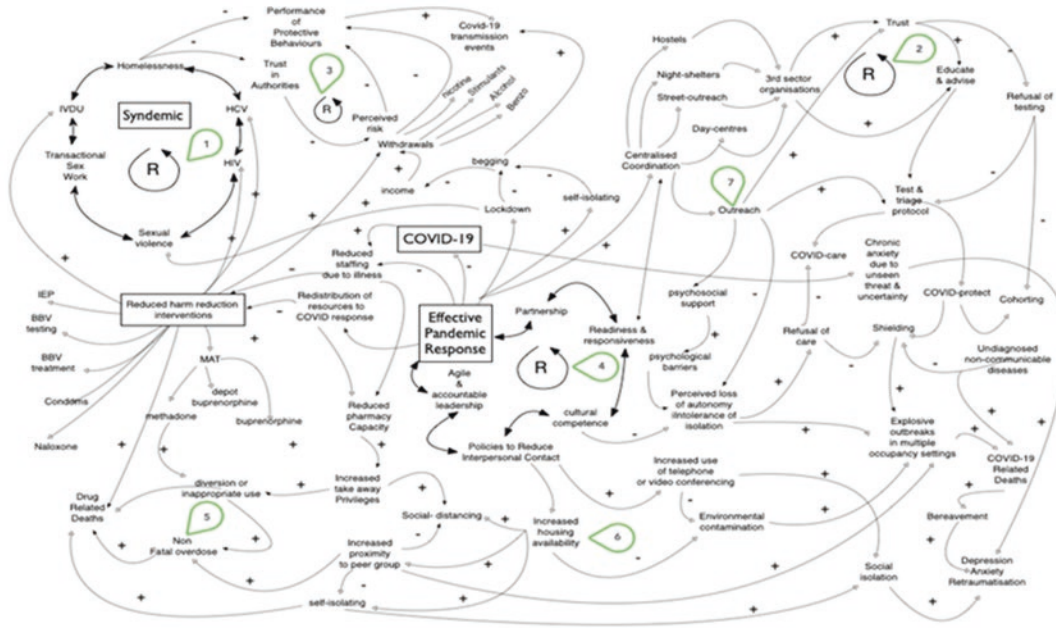


Fig. 88.1 Causal loop diagram identifying potential issues in managing the acute phase of the pandemic during a syndemic (In the diagram, the (-) symbol denotes a negative or reducing effect one variable has on the other, while (+) indicates the opposite. 'R' within a loop indicates a reinforcing series of variables.)

entered into an equation to identify a statistically significant effect [69]. Unfortunately, such practices ultimately undermine the effectiveness of the syndemic theory in not only understanding the impact of pathogenic social contexts on the mortality and morbidity of vulnerable groups but also in designing and accurately evaluating complex interventions. Table 88.2 illustrates three proposed mechanisms of interaction between epidemics to create a syndemic and suggested empirical methods to investigate them.

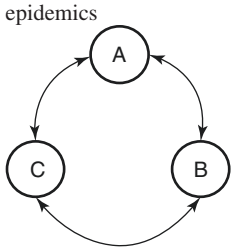
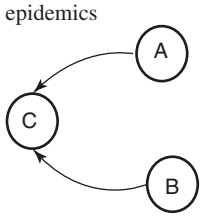
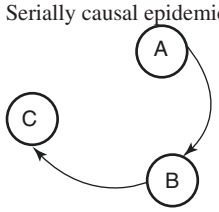
88.5 Applying Syndemic Theory and Complex Systems Thinking

We use a causal loop diagram to visualise an application of syndemic theory through complex systems thinking. Causal loop diagrams are a visual aid to show how different variables within a system are interrelated. There are other methods of visualising complexity which include graph visualisation, network visualisation, and node–link diagrams [56, 74]. The challenge is to describe complexity in a way that allows us to grapple with the issues it raises while not simultaneously oversimplifying and forgetting the bigger picture.

88.5.1 What Happens When a Syndemic Collides with a Pandemic? The Acute Phase

Figure 88.1 describes some of the elements involved in efforts to control the syndemic of homelessness, violence, and blood-borne viruses and their interaction with interventions to manage the COVID-19 pandemic in this vulnerable population. In recognition of the particular difficulties the homeless population would have in following public health advice during the pandemic, the National Health Service (NHS) in the UK developed specific and detailed guidance [48]. This guidance required local authorities to

Table 88.2 How do epidemics interact to form a syndemic?

Types of interaction	Description	Proposed research methods
Mutually causal epidemics 	This is the classic description of the syndemic, first described by Singer [64], i.e., the SAVA (substance abuse, violence, and AIDS) syndemic. Essentially epidemics A & B, B & C, and A & C are mutually causal	*Agent-based modelling.* Theory-led assumptions as to how a syndemic forms from different epidemics are explicitly detailed. The theorized modelled syndemic may be based on anthropological data, with emergent descriptions, compares against epidemiological data. Agent-based modelling can be used to simulate population-wide effects of complex interventions, for example, how stigma and trust in authorities may interfere with uptake of public health advice to limit COVID-19 spread. Examples include work by Zhang et al. [75] in investigating the obesity epidemic *System dynamics* is a mathematical modelling technique to frame, share understanding and unpick complex interactions [29]. Causal loop diagrams illustrated in Fig. 88.1 can be converted into stock and flow diagrams or can be used as they are to perform system dynamics via various computer programmes (Binder et al., [10]
Synergistically interacting epidemics 	In this syndemic, both A & B can cause C. When both co-occur, they have a synergistic effect which results in a much larger epidemic of C. This syndemic pattern is described by Singer & Clair [65]. Examples include the synergistic effects of alcohol abuse and HIV on the morbidity and mortality for patients with HCV coinfection [55]	
Serially causal epidemics 	This proposed pathway to a syndemic runs parallel with theories of accumulated risk exemplified by life course epidemiology [55]. Most topical in many countries currently is the association of adverse childhood experiences [8] as a life course determinant of adult health [27]	*Social network analysis* In the social network perspective, individual risk factors as well as the interconnections between key risk factors are important across the lifetime to explain how epidemics become a syndemic. In this model, low-prevalence health risks can become critical if they are strongly and closely connected to other risks. These high-density nodes become good targets for intervention. Examples of this include work by Tomori et al., [68] and McNally et al., [46] *Structural equation modelling* Hypothesised associations between several different variables are tested statistically. Examples include work by Khan et al. [35] to understand the impact of poverty and unemployment on alcohol abuse

Adapted from Tsai [69]

coordinate their resources with health, third sector organisations, and addiction services and included the following:

- Arranging appropriate accommodation, which at a minimum needed to have en-suite washroom facilities to minimise unnecessary interaction
- Identifying individuals needing to be shielded due to comorbid health conditions which increase their risk of poor outcomes from a COVID-19 infection
- Providing the conditions to support the shielding process for this identified group, to keep them separate from their peers and community
- Case finding through testing of symptomatic individuals and keeping them isolated for the duration of their illness (2 weeks) or until a negative test is obtained

The diagram is not intended to be a comprehensive illustration of every contingency but more to illustrate the implications of a syndemics perspective. The authors have some experience working through some of these pathways in the homeless and substance-using populations as the COVID-19 pandemic has unfolded [31]. The first reinforcing loop (1) is a visual representation of the synergistic effect of intravenous drug use, homelessness and violence upon HIV and hepatitis C (HCV) transmission. Opiate substitute therapy (OST), injecting equipment provision (IEP), condom supply, and HCV and HIV testing and treatment are important individual services. Collectively, as a complex public health intervention, these services have a greater impact than they do individually because of their impact on several elements of the syndemic. Furthermore, interrupting the provision of harm reduction services during the pandemic will potentially increase syndemic effects and contribute to drug-related deaths. In recognition of this, the Scottish government has specifically identified harm reduction and addictions services as essential through the pandemic [62].

Reinforcing loops (2) and (3) focus on the importance of trust as a driver for the success of public health interventions. Indeed, this has been highlighted as a key component in the acceptance of and compliance with public health advice [14, 15, 28, 52, 71]. Marginalised groups such as people who are homeless or people who use drugs have had a tendency to distrust institutions with authoritative powers, for example health or social services [50]. This mistrust is not the preserve of marginalised groups. The ability to retain the trust of the general public is increasingly seen as invaluable by many commercial, third sector and statutory institutions and organisations [30, 38].

There are a number of explanations for this which include media and government responses to actual and perceived failures within healthcare services [51], frustrations with healthcare rationing and unmet public expectations [20], and a cultural shift towards challenging the authority of experts, particularly if they are perceived to be detached from the realities of everyday life [72]. Indeed, and in line with Wilson et al., [73], syndemic theory can be useful here to understand the link between trust, structural violence (the suffering that comes from being stigmatised or oppressed due to socioeconomic status, homelessness or some other social factor), trauma and the motivation that individuals have to adopt health protective behaviours such as social distancing and self- isolating.

Carver et al. [18] unpick the service elements most valuable to the homeless population when seeking help for substance use disorders and identify the centrality of non-judgemental, compassionate and supportive relationships. Many frontline workers in the homeless sector have built these trusting supportive relationships with their clients over many years [9, 18, 40, 41]. Efforts to successfully remove barriers to homeless individuals complying with public health interventions to limit the spread of COVID-19 such as arranging suitable housing and welfare, nutritional, health and addiction support are contingent on building upon these invaluable, hard-won, human connections.

The restoration of public trust in healthcare requires an understanding of what is at the core of this concept [33], how it is lost and what strategies may return it [16]. Trust, relationships, social capital, reciprocity and similar concepts are difficult to measure or observe, yet are pivotal to the efficacy of public health interventions [73]. The application of syndemic theory necessitates that we understand psychosocial evidence in an equivalent way as physiological and biomedical evidence of the disease and offers a framework and the tools to do so.

It is worth at this point identifying examples of emergence, feedback and adaptation defined earlier in this chapter. Referring to (5) and (6) in Fig. 88.1, a transient rise in non-fatal drug overdose (NFO) rates among people who have a long history of homelessness may be an *emergent* property following interventions to enable them to self-isolate and practice social distancing. These interventions include rapid access to housing and the provision of opiate substitute therapy where required.

While protective against COVID-19 transmission, there are some issues which may increase

NFO rates at least in the early stages. This includes concentrating a large number of individuals with substance use issues in close proximity to each other, increasing their exposure to negative peer influences. During the initial phase of opiate substitute therapy, prescribers often do not provide take-home doses until the patient has a degree of social stability. In the context of the COVID-19 pandemic, this may not be possible due to reduced pharmacy capacity to supervise the daily consumption of medication or due to a need to shield the patient from unnecessary social contact. Individuals who have not been used to take-home doses may not take their medication as prescribed or be victimised by others because of their possession of valuable medication. In other words, in the short term at least, interventions widely seen as positive and supportive may increase substance-related harms.

The importance of *adaptation* is illustrated in (4). Bearing in mind that most countries have not the experience of managing a pandemic of this nature before, a region's COVID-19 response is more likely to be effective if authorities are able to coordinate their efforts rapidly and flexibly. To use the analogy of a plant growing around obstructions to reach the sunshine and thrive, agile and accountable governance and management structures, strong partnership working and culturally informed practices can contribute to the implementation of an effective COVID-19 containment strategy.

An example of *feedback* is observed here at (7). Marginalised groups such as people who are homeless or who use substance have often been through complex trauma. Fundamental to trauma-informed interventions are principles such as providing choice, collaboration and opportunities for empowerment, all of which are essentially about respecting the autonomy of the individual [4, 34]. While outreach interventions often closely fit with trauma-informed principles, public health messages which appear restrictive of civil liberties, freedom of movement or contingent on the tolerance of social isolation are likely to challenge this sense of autonomy. Getting the balance right here is essential to avoid situations of treatment refusal and to preserve the efficacy of interventions to reduce COVID-19 transmission events.

88.6 Multilevel Analysis

Based on theoretical models such as the risk environment framework [57, 58], the socioecological model [13] and the eco-social model [37], multilevel analysis looks at data nested within hierarchies. An individual is part of an interpersonal network within a community which accesses a health system which in turn is influenced by the political economy of the country. Failing to recognise these hierarchies and not accounting for them in mathematical modelling produce incorrect inferences. An example is how large-scale social forces such as economic upheaval or war can impact upon the individual's choices and risks leading to increased exposure to HIV (Tim [59]). Critically Bradley et al. [12] point out that the complexity involved in researching priority areas around COVID-19 necessitates the use of multidimensional and multilevel perspectives. Table 88.3 goes through some of the issues that will need to be considered both during the acute and recovery phases of the pandemic.

The micro-level here refers to the smallest level of interaction. This could be at the level of interpersonal relationships or communication and could also include the internalisation of perceived public opinion to form their self-identity. This term also indicates individual characteristics, capacities or abilities which influences behaviour.

The meso-level refers to organisational-level behaviour. This can range from individuals developing a sense of solidarity with each other and forming a community group, organisational behaviour in the face of a changing environment or social norms with a group.

The macro-level refers to large-scale patterns or influences, for example the impact of laws, the economy or widespread public opinion.

Table 88.3 Summary of problems and interventions in the acute and post-COVID-19 phases

Level of analysis	Acute phase(s) of uncertain duration Public health interventions and supportive relief measures	COVID-19 recovery phase Transitioning out of socioeconomic upheaval
Micro Individual-level interactions personal decisions and agency Individual values, strengths, capabilities, life experiences	*Problems* Distrust of authority Re-traumatisation Fear of isolation Alternate rationalities influenced by substance use Stigma	*Problems* Coping with disaster Loss and bereavement Trauma Chronic fear and anxiety Helplessness Increased substance use
	Opportunities Shared decision-making Co-producing services Build or attach to peer and frontline worker relationships Psychologically informed environments and interventions	*Opportunities* Maintaining capacity to provide mental health care Removing barriers to treatment Building upon collaboration across sectors, disciplines and service-users
Meso Organisational service delivery Third sector Community groups Community engagement Community level norms and practices	*Problems* Deprioritising of addictions services Re-deployment Staff illness Unresponsive management structures	*Problems* Re-orienting services towards future pandemic preparedness Catch up with urgent care delayed by the current pandemic Increased demand on services due to trauma and chronic anxiety and stress Unrecognised value of addiction and mental health services
	Opportunities Sharing experience and knowledge Digital platforms Advocacy Build upon networks, for example public health	*Opportunities* Developing novel technological solutions Targeting digital inequality Developing peer support, co-production and collaboration with service-users The definition of essential workers and their importance in society have changed for the better Collecting data and research to show the value of psychological and psychosocial factors in physical health responses
Macro Policy level (macro-economic, public health, social, legal) Public discourses Media	*Problems* Economic or public health crisis? Tensions between the needs of economic security and public health Relief measures have had a direct effect on the public purse through increased spending, for example, increased expenditure on health care, while at the same time there is a reduction in tax income due to reduced economic productivity	*Problems* Avoiding collapse through relief measures Austerity Reduced spending on health and social services Benefits cuts Shrinking of the state

(continued)

Table 88.3 (continued)

Level of analysis	Acute phase(s) of uncertain duration Public health interventions and supportive relief measures	COVID-19 recovery phase Transitioning out of socioeconomic upheaval
	Opportunities 1. Recognition of the importance of the social net and publicly well resourced publicly funded healthcare 2. Recognition of the importance of civil liberties may lead to increased public participation 3. A number of long-debated initiatives such as universal basic income and housing first may become relevant again 4. Improved environmental health and reduction in the carbon footprint	*Opportunities* 1. Critical times require well-designed government action and effective public service delivery 2. A monetary and fiscal policy, which avoids desperate measures, ensuring continuity of public services provision for vulnerable people, contributes to macroeconomic stability

88.7 Conclusions

Syndemic theory differs from conventional health models by incorporating the upstream social determinants of health into explanations of disease clustering from the outset. This means that complex population-based interventions can be designed which address macro-level social elements, for example societal and institutional stigma. Complex public health interventions offer a number of benefits, not least, the avoidance of duplication through multiple independent initiatives or competing smaller projects [69].

There is however the issue of local areas often having different priorities, resources and demographics. Awaiting consensus across several administrative regions on one comprehensive intervention may result in an unresponsive local health service with consequent risks of increased mortality and morbidity. Similarly, different communities may have different vulnerabilities. Worldwide, large communities of displaced people and international migrant workers may live in conditions that increase their vulnerability to COVID-19. They are also at risk of income loss, healthcare insecurity, postponement of decisions on their legal status and an inability to protect themselves or their families from violence [36]. Population-level initiatives to reduce viral transmission must address these needs in order to be successful.

Single health issue interventions or quality improvement activities by services have an important role in meeting the needs of individuals suffering from syndemic conditions. Conceptualising these interventions within a complex systems approach allows us to understand its contribution to the functioning of the overall system. For example, removing barriers to medication-assisted therapy during the pandemic has the obvious outcome of stabilising drug use and removing the suffering of withdrawals. It may also rebuild trust between people who use drugs and authorities, and through this, improve compliance with social distancing.

The provision of good-quality housing to enable homeless individuals to self-isolate during the pandemic will reduce their immediate risk of COVID-19 infection. It may also signal to these individuals that they are cared for by society. Supported and stable housing may provide opportunities for people who use drugs to remove themselves from destructive social networks and experience sobriety for the first time. This in turn could have benefits or disadvantages such as a deterioration in mental health due to the recollection of past trauma. Using network science, agent-based models or other syndemic and systems analytical tools allow us to develop, design and better evaluate interventions [69]. We are

able to look at individual strands, while also keeping an eye on the overall complex tapestry.

Syndemic and complex systems approaches support a recent position paper by Holmes et al. [28] regarding mental health science research priorities during and following the COVID-19 pandemic. The paper recommends a research strategy that is global, collaborative, multidisciplinary, cross-sectoral and incorporating people with lived experience which addresses the psychological, social and neuroscientific underpinnings of the mental health impacts of the pandemic. The essential role that the social sciences, humanities and technology have in terms of understanding the uptake and acceptance of evidence and public health measures and in reducing fear and stigma has been highlighted and should be capitalised upon to develop future comprehensive and complex interventions.

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Part VIII

Psychiatric Comorbidities & Complications of Alcohol and Other Drugs

Kathleen Brady and Giuseppe Carrà

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Psychiatric Comorbidities and Complications of Alcohol, Other Drugs: An Introduction, and International Perspectives: An Introduction and International Perspectives: An Introduction

Kathleen T. Brady and Giuseppe Carrà

The co-occurrence of substance use disorders (SUDs) with other psychiatric disorders has been an area of increasing focus over the past 30 years. This intense focus has increased the knowledge base with regard to the prevalence of co-occurring disorders, the neurobiological interface between substance use and other psychiatric disorders, and pharmacologic and psychotherapeutic treatment options. In addition, a critical focus on workforce training and designing systems of care that can optimally address the treatment needs of individuals with co-occurring disorders is needed. In these efforts, sharing knowledge across cultural and national boundaries is essential.

An international perspective on co-occurring disorders is particularly important for a number of reasons. Just as there are cultural influences in definitions, recognition, diagnosis, and treatment approaches to substance use disorders, there are important cultural influences in other psychiatric disorders and in the approaches to comorbidity. As articulated in the overview, while different countries experience varying levels of recognition of the importance of the co-occurrence of substance use and substance use disorders in mental health-care systems, the concept of "dual diagnosis" is becoming increasingly well accepted, and recognition of the importance of co-occurring disorders is rapidly expanding around the globe. In this context, the importance of recognizing that "ethnic, racial and cultural groups manifest their medical illnesses, including psychiatric illnesses, within the context of their culture, tradition, beliefs and heritage" is acknowledged as a critical issue.

The chapters that follow are written by clinicians and scientists from a wide range of countries in an attempt to give the reader a broad and international perspective on co-occurring disorders. The chapter on psychotic disorders by Dr. Carretta and colleagues provides an excellent overview of the epidemiology of co-occurring psychotic disorders and SUDs as well as a scholarly discussion of potential etiologic connections (Chap. 94). The area of cannabis and psychotic disorders is particularly well covered as this has been a topic of intense investigation and discussion at an international level for the past 25 years. Drs. Nunes and colleagues have written a comprehensive chapter covering the topic of

K. T. Brady (✉)
Department of Psychiatry and Behavioral Sciences, Clinical Neuroscience Division, Medical University of South Carolina, Charleston, SC, USA
e-mail: bradyk@musc.edu

G. Carrà
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Mental Health Department, University of Milano-Bicocca, Monza, Italy

N. el-Guebaly et al. (eds.), *Textbook of Addiction Treatment*,
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co-occurring mood and substance use disorders. In particular, their discussion of the approach to differential diagnosis and treatment of individuals with these comorbidities is detailed and useful across global boundaries. Their discussion of mood disorders in opioid dependence is particularly timely and valuable in light of the opioid overdose epidemic in the United States over the last decade.

Dr. Bartoli and colleagues have extensively reviewed epidemiological and clinical issues with regard to the comorbidity between anxiety and alcohol or SUDs whose etiologic links and temporal relationships are still unclear and, probably, heterogeneous and multifactorial. Alcohol and substances may be misused to self-medicate anxiety, avoidant, and phobic symptoms, but also anxiety disorders may be consequences of alcohol and/or substance misuse. Dr. Levin and colleagues have also provided a scholarly and comprehensive chapter addressing the issue of co-occurring ADHD and SUDs, including a discussion of the updated DSM-V criteria for both ADHD and SUDs. This comorbidity is an issue of particular concern in the United States where the diagnosis of ADHD has increased dramatically in prevalence over the past 30 years. In this regard, other nations and health-care systems may be able to learn from experiences of the United States concerning potential problems stemming from both under- and overdiagnoses of ADHD. The chapter on substance-induced disorders by Baldacchino and Sharma provides an excellent overview of general concepts in the dual diagnosis and comorbidity literature from an international perspective before an in-depth and comprehensive discussion of specific substance-induced psychiatric syndromes (Chap. 90). The chapter by Brady and colleagues (Chap. 93) tackles the very common and problematic area of trauma and addictions. Considering the level of conflict and trauma across the globe today, this is an area of international importance, and new pharmacotherapeutic and psychotherapeutic treatments under development are discussed.

The chapter by Fraser and colleagues (Chap. 96) explores the complex interface between addictive disorders and personality disorders, highlighting their interactions, and how this might inform treatment choices, specifically the need for comprehensive approaches for the patients who tend to be stigmatized and marginalized.

In sum, this section provides a thorough and comprehensive review of the co-occurrence of psychiatric and SUDs from multiple perspectives. We have much to learn from sharing evidence and observations across cultural, geographic, and political boundaries in order to develop the most sophisticated understanding of this complex patient population. This improved understanding is essential to expanding treatment options and improving treatment outcomes worldwide.

Substance-Induced Mental Disorders

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Alexander M. Baldacchino and Bhags Sharma

Contents

Abstract

Comorbidity is a condition that describes the presence of two or more diagnosable conditions, either happening at the same time or having a close temporal relationship, in the same individual. This is usually more focused on the presence of psychological/psychiatric problems and associated polydrug use and misuse. This chapter will try to identify and clarify the nature and relationship of the different avenues of clinical presentations presenting as substance-induced mental disorders.

A. M. Baldacchino
Population and Behavioural Science Division (Psychiatry and Addictions), University of St Andrews and NHS Fife, St Andrews, UK

B. Sharma (✉)
Addiction Services, NHS Fife, Scotland, UK
e-mail: bhags.sharma@nhs.net

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They include the following:

- Substance use and withdrawal from substances may lead to psychiatric syndromes or symptoms.
- Intoxication and dependence may produce psychological symptoms.
- Substance use exacerbating or altering the course of preexisting mental disorder.
- A primary mental disorder precipitated by a substance use disorder, which may lead to psychiatric syndromes.

Keywords

Comorbidity · Dual diagnosis · Mental health

Although there are several different classification schemes for psychoactive drugs (pharmacological, legal, medical), the most common organization is based on their effect on behavior and cognition. According to this scheme, psychoactive drugs can be classified into three broad categories: (1) sedatives, (2) stimulants, and (3) hallucinogens. Substance-induced mental disorders will be described on the basis of this classification in this chapter.

90.1 Introduction

Four categories of dual diagnosis involving substance misuse have been suggested by Krausz [31]:

- A primary diagnosis of a mental disorder, with a subsequent (dual) diagnosis of substance misuse that adversely affects mental health
- A primary diagnosis of drug dependence with psychiatric complications leading to mental disorder
- Concurrent diagnosis of substance misuse and mental disorders
- A dual diagnosis of substance misuse and mood disorder, both resulting from an underlying traumatic experience, for example, post-traumatic stress disorder.

Central to these explanations is the distinction between "primary" and "secondary" in terms of cause and effect. However, the distinction has also been made in terms of temporal appearance or age at lifetime onset [17]. While such a distinction has face validity in suggesting that the first temporal disorder is independent of subsequent disorders, it does not clarify whether the secondary disorder is independent of the first or how the disorders may be interrelated [47].

However, it is widely recognized that certain mental disorders have characteristic ages of onset and can thus be distinguished temporally as primary or secondary. For example, attention deficit disorder (ADD) and conduct disorder begin in childhood; alcohol and drug abuse in early to mid-adolescence; and anxiety, mood, and psychotic disorders in late adolescence and adulthood.

The operational use of concepts of substance use and misuse relies heavily on the etiology, clinical practice, particular cultures, and ideology [58] as well as the purpose(s) behind their use. Berridge points out that "definitions of alcoholism and drug addiction are historically constructed, are the products of particular historic sets of circumstances and interrelationships [7, 49]. Disease concepts, for example, may have been common in the 1890s and 1950s, but the components of the theoretical basis were very different in those decades" [6].

Many terms have been used over the past century or more to describe or define problems related to the use of alcohol, drugs, and other substances.

Some of these terms are, to say the least, very ambiguous and fluid. It is important to appreciate the latter point since these terms are in turn employed in some of the descriptions or definitions of dual diagnosis, comorbidity, etc. The definition of addiction dependence, etc., is key to intervention with substance abusers as it classifies abusive drug/drinking behaviors and impacts on the type(s) of treatment that is given.

90.2 Dimensions of Substance-Induced Mental Disorders

The difficulty of making a diagnosis of a substance-induced mental disorder is because of the different points of view from mental health and addiction services that tend to confuse the situation. Furthermore, Abdulrahim [1] suggests that the nature and relationship of comorbidity is complex and is so for the following reasons:

- Substance use and withdrawal from substances may lead to psychiatric syndromes or symptoms.
- Intoxication and dependence may produce psychological symptoms.
- Substance use may exacerbate or alter the course of preexisting mental disorder.

- A primary mental disorder may precipitate a substance use disorder (SUD), which may lead to psychiatric syndromes.

90.2.1 Examples

90.2.1.1 Cannabis-Induced Mental Disorders

An issue which has caused considerable debate in this area is the precise mechanism of the link between cannabis and psychosis. Specifically, cannabis use may alter the onset, course, and clinical expression of the psychotic episode.

There are several theories including:

A. Cannabis use occurs as a means of self-medicating for the effects of a prodromal or florid psychosis episode/illness [28].
B. Latent form of schizophrenia. Cannabis use interacts synergistically with a predisposition to psychosis to result in the emergence of psychotic symptoms earlier. It assumes that cannabis is just one of many confounding factors, including a genetic predisposition, which precipitates psychosis. According to this theory, the psychosis will not necessarily reduce or cease with a withdrawal from cannabis use and will not present with a distinctive psychopathology [24, 37].
C. Cannabis worsens or ameliorates an established psychosis [11].
D. Cannabis use directly causes toxic effect resulting in specific psychosis. Psychosis would not occur in the absence of cannabis use, and the fact that cannabis is the cause of the psychosis can be inferred from the symptoms or psychopathology of the psychosis [20].
E. Coincidental presentation of two prevalent disorders which peak in a young age group. Understanding how clusters of disorders through either concurrent or sequential links may promote a specific type of psychopathology [12].

Another possibility is that cannabis and associated psychosis are not different from psychotic symptoms in the presence of other substances such as amphetamine, cocaine, and alcohol use. For example, Jordaan et al. [26] conclude that since patients with alcohol-induced psychotic disorder have fewer negative and disorganized symptoms, better insight and judgment, and less functional impairment than patients with schizophrenia, this alcohol-induced psychotic disorder is a distinct entity. This resonates with the conclusions that alcoholic hallucinosis was not a variant of schizophrenia but a distinct condition [21].

90.2.1.2 MDMA-Induced Neurotoxic Damage and Mental Disorders

That substance use could cause mental disorders or at least can intensify such problems is supported by both psychological and neurobiological data. For example, it is known that the effect mechanism of MDMA significantly concerns the serotonin system [5, 27, 30, 42] and chronic MDMA use is supposed to have a neurotoxic effect on the serotonin system [34]. Since the use of MDMA is linked to decreased sensitivity of serotonin receptors, it is a well-supported assumption that this bodily change could have a significant role in the often experienced symptoms of depression of MDMA users. This view seems to be strong, although it has been often stated that emotional instability might precede substance use, and it may have a role in the development of substance use; thus, a circular causality might be assumed.

90.2.1.3 Chronic Opioid Use and Neuropsychological/Cognitive Impairment

Given the current emphasis on patients suffering from co-occurring substance use disorders (SUD) and mental disorders, one may forget that dual diagnosis can also include patients displaying both SUD and cognitive impairment. For example, chronic exposure to opioids has been reported to be associated with a number of neuropsychological impairments both during active use and after a period of abstinence. A wealth of studies have examined the acute, subacute, and chronic

effects of opioids on neuropsychological performance using a broad variety of measures sensitive to component aspects of attention, memory, learning, and executive functioning [14, 18].

However, for methodological reasons, defining the nature and extent of opioid-related impairments remains elusive. For instance, research on memory functions has resulted in a number of studies showing impairments in word/pattern recognition, learning and recall of words/figures, paired associate learning, and retrieval [15, 19, 41, 44]. However, other studies failed to replicate these findings of memory deficits in chronic, opioid-dependent individuals [13, 39]. In addition to memory function, studies on attention also suggest inconsistent findings. Studies have shown either no impairments in attention [13, 53] or a significant reduction in attention span [48, 54] in chronic, opioid-dependent individuals.

Neuropsychological studies of chronic opioid users have identified similarly inconsistent deficits in executive function measures. These have included impairments in cognitive flexibility [43], strategic planning [19], decision making [9, 61], and risk taking [44, 62]. However, other studies found no clear deficits when comparing the performance of healthy controls with that of opioid-abstinent, polysubstance users, head injury patients, or patients with chronic pain [22, 46].

A meta-analysis by Baldacchino et al. [4] suggests that chronic opioid exposure is associated with deficits across a range of different neuropsychological domains. However, the only domains where meta-analysis suggests robust impairment were those of verbal working memory, risk taking, and cognitive flexibility (verbal fluency).

90.2.2 Presentations

Although there are several different classification schemes for psychoactive drugs (pharmacological, legal, medical), the most common organization is based on their effect on behavior and cognition. According to this scheme, psychoactive drugs can be classified into three broad categories: (1) sedatives, (2) stimulants, and (3) hallucinogens. Substance-induced mental disorders will be described on the basis of this classification (Table 90.1).

Table 90.1 Substance-induced mental disorders

Sedatives		Stimulants	Hallucinogens
Acute effects	Relaxation, sedation, disinhibition and impaired judgment, slurred speech, ataxia, nystagmus, auditory hallucinations with delusions, labile mood, stupor, and coma. Impairment of motor coordination and cognition	Increased alertness, energy, and confidence; reduced hunger and sleep; euphoria, anxiety, and paranoia	Relaxation, sedation, disorientation, euphoria, and increased sensory awareness with hallucinations and delusions. Sometimes dysphoria, an overwhelming sense of fear often leading to panic attacks. Synesthesia
Withdrawal effects	Anxiety, agitation, disorientation, hallucinations (tactile, visual, auditory), and insomnia	Fatigue, anxiety, and depression (“crash”)	Emotional and behavioral disturbance, anxiety, depression, insomnia, and loss of appetite
Chronic effects	Depressive and anxiety symptoms including guilt and hopelessness confusion, ataxia, ophthalmoplegia, nystagmus, anterograde memory loss, and confabulation. Others include deficits in abstract thinking, perceptual motor skills, and visuospatial and verbal learning	Depressive and psychotic symptoms. Cognitive impairments	Cognitive impairment and possible long term, anxiety, depressive, and psychotic symptoms. Suicidal ideations. Cognitive impairments

90.2.3 Sedative-Induced Mental Disorders

Sedatives depress or inhibit brain activity and produce drowsiness, sedation, or sleep, relieve anxiety, and lower inhibition. Although the depressant compounds do not share a common neural mechanism of action, most of them either decrease the metabolic activity in the brain or increase the transmission of the principal inhibitory neurotransmitter of the brain, gamma-aminobutyric acid (GABA). Common depressants include barbiturates, benzodiazepines, opioids, and alcohol [16].

There are several mental disorders presenting as a direct consequence to excessive consumption of alcohol. The conditions presented with benzodiazepine and other sedatives tend to have the same quality but not necessarily severity of the psychopathology arising.

90.2.3.1 Alcohol-Induced Amnesia (Blackout)

Loss of memory is related to periods when intoxicated with alcohol. Anterograde memory loss tends to be a result of lack of recall rather than registration [25]. Two types have been identified:

(a) "En bloc" – discrete start and finish points with complete loss of memory for interim events
(b) Fragmentary – partial amnesia with islands of recollection still intact

90.2.3.2 Alcohol-Induced Psychosis/ Hallucinosis

This mental disorder presents with a sudden onset of auditory hallucinations and delusions in the presence of clear "sensorium" in individuals with a history of alcohol abuse. Auditory hallucinations are usually derogatory in nature or portray negative connotations [26]. These symptoms usually improve quickly (usually within a week) although they can become chronic due to ongoing alcohol misuse where they tend to persist. Patients with alcohol-induced psychosis can present with later onset of psychosis, lower educational level, more anxiety and depressive symptoms, fewer negative and disorganized symptoms, and less functional impairment than patients with schizophrenia [26].

90.2.3.3 Alcohol Withdrawal Syndrome (AWS)

This arises in alcohol-dependent patients, usually within 24–48 h of stopping alcohol consumption [35]. AWS can occur unexpectedly in an alcohol-dependent patient following hospital admission and intentionally in those seeking abstinence. Alcohol withdrawal is common and usually mild but can also lead to withdrawal seizures and delirium tremens, both of which may be fatal [35]. The definition of alcohol withdrawal encapsulates the key clinical findings of AWS including anxiety, agitation, tremor, delirium, disorientation, hallucinations (tactile, visual, auditory), and insomnia.

90.2.3.4 Delirium Tremens

This is characterized by an acute confusional state with fluctuating levels of cognition and consciousness over the day following alcohol withdrawal in a patient with alcohol dependence. It usually occurs 2–4 days after last alcohol consumption unlike simple alcohol withdrawals which occur within a few hours of stopping alcohol. Autonomic symptoms including sweating, nausea, palpitations and tremor, hypertension, and tachycardia are invariably present. It occurs in about 5% of withdrawal episodes in admitted patients [33]. Important clinical features include visual hallucinations and severe tremors. Other symptoms include fear, paranoid delusions, and psychomotor agitation.

90.2.3.5 Wernicke's Encephalopathy and Korsakoff Psychosis

Chronic alcohol consumption can result in thiamine deficiency via inadequate dietary intake, malabsorption of thiamine from the gastrointestinal tract, and impaired utilization of thiamine in the cells. Thiamine is an essential cofactor for several enzymes involved in brain cell metabolism that are required for the production of precursors for several important cell components as

well as for the generation of the energy-supplying molecule ATP. Accordingly, thiamine deficiency can cause a number of processes that are toxic to brain cells [32].

Wernicke's encephalopathy is a relatively common and potentially dangerous neuropsychiatric condition caused by thiamine (vitamin B1) deficiency [8]. If not treated, it can result in a chronic form of the disease known as Korsakoff psychosis. As a result of the close relationship between Wernicke's encephalopathy and Korsakoff psychosis, reference is often made to the Wernicke-Korsakoff syndrome [57].

The symptoms of Wernicke's encephalopathy include mental confusion, oculomotor disturbances, and gait ataxia (an impaired ability to coordinate movements, particularly of the lower extremities). Patients will also manifest deficits in memory function, abstract problem solving, perceptual motor skills, visuospatial function, verbal learning, and motor function.

Korsakoff syndrome consists of memory impairments (preserved primary memory, impaired recent memory, and extensive retrograde amnesia) occurring in clear sensorium. Other psychopathology includes poor insight into the memory deficit with resulting confabulation, absence of impairment or loss of consciousness, and absence of global cognitive impairment [29].

90.2.4 Stimulant-Induced Mental Disorders

Stimulants produce behavioral arousal. As with the sedatives, there are a variety of substances, each with a different neural mechanism of action. These drugs act by increasing the activity of three neurotransmitters in the brain: serotonin, dopamine, and norepinephrine [56]. Examples of stimulants are cocaine, caffeine, and nicotine. Other examples of stimulants are amphetamines and amphetamine-like substances such as methamphetamine. Smoking, sniffing, ingesting, inhaling, and injecting are the most common methods through which these drugs are used.

Stimulant-induced mental disorder presents in the acute stage with euphoria and in vulnerable groups with severe anxiety, paranoia, and manic-type (increased energy, mental alertness, increased sexuality, and extended periods of wakefulness) psychopathology [23, 36]. This is associated with improved attention and suppressed appetite [55]. It can also cause perceptual disturbances especially "formication." This is described as a sensation that resembles that of insects crawling (tactile hallucination) on (or under) the skin. It is one specific form of a set of sensations known as paresthesia, which also include the more common prickling, tingling sensation of "pins and needles." As the effects of the drugs subside, the user feels dysphoric, tired, irritable, and mildly depressed, which may lead to subsequent drug use to regain the previous experience [51, 52].

Chronic use of excessive amounts of stimulants can intensify symptoms or precipitate a psychotic episode similar to schizophrenia in vulnerable individuals [59, 63].

90.2.5 Hallucinogen-Induced Mental Disorders

Hallucinogens and psychedelics do not share a common mechanism of action, but all induce hallucinations. These drugs can be either natural such as mescaline, which is derived from the peyote cactus, or synthetic such as lysergic acid diethylamide (LSD), but they are typically classified pharmacologically according to the affected neurotransmitter system. Cholinergic psychedelics (drugs altering acetylcholine transmission) include physostigmine, scopolamine, and atropine. Drugs that alter norepinephrine transmission include mescaline and ecstasy. Drugs that alter serotonin transmission include LSD and psilocin. Other drugs in this category include the psychedelic anesthetics phencyclidine (PCP) and ketamine [40, 50, 60].

Cannabinoids, psychoactive substances derived from the hemp plant *Cannabis sativa*, are often classified as hallucinogens. There are two types of acute effects on mental function – euphoric and calming. Besides the dramatic impact on emotional functions, acute cannabis

intoxication can induce cognitive impairments, sometimes persisting for weeks or months following abstinence. This usually presents as a fragmentation of thought process, major disruption of temporal understanding, distortion of perceptual stimuli, and poor attention and concentration. "Cannabis psychosis" may not be qualitatively any different from other forms of psychosis [3]. Some specific psychopathologies stated include confusion, disorientation, amnesia, depersonalization, delusions, hallucinations, paranoia, ideation, psychomotor agitation, labile affect, and hostility [2].

Chronic exposure to cannabis leads to a cannabis withdrawal syndrome [10] characterized by the frequently reported symptoms of emotional and behavioral disturbance which includes depression, anxiety and irritability, nausea, abdominal discomfort, decreased appetite, weight loss, physical discomfort, and insomnia with strange dreams [10]. A chronic buildup of cannabinoids produces both short-term and long-term cognitive impairments. There is insufficient knowledge to determine the level of risk associated with cannabis use in relation to long-term psychotic symptom [38].

90.3 Conclusion

Substance-induced mental disorders are important conditions that need to be contextualized within the substance use history but also need to be well managed to prevent further deterioration. Substance-induced mental disorders also need to be understood within the context of the overall lack of defined and strict operational definitions used in the field of comorbidity or dual diagnosis.

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Co-occurring Mood and Substance Use Disorders

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Jonathan M. Wai, Matisyahu Shulman, Edward V. Nunes, Deborah S. Hasin, and Roger D. Weiss

Contents

J. M. Wai · M. Shulman · E. V. Nunes (✉)
Division on Substance Use Disorders, Department of Psychiatry, Columbia University Irving Medical Center, New York State Psychiatric Institute, New York, NY, USA
e-mail: nunesed@nyspi.columbia.edu

D. S. Hasin
Department of Epidemiology, Columbia University Mailman School of Public Health, New York State Psychiatric Institute, New York, NY, USA

R. D. Weiss
Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA

Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Abstract

Mood disorders, which include depressive and bipolar disorders, are among the most common disorders observed to co-occur with substance use disorders. These disorders have been associated with a worse prognosis among substance use disorder patients, and vice versa. Furthermore, treatment of co-occurring mood disorders has been shown to improve treatment outcome among substance-dependent patients with improvement in both mood and substance use. At the same time,

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mood symptoms among patients with substance use disorders frequently remit when patients reduce substance use or achieve abstinence without specific mood disorder treatment. Thus, it is important for clinicians working with substance-abusing patients to be able to recognize mood disorders in the clinical history, distinguish mood disorders that require specific treatment, recommend appropriate treatment options, and monitor clinical course. This chapter reviews the evidence on the diagnosis and treatment of co-occurring substance and mood disorders, with emphasis on depressive disorders.

Keywords

Attention Deficit Hyperactivity Disorder - Bipolar Disorder - Mood Disorder - Social Anxiety Disorder · Major Depressive Disorder · Substance Use Disorders

Highlights

1. Substance use disorders have a high prevalence of comorbid mood disorders, and vice versa.
2. There is substantial overlap in the symptoms of substance use disorders and mood disorders.
3. An understanding of both mood and substance use disorders is essential for the assessment and treatment of either.
4. Differentiation of symptoms arising from a mood vs. substance use disorder can be differentiated through careful history taking or use of a clinical research tool.
5. A substance use disorder should always be treated when diagnosed, and this may resolve mood symptoms.
6. In cases with significant mood symptoms, or symptoms that do not resolve with substance abstinence, targeted mood disorder treatment may be warranted.

91.1 Introduction

The co-occurrence of mood and substance use disorders has been a source of considerable controversy, sparked by the complexity of potential relationships and overlap between mood syndromes and substance-related disorders. For example, in patients with alcohol use disorder, do depressive symptoms represent side effects of chronic alcohol exposure that will resolve if the patient achieves abstinence? Or do they represent an independent mood disorder that requires specific treatment, either with behavioral therapy, medication, or a combination of the two? In any given patient, either of these explanations may be correct. Effective management of co-occurring mood symptoms in substance-abusing patients requires a nuanced awareness of the differential diagnosis of the mood symptoms and the expected effects of abused substances. This chapter will attempt to provide a guideline for clinicians to the differential diagnosis and therapeutics of mood syndromes among substance-dependent patients, based on the current evidence.

The co-occurrence of bipolar disorders and substance use disorders is covered in detail in a separate chapter of this text. However, because it is very important to consider bipolar disorders in the differential diagnosis when conducting a diagnostic evaluation and planning treatment, this chapter provides an overview of the diagnosis of bipolar disorders.

91.2 Prevalence and Co-occurrence

91.2.1 DSM-IV and DSM-5

As much of the existing literature on co-occurring mood and substance use disorders was conducted with DSM-IV mood disorder, "substance abuse," or "substance dependence" diagnostic criteria, the empirical evidence cited in this chapter derives from investigations that use both DSM-5 and DSM-IV [2] or earlier criteria sets. The criteria for depressive disorders (major depression, persistent depressive disorder (previously known as dysthymia)) and bipolar disorders (bipolar I, bipolar II, cyclothymia) have changed little between DSM-IV and DSM-5. DSM-5 added a new category of disruptive mood dysregulation disorder (DMDD) to the group of depressive disorders to distinguish children with predominantly irritable mood, but without other features of

bipolar disorder, from children in the bipolar spectrum. The substance-induced diagnoses (substance-induced depressive disorder, substance-induced bipolar disorder) are similar conceptually in DSM-5 and DSM-IV with some subtle differences reviewed below.

A thorough review of the diagnostic criteria for depressive and bipolar disorders is beyond the scope of this chapter. Readers who are not familiar with these diagnostic criteria should review the DSM-5 [3], which provides detailed descriptions.

The substance use disorders were changed in DSM-5, in that substance dependence (DSM-IV) and substance abuse (DSM-IV) have been combined into one category, named substance use disorder (DSM-5). This was done because the weight of the evidence indicated the criteria for DSM-IV substance abuse, which involved hazardous use (e.g., driving while intoxicated), social or interpersonal problems related to use, or failure to perform in major role responsibilities, were intermixed across the severity spectrum with substance dependence criteria, representing part of a chronic pattern of substance use with loss of control, tolerance, dependence, and adverse consequences [33]. Another difference between DSM-IV and DSM-5 is the addition of "craving" as a criterion for substance use disorder in DSM-5.

In terms of the evidence on the co-occurrence of mood and substance use disorders, these changes should make little difference, as substance dependence (DSM-IV) and substance use disorder (DSM-5) are conceptually similar, representing a chronic pattern of substance use with loss of control, tolerance, physical dependence, and actual or threatened adverse consequences.

Thus, the DSM-5 criteria for mood and substance use disorders are similar enough to DSM-IV (and prior) criteria that the evidence on co-occurrence based on earlier criteria can be expected to generalize to the DSM-5 framework.

91.2.2 Depressive Disorders

91.2.2.1 Major Depressive Disorder

Major depressive disorder represents an episode, lasting 2 weeks or more, of relatively severe depression, characterized by a persistent state, "most of the day, nearly every day", of either depressed mood or markedly diminished interest or pleasure in usual activities, or both, along with at least three or four associated symptoms, again occurring nearly every day (anorexia and weight loss, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or low energy, feelings of worthlessness or guilt, trouble concentrating or making decisions, recurrent thoughts of death or suicide) [3]. Major depression may occur as a single episode, but a chronic course is not uncommon, in which there are recurrent major depressive episodes, followed by partial remissions during which some of the depressive symptoms persist.

91.2.2.2 Persistent Depressive Disorder

Persistent depressive disorder (DSM-5), called *dysthymia* in DSM-IV, represents a chronic syndrome of depressed mood "more days than not… for at least 2 years" [3], along with at least two of the following associated symptoms – either low appetite or overeating, insomnia or hypersomnia, fatigue or low energy, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. Persistent depressive disorder may be specified "with persistent major depression" or "with intermittent major depressive episodes" to indicate the confluence of major depressive episodes with the chronic low-grade symptoms.

91.2.2.3 Prevalence and Co-occurrence of Depressive Disorders with Substance Use Disorders

Like substance use disorders, depressive disorders are among the most commonly occurring mental disorders. Community surveys indicate 10% or more of individuals have experienced a depressive disorder during their lifetime [30, 34]. Depressive disorders are responsible for substantial suffering, functional impairment, lost productivity [21], and suicide risk. Large community surveys, such as the Epidemiological Catchment Area study (ECA) [63], the National Comorbidity Survey (NCS) [39–41], and the National Epidemiologic Survey on Alcoholism and Related Conditions (NESARC) [24, 25, 30], consistently

show that the presence of a depressive disorder significantly increases the risk of alcohol or drug dependence (or vice versa) and a 2014 meta-analysis found that depression increases the risk by a factor of 2.4 for alcohol use disorder and 3.8 for illicit drug use and major depression [44]. Treatment-seeking samples tend to display even greater comorbidity due to the relatively greater severity of illness of treatment seekers. Across numerous studies of such samples, the prevalence of major depression has ranged from 15% to 50%, making it one of the most common co-occurring psychiatric disorder encountered among drug- or alcohol-dependent patients in treatment [29].

91.2.2.4 Prognostic Effects of Depressive Disorders on Substance Use Disorders

Many (although not all; [19, 46]) longitudinal studies have found that the presence of depression in patients with substance use disorders is associated with worse treatment outcome and prognosis. These findings suggest the importance of identifying and treating depression among substance-dependent patients, since the implication is that treatment of the depression has the potential to improve prognosis. Importantly, the findings of the adverse prognosis of depression are most consistent among studies where a depressive disorder (mainly major depression) is diagnosed by clinical history and structured diagnostic assessment. Findings on the association between depression and prognosis of substance use are less consistent when depression is measured only with cross-sectional scales [29]. For example, one study that followed alcohol-dependent patients for a year after an index hospitalization found that a diagnosis of major depression was associated with poor drinking outcome over the coming year, while the Hamilton Depression Rating Scale score at baseline was not [26].

91.2.3 Bipolar Disorders

Bipolar disorders are rarer in the general population but are more strongly associated with co-occurring substance use disorders. Large community surveys yield estimates of the lifetime prevalence of bipolar I disorder ranging from 1% to 3%, another 1% for bipolar II disorder, and 2% or more having subthreshold disorders in the bipolar spectrum [24, 50]. Although bipolar disorders are characterized by the presence of manic or hypomanic episodes during the lifetime, these episodes alternate with episodes of major depression or chronic depression, and the depressed periods typically predominate, particularly later in the course of the illness. Thus, bipolar disorder patients are most likely to present clinically as depressed. When evaluating a depressed, substance-using patient, it is therefore very important to search the history for evidence of past manic or hypomanic episodes, because the treatment of bipolar disorders differs significantly from the treatment of depressive disorders. The cornerstone of the treatment of bipolar disorder is mood stabilizer medications – lithium, anticonvulsants, or neuroleptics. Treating bipolar depression with antidepressant medications alone can be ineffective and may cause worsening of mood instability.

91.2.3.1 Bipolar I Disorder

Bipolar I disorder is characterized by the presence of one or more manic episodes over the course of one's lifetime. Manic episodes are characterized by a week or more of persistently elevated, expansive, or irritable mood, accompanied by at least three associated symptoms, including grandiose thinking, decreased need for sleep, increased talkativeness, racing thoughts, distractibility, increased activity level, and risky behavior that the person would not usually engage in. The syndrome is severe and causes marked impairment in functioning. Mania may become psychotic with paranoid or grandiose delusions (e.g., a patient becomes convinced that he/she is a messiah or on a special mission from God). Typically, the course of bipolar I includes episodes of major depression, may also include hypomanic episodes, and typically runs a course that is predominated by depressive symptoms.

91.2.3.2 Bipolar II Disorder

Bipolar II disorder is characterized by one or more hypomanic (as opposed to manic) episodes,

along with one or more episodes of major depression over the lifetime. A hypomanic episode resembles a manic episode, except that hypomania may be shorter, and is less severe. There must be a change in functioning to meet criteria for hypomania, but hypomania does not cause marked impairment or psychosis. Again, bipolar II frequently runs a predominantly depressive course.

91.2.3.3 Co-occurrence of Bipolar and Substance Use Disorders and Prognostic Effects

Large-scale community surveys indicate that the presence of a bipolar disorder increases the odds of having an alcohol use disorder by a factor of five or more and a drug use disorder by a factor of eight or more [6, 24, 30, 39, 40, 63]. In outpatients seeking treatment for substance use disorders, bipolar disorder is less commonly encountered than depressive disorders because bipolar is less frequent in the general population. However, patients with co-occurring bipolar and substance use disorders are particularly likely to be encountered in inpatient settings dealing with more severely ill dually diagnosed patients.

The co-occurrence of bipolar and substance use disorders is associated with worse outcome for both disorders. Patients with bipolar disorders can be very difficult to manage until the disorder is recognized and successfully treated with mood stabilizers. Conversely, finding the right mood stabilizer regimen for a given patient can be dramatically effective. This, again, suggests the importance, when evaluating substance-dependent patients, of taking a careful history for past episodes of mania or hypomania.

91.2.4 Co-occurring Depression and Substance Use as a Signal for Other Disorders

An analysis of the NESARC data on co-occurrence of mood and substance use disorders yielded an interesting finding [32]. When the association between major depression and substance use disorders is analyzed in such a way as to control for the presence of other disorders (bipolar disorder, anxiety disorders, etc.), the odds ratio of association between depression and substance use disorders is substantially reduced. This suggests that the apparent association between depression and substance use disorders may be explained, at least in part by the presence of the other co-occurring disorders, including anxiety disorders, since anxiety is a commonly occurring symptom among those with depression. In contrast, the association between bipolar disorder and substance use disorders remained significant after controlling for the other disorders. Substance use disorders have high rates of co-occurrence with anxiety disorders, such as panic disorder, social anxiety disorder, and post-traumatic stress disorder (PTSD); attention deficit hyperactivity disorder (ADHD); and personality disorders, including antisocial personality and borderline personality. Each of these disorders, in turn, has high co-occurrence with depressive disorders or symptoms or has symptoms that resemble depression. Thus, in substance-dependent patients, depressive symptoms may be a signal that other disorders are also present. It is therefore important to take a careful history looking not only for bipolar disorder but also for anxiety disorders, ADHD, or personality disorders. These disorders have distinct behavioral and pharmacological treatment indications and instituting appropriate treatment will be important to securing the best clinical outcome.

91.3 Diagnosis of Co-occurring Mood Disorders with Substance Use Disorders

In approaching the differential diagnosis of a patient with a substance use disorder and mood symptoms, it is important to recognize the multiple potential relationships between mood symptoms and a substance use disorder. There may be an independent mood disorder (e.g., major depressive disorder or bipolar disorder), or the depressive symptoms may be a manifestation of another co-occurring disorder such as PTSD or ADHD. Mood and substance use disorders may both be caused by common genetic or environmental risk factors. Stress is the most obvious

example of this, as stress is a causal risk factor for both mood disorders and substance use disorders.

Substance use may also cause mood symptoms, either as part of substance intoxication or withdrawal or from the toxic effects of chronic exposure to substances. Individuals with substance use disorders also often experience negative consequences and losses (e.g., medical problems, loss of employment or family), which may trigger depressive symptoms.

Substance-related or substance-induced mood symptoms will generally resolve if the patient is able to achieve abstinence. Hence, it is generally appropriate to initiate treatment for a substance use disorder, while sorting out the co-occurring mood disorder. If the patient's substance use is substantially reduced or resolved, the mood symptoms may resolve with it. A number of studies across alcohol- and drug-dependent samples have shown that initiation of treatment for substance use disorders and achievement of abstinence are associated with marked improvement in mood symptoms [7, 8, 45, 72, 75, 79].

It is also important to bear in mind that resolution of a depressive syndrome with treatment of the substance use disorder alone is not pathognomonic of a substance-induced depression. Depressive disorders, particularly in the mild to moderate range of severity, respond well to psychotherapy, such as cognitive behavioral therapy (CBT) or interpersonal therapy (IPT). Treatment for substance use disorders generally includes nonspecific psychotherapeutic elements, such as development of a supportive clinician-patient relationship and treatment alliance, which are likely to be helpful with treating depression. Further, many treatments for substance use disorders include components on coping with stress and with dysphoric moods that overlap with cognitive behavioral techniques for treating mood and anxiety disorders. Furthermore, reductions in substance abuse and related problems in response to treatment are likely to reduce stress and improve self-efficacy, and likely to help depression. In summary, good treatment for substance use disorders may also be effective for treatment of an independent depressive disorder.

91.3.1 DSM-IV/DSM-5 Approach to Co-occurring Mood and Substance Use Disorders

Before the advent of DSM-IV, there was no clear consensus on how to diagnose co-occurring mood disorders in the setting of substance use disorders. There was recognition that some co-occurring mood disorders were independent of substance use while others were caused by substance use. However, determining the optimal way to handle the large proportion of cases, (in which the temporal relationship between the disorders was unclear or when the patient does not quickly achieve abstinence) had not been addressed. DSM-IV advanced the field by distinguishing between independent mood disorders, substance-induced mood disorders, and mood symptoms that are usual effects of substances and for providing some criteria to make the distinctions. DSM-5 has retained this system. Substance-induced mood disorder provides a category in which to place the unclear cases, in which a mood disorder syndrome exceeds the symptoms that would be expected from intoxication and withdrawal, but the syndrome has not occurred in the absence of regular substance use. It has generated meaningful research as to its prognosis and course, as reviewed below.

91.3.1.1 Independent Mood Disorder

An independent mood disorder is diagnosed if the patient meets full criteria for the mood disorder (e.g., major depression, persistent depressive disorder, bipolar I) and the symptoms can be established by history to be temporally independent of substance abuse (prior onset or emergence or persistence during periods of abstinence). DSM-IV also suggested that an independent disorder could be diagnosed if its symptoms were substantially in excess of effects expected to be caused by the substance(s) the patient was taking. DSM-5 deals with this by specifying that a substance-induced disorder is only diagnosed if the mood syndrome and symptoms are consistent with symptoms known to be caused by the substance(s). The clinical implications are similar. In the criteria sets for substance-induced mood disorders, DSM-5

suggests that a mood syndrome co-occurring with substance use may be considered an independent disorder (and thus distinguished from substance-induced disorder) if the mood syndrome had its onset before the onset of substance abuse, or persists for about 1 month or more after abstinence is achieved, or there is a clear history of independent mood disorder episodes. An example might be a current major depression syndrome that had its onset concurrent with substance abuse in the current episode, but there is a clear history of one or more major depressive episodes during past abstinent periods.

91.3.1.2 Substance-Induced Mood Disorder

A substance-induced mood disorder is diagnosed if there is a "persistent disturbance in mood," which (a) develops at or soon after substance intoxication or withdrawal and (b) the substance(s) in question is "capable of producing the symptoms," and the syndrome is not better explained by a diagnosis of an independent mood disorder. There must be significant distress or impairment. Further, with respect to distinguishing a substance-induced mood disorder from usual effects of substances, the DSM-5 criteria state that a substance-induced mood disorder should be diagnosed, instead of a diagnosis of substance intoxication or withdrawal, only if "the mood symptoms predominate and are sufficiently severe to warrant clinical attention." DSM-IV worded this slightly differently, indicating that substance-induced mood disorder should be diagnosed when the mood and related symptoms (e.g., insomnia) exceed what would be the expected effects of intoxication or withdrawal and warrant clinical attention. Again, the clinical implications are similar.

91.3.1.3 Usual Effects of Substances

Mood symptoms, such as depressed mood, insomnia, and weight loss, can also be due to substance intoxication or withdrawal. DSM-IV and DSM-5 contain detailed criteria sets for the intoxication and withdrawal syndromes of alcohol, nicotine, and each of the other commonly abused drugs. Clinicians should be mindful of these lists of symptoms when evaluating patients with co-occurring mood symptoms and substance use. These symptoms have various time frames, but generally, symptoms of intoxication last only for the few hours during and after substance ingestion while blood levels are peaking and before they substantially decrease. Symptoms of withdrawal usually evolve and resolve over a period of a few days. Subacute withdrawal syndromes (also called protracted withdrawal), sometimes lasting a few weeks, have been described, particularly for alcohol and opioid dependence. Depressed mood and related symptoms (e.g., anxiety, fatigue, hypersomnia, insomnia, difficulty concentrating, irritability) occur variously as part of the withdrawal syndromes of most of the common addictive substances.

In summary, when conducting a diagnostic evaluation on a substance-using patient, familiarity with the intoxication and withdrawal effects of the substance(s) involved is important to distinguish mood symptoms that are best explained as components of intoxication or withdrawal from symptoms that are better explained as a substance-induced disorder.

91.3.1.4 Co-occurring Bipolar and Substance Use Disorder

Episodes of frank mania are generally too persistent (week or more) and too severe to be explained as substance-induced. For example, cocaine intoxication may produce a syndrome closely resembling mania (increased activity, hyperloquaciousness, grandiosity, lack of need for sleep, and psychosis with paranoid or grandiose delusions), but this typically only lasts for the duration of the drug binge, a day at most, after which there will be a crash with the typical depressive withdrawal symptoms (fatigue, hypersomnia, depressed mood, etc.). Hence, a history of one or more episodes of frank mania in a patient presenting with co-occurring mood symptoms and substance problems is clear evidence of co-occurring independent bipolar disorder that requires appropriate mood stabilizer medication. Methamphetamine psychosis can last considerably longer, however, and can cause a more complicated differential diagnostic process.

Hypomania can be more difficult to identify both in the present and historically. Hypomania is milder, and patients may not report it because they do not remember it or did not experience it as a departure from normal functioning. Moreover, periods of elevated mood, and increased energy and activity, may be difficult to distinguish from periods of normal mood – for example, when a chronically depressed patient becomes euthymic or when a patient has an exciting life event such as a new job or another major success. Periods of hypomania can be difficult to distinguish in a patient with heavy stimulant use, given the shorter duration of hypomania and the overlap in symptoms between hypomania and cocaine or stimulant intoxication (e.g., euphoria, increased sociability). As with depressive disorders, to confirm an independent bipolar II disorder, it becomes important to seek episodes in the history in which syndromes of hypomania occurred in the absence of stimulant-like substances.

91.3.2 Course and Prognosis of DSM-IV Independent and Substance-Induced Depression

Before DSM-IV, considerable evidence existed that independent depressive disorders could be identified with distinct prognostic and treatment implications. Brown and Schuckit demonstrated that a history of major depression before the onset of alcohol problems over the patient's lifetime (primary depression) was associated with depressive symptoms that persisted despite 3–4 weeks of abstinence in a sample of individuals hospitalized with alcohol use disorder [7, 8]. Rounsaville and colleagues, using the Schedule for Affective Disorder and Schizophrenia, a structured diagnostic instrument, found major depression to be associated with worse prognosis among drug-dependent patients [13, 67, 68]. We and others found that depression with evidence of temporal independence from substance use either by history [49, 53, 54] or through observed persistence of depression symptoms during abstinence [15, 47, 69] responded to antidepressant medication.

91.3.2.1 Structured Diagnostic Assessment

With the advent of DSM-IV, the Structured Clinical Interview for DSM-IV (SCID) incorporated a module for substance-induced mood disorder and logic for diagnosing a mood syndrome as independent or substance-induced. However, the determinations were left largely up to clinical judgment with little guidance in the interview as to how to make the distinction. The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) [31] was developed to operationalize the diagnosis of co-occurring substance and other mental disorders within the DSM-IV framework. For a given syndrome, such as major depression, the interviewer is asked, for each criterion symptom, to judge whether that symptom appears attributable to usual effects of substances. The substances that might cause that symptom, either as intoxication or as withdrawal effects, are listed. For example, when a depressed patient reports insomnia, the interviewer is asked to determine whether substances that might cause insomnia (stimulant intoxication or alcohol, sedative, or opioid withdrawal) could explain the insomnia. The insomnia is only scored as positive to contribute to a diagnosis of a depressive disorder if it can be determined either not related to or exceeding the expected effects of the substance use. If sufficient criteria are endorsed to allow diagnosis of a depressive syndrome, then the interviewer is asked to determine whether the depressive syndrome is temporally independent of current substance use in terms of its onset and persistence during abstinence. If the history indicates that the depressive episode started before the onset of substance use or persists during a substantial abstinent period (e.g., a month or more), then it is diagnosed as independent. Otherwise, it is diagnosed as substance-induced.

Thus, the PRISM provides an operationalized definition of substance-induced depression that is quite stringent. It requires criteria for a full depressive syndrome (e.g., for major depression) to be met, and it requires that the symptoms con-

tributing to that syndrome not be better explained as toxic or withdrawal effects.

91.3.2.2 Prognostic Effects

Subsequent research with the PRISM established good to excellent reliability of diagnoses of independent and substance-induced major depression [31]. Further, there were clear prognostic effects. In a longitudinal study, substance-dependent patients entering an inpatient treatment facility were diagnosed with the PRISM while hospitalized, then followed for 1 year after discharge. Substance-induced major depression was found to predict failure to achieve abstinence after discharge from hospital, while independent major depression was found to predict relapse to substance use after periods of abstinence [28, 71]. Both independent and substance-induced depression were associated with suicidal ideation [1]. Further, over half of cases diagnosed as substance-induced depression at baseline converted into an independent depression over the year's follow-up, based on the major depression persisting during a period of at least a month of abstinence [55]. Predictors of conversion to independent depression included a history of an independent major depression and either PTSD or borderline personality disorder [55], again suggesting the importance of identifying other disorders that commonly co-occur with both mood and substance use disorders.

Studies with other samples and diagnostic methods have similarly suggested the validity and prognostic significance of independent and substance-induced depressive disorders as conceptualized by DSM-IV/DSM-5 [64, 65, 73] and the finding that a substantial proportion of substance-induced depression will convert to an independent depressive disorder over time [62].

91.3.2.3 A Note About Terminology

The term "substance-induced depression" carries a causal implication, namely, that the substances cause the observed depression syndrome. This can cause clinicians to underestimate the potential clinical significance of a substance-induced depression, both because intoxication and withdrawal effects are also induced by substances and because, as reviewed above, some depressions diagnosed as "substance-induced" will turn out to be independent depressions if followed into a period of abstinence. Substance-induced is to some extent a holding category for depressions for which the status as independent is uncertain at the time of diagnosis. It might be useful for clinicians to think of this as "substance-induced until proven otherwise," to emphasize that continued clinical attention is warranted and that the depression may turn out to be independent or to warrant specific treatment.

In summary, these studies suggest that substance-induced depression is a valid and useful category. It represents a diagnostic entity that lies between usual toxic effects of substances and an independent mood disorder. As the DSM-IV and DSM-5 criteria suggest, substance-induced depression "warrants clinical attention" because it carries adverse prognostic effects (suicidal ideation, lower likelihood of achieving abstinence) and is likely to convert to an independent depression over time. Further, as the DSM-5 criteria suggest, a history of independent depression may be considered sufficient evidence to diagnose a current depression as independent, rather than substance-induced. Other co-occurring disorders such as PTSD should also be suspected.

91.3.3 Summary and Recommendations for Diagnostic Assessment

91.3.3.1 Screening Instruments

Instruments that assess cross-sectional mood symptoms (e.g., Beck Depression Inventory, Hamilton Depression Rating Scale, Brief Symptom Inventory, or Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR)) are useful for screening. However, by themselves they do not indicate the presence of any specific mood disorder and have unclear prognostic or treatment implications.

91.3.3.2 Clinical History and DSM-IV/DSM-5 Criteria

A substance-dependent patient with mood symptoms should be evaluated by taking a

careful lifetime clinical history. The history should seek to establish the onset of substance use disorders over the lifetime and substantial periods of abstinence lasting a month or more. The history should then establish the onset and course of mood syndromes (major depressive episodes, persistent depressive disorder, mania, hypomania), in the context of the lifetime course of substance use and apply the DSM-5 criteria for independent or substance-induced disorders. Among other things, this means establishing that symptoms of a mood disorder are not better explained as usual effects of substances or exceed what would be expected from the usual effects of substances. A mood disorder that cannot be established to be temporally independent of substance abuse, but exceeds the expected effects of substances, is diagnosed as substance-induced. For substance-induced syndromes, we also recommend noting the full syndrome that is in evidence, for example, "substance-induced major depression" if the full criteria for major depression are met (i.e., five or more criteria are met), as some of the stronger prognostic data pertain to substance-induced depression defined in this way [1, 28, 55, 71].

91.3.3.3 Search the History for Mania or Hypomania

The presence of one or more episodes of mania and hypomania indicates a bipolar disorder, which carries prognostic and treatment implications distinct from depression. Mania and hypomania may be difficult to elicit in the history. It is often helpful to interview family members, who may recall such episodes when the patient does not.

91.3.3.4 Look for Other Co-occurring Disorders

We also recommend a thorough review of the history for other disorders that commonly co-occur with mood disorders, including PTSD, social anxiety disorder, and other anxiety disorders; ADHD; and borderline personality. The presence of mood symptoms may signal the presence of one of these disorders. Such disorders have symptom patterns that are distinct from typical substance effects – substance use does not cause phobias, social anxiety, or re-experiencing symptoms of PTSD. Some have clear childhood onset (e.g., ADHD, social anxiety disorder), well before the onset of substance problems. Moreover, they have distinct treatment indications for both behavioral therapy and medications.

91.4 Treatment of Co-occurring Mood Disorders

91.4.1 Depressive Disorders

91.4.1.1 Antidepressant Medications

A number of placebo-controlled trials have examined the effect of antidepressant medication on mood and substance use outcome among substance-dependent patients with diagnosed mood disorders. Two meta-analyses [52, 78], published 15 years ago, reached similar conclusions, namely, that antidepressant medications are useful in improving both mood outcome and substance use outcome; these findings are more clear among alcohol-dependent patients. However, several national medical guidelines suggest medications should be avoided until an individual is abstinent for an extended period and continues to experience depression [5, 84]. This recommendation is based on the evidence that many individuals' depression will spontaneously remit with abstinence. Some recent studies have also implied antidepressants might worsen alcohol use disorder, particularly among those with the 'early onset' subtype of alcohol use disorder characterized by onset before age 25 and externalizing psychopathology [14, 42, 60]. Other evidence shows that studies have been mixed, with some negative trials [16, 27, 43, 61]. These include a large trial among alcohol-dependent outpatients that showed a high placebo response rate and no medication effect on mood or substance use outcome, despite patients being diagnosed with independent major depression using the PRISM. Other more recent trials have also been positive, at least in showing a beneficial effect of antidepressant medication on mood outcome [36, 48, 66].

91.4.1.2 Placebo Response and Other Factors Associated with Response to Antidepressants

A striking finding from the antidepressant trials is the wide variation in placebo response among studies, which varies from 20% to more than 70%, and the strong relationship between placebo response and study outcome. Studies with low placebo response tended to show beneficial effects of antidepressant medication on mood and substance use outcome, while studies with high placebo response showed no benefits of medication, a pattern observed in the original meta-analysis [52] and evident in the more recent studies [16, 27, 36, 43, 48, 61, 66]. Several other study features were also found to be related to low placebo response and to benefit of medication, including (a) diagnosis of depression after abstinence has been established, particularly enforced abstinence on an inpatient unit; (b) diagnosis of a depressive disorder, as opposed to merely depressive symptoms; (c) noradrenergic or mixed-mechanism antidepressants (serotonin reuptake inhibitors have shown little evidence of efficacy); and (d) concurrent manual-guided psychosocial intervention (psychosocial interventions were associated with high placebo response and absence of benefit of medication). These are described further in Table 91.1 along with their possible mechanisms and implications for clinical practice.

The phenomenon of high placebo response is not surprising, given the evidence from the wider literature on treatment of depression, which shows cognitive behavioral and other psychosocial interventions to be effective, and where high placebo response is often observed, particularly among patients with only mild to moderate depressive symptoms. Generally, the level of severity of depression in clinical trials needs to be high (severe) before there is consistent evidence

Table 91.1 Factors associated with low placebo response and beneficial effect of antidepressant medication in placebo-controlled trials among patients with depression and substance use disorders

Factor associated with low placebo response and medication efficacy	Potential mechanism	Implications for clinical management
Abstinence established before diagnosing depression	Withdrawal effects and substance-induced depression resolve with abstinence, leaving independent depressions more likely to benefit from medication	Initiate treatment with hospitalization for severely ill patients or evidence-based psychosocial treatment (e.g., cognitive behavioral relapse prevention). Some depression will resolve. Depression that persists should be considered for antidepressant medication
Diagnosis of a depressive disorder, rather than merely depressive symptoms	Depressive symptoms are more likely to represent withdrawal effects or be substance-induced	Base diagnosis of depression on careful clinical history and application of DSM-IV/DSM-5 criteria for independent or substance-induced depression
Noradrenergic or mixed-mechanism antidepressants	Less evidence of efficacy for serotonin reuptake inhibitors (SRI) among substance-dependent patients may relate to the study samples (high placebo response) rather than lack of efficacy. However, several trials suggest SRI makes drinking worse among early onset alcoholics	SRIs may still be considered the first-line treatment based on their good safety and tolerability, but consider switching to a noradrenergic or mixed-mechanism medication (e.g., venlafaxine, duloxetine, mirtazapine, nefazodone) if non-responsive to SRI
Concurrent manual-guided behavioral intervention	Behavioral interventions for substance use disorders (e.g., cognitive behavioral relapse prevention) typically contain elements likely to help with depression (e.g., support, coping skills)	Initiate psychosocial treatment for the substance use disorder as a first step

that antidepressant medication is superior to placebo [22]. For the treatment of substance-dependent patients with depression, then, a reasonable first step is to initiate treatment for the substance use disorder. For more severely depressed or substance-dependent patients, hospitalization may be needed to induce abstinence. Or, on an outpatient basis, evidence-based behavioral treatment or medication for the addiction can be offered. If the depression fails to respond once addiction treatment is initiated, then specific antidepressant treatment should be considered.

91.4.1.3 Depression in Individuals on Medication for Opioid Use Disorder

Individuals with Opioid use disorder (OUD) and comorbid depression represent a unique population as all individuals with OUD should be started on an approved maintenance medication for opioid use disorder (methadone, buprenorphine, or injection naltrexone), which are effective treatments for reducing or eliminating opioid use and protect against the risk of overdose and death. Depressive symptoms have been shown to improve after initiating of each of these medications. Substantially improved depression after starting MOUD would preclude the need or benefit of further antidepressant medication. A recent meta-analysis [35] found evidence to support the effectiveness of tricyclic antidepressants, but not SRIs. The meta-analysis also supports the effectiveness of cognitive behavioral therapies in patients maintained on methadone. The findings suggest initiation of MOUD as a first step for patients with OUD and depressive symptoms, and reserving antidepressant treatment for patients whose depression does not improve after stabilization on MOUD.

91.4.1.4 Behavioral Treatments

As noted above, manual-guided psychosocial treatments for substance use disorders are associated with high placebo response rates in the antidepressant medication trials, suggesting these interventions have some efficacy at treating depression in this population. Some controlled trials have examined cognitive behavioral treatments for depression among substance-dependent patients, with some evidence of efficacy [9–12, 18, 37, 56]. Psychosocial and behavioral treatments have solid evidence of efficacy for treatment of mood and anxiety disorders, and their use avoids risks of drug interactions that may be of concern when prescribing antidepressant medications to substance-dependent patients. Integrated treatments that target both the mood and substance use disorders have been found to be especially helpful for both mood and substance use outcomes [4, 51]. Thus, such behavioral interventions may be considered as a first step, before medication, particularly when the severity of depression is in the mild to moderate range.

It should be noted that several automated interventions have been developed to try to standardize and increase access to evidence-based psychosocial interventions for individuals with comorbid substance use disorders and mood disorders. These programs usually include elements of CBT skills training along with motivational interviewing delivered either online or via a smartphone application. Examples of such programs with good research evidence are Breaking Free [20] and SHADE [38].

91.4.1.5 Treatment of the Substance Use Disorder

Again, it bears emphasizing that when a patient presents with combined substance use and mood disorders, treatment should begin by identifying the substance as a problem and initiating treatment for the substance use disorder. This could range from brief motivational intervention to a more formal treatment regimen. Successful treatment of the substance use disorder, with resultant reduction in substance use or abstinence, eliminates the toxic effects the substance may likely be having on the nervous system and is likely to improve or even eliminate symptoms of depression [7, 8, 45, 72, 75, 79]. That said, when a depressive disorder persists after initiation of treatment for the addiction, specific antidepressant treatment, either behavioral, medication, or a combination of the two, should be initiated.

91.4.1.6 Combined Medications for Depression and Substance Use

There have been a few studies of medications for treatment of addictions, such as disulfiram and naltrexone [57, 58], buprenorphine, or methadone [54, 75], among patients with substance and mood or anxiety disorders or symptoms. These studies suggest such medications are at least well tolerated and potentially effective at improving mood symptoms, probably because they are effective in reducing or eliminating substance use.

One innovative study examined the combination of sertraline and naltrexone for alcohol-dependent patients with depression, finding the combination superior to either medication alone or placebo [59]. Medications for treating substance use disorders are generally underutilized and should always be considered as part of treatment planning generally, as well as specific treatment planning for patients with combined mood and substance use disorders.

91.4.2 Bipolar Disorders

Thorough reviews of medication treatments of bipolar disorder can be found in published reviews elsewhere [76, 77], and treatment of bipolar disorders in the setting of substance use disorders is covered in detail in a separate chapter of this text. Briefly, lithium, anticonvulsants (e.g., valproate, carbamazepine, lamotrigine), and neuroleptics (particularly second-generation agents such as quetiapine, risperidone, and aripiprazole) are the mainstays of treatment for bipolar disorder. Among these, lithium [23] and valproate [70] have been tested in controlled trials and found effective for patients with co-occurring bipolar and substance use disorders. Despite the typical predominance of depressive symptoms and syndromes among bipolar patients, antidepressant medications are often ineffective or even counterproductive among bipolar patients. This again highlights the importance of making the differential diagnosis between bipolar and depressive disorders with the clinical history.

Behavioral treatments can also be helpful as adjuncts to medication treatment for bipolar disorder by building treatment alliance, medication adherence, and coping skills [17, 74]. Weiss and colleagues have developed a group behavioral treatment for patients with combined bipolar and substance use disorders, integrated group therapy (IGT), which has shown evidence of efficacy in a series of controlled trials [80–83]. Interestingly, among its key features, IGT encourages patients to think of their combined mood and substance problems as a single disorder ("bipolar substance abuse"). This stands in contrast to the DSM approach, reviewed above, which involves establishing separate mood and substance use disorder diagnoses. It suggests that a co-occurring mood and substance use disorder may be more than the sum of the separate diagnoses and best treated in an integrated fashion.

91.5 Conclusion

As we hope this chapter has illustrated, considerable evidence has accumulated that mood disorders can be distinguished from substance-related syndromes and effectively treated. This can be accomplished through a careful clinical history and longitudinal observation of the response of mood symptoms and substance use as treatment is implemented to make the differential diagnosis between independent versus substance-induced mood disorders versus intoxication or withdrawal effects of substances, based on DSM-IV/DSM-5 criteria. In all cases, it makes sense to initiate treatment of the substance use disorder as a first step. Substance-induced depression, and even cases that meet criteria for an independent depressive disorder, may respond to behavioral treatment for the substance use disorder. However, for cases that do not respond, specific antidepressant treatment should be considered – either medication or behavioral treatment or both. It has been shown that many cases of substance-induced depression, particularly if a full major depressive syndrome is present, will be observed to persist during abstinence over

follow-up, thus converting to independent depression. For clear-cut or severe cases of major depression, initiation of antidepressant treatment may be considered concurrent with substance abuse treatment from the outset. A careful search of the history should be conducted for episodes of mania or hypomania, indicating the presence of bipolar disorder. Bipolar disorder should generally be treated with mood-stabilizing medications concurrent with the initiation of treatment for the substance use disorder.

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92 Comorbid Anxiety and Alcohol or Substance Use Disorders: An Overview

Francesco Bartoli, Daniele Carretta, and Giuseppe Carrà

Contents

Abstract

The comorbidity between anxiety and alcohol or substance use disorders represents a common and serious clinical challenge, characterized by a high worldwide prevalence. The co-occurrence of these disorders complicates treatment, management and prognosis of both disorders, but it remains often unrecognized and untreated. Mental health professionals should accurately assess and evaluate this comorbidity, although related etiological links and temporal relationships are still unclear and, probably, heterogeneous and multifactorial. Individuals may misuse alcohol and substances to self-medicate their anxiety, avoidant and phobic symptoms, and, on the other hand, anxiety disorders may be induced by alcohol and/or substance misuse. Integrated treatment appears the most promising approach, but there is paucity of evidence on pharmacological and non-pharmacological treatments addressed to both anxiety and substance use disorders. This chapter provides a comprehensive overview of main epidemiological and clinical issues, etiological/temporal

F. Bartoli (✉)
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Department of Mental Health and Addiction, ASST Nord Milano, Milan, Italy
e-mail: francesco.bartoli@unimib.it

D. Carretta
Department of Mental Health and Addiction, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

G. Carrà
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Department of Mental Health and Addiction, ASST Nord Milano, Milan, Italy

Division of Psychiatry, University College London, London, UK

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links hypotheses, and treatment options for the comorbidity between anxiety and addictive behaviors.

Keywords

Anxiety · Alcohol · Substances · Illicit drugs
Addiction · Dual diagnosis

92.1 Introduction

Anxiety is a physiological defensive response for approaching or avoiding threatening stimuli [36]. Excessive levels of anxiety may impair performance and lead to suboptimal behavioral responses and ultimately to mental disorders [36]. Clinical evidence demonstrate that people with anxiety disorders, such as social phobia, generalized anxiety, panic, agoraphobia without history of panic, and specific phobia disorders, often misuse alcohol, prescription (e.g., benzodiazepines) and/or illicit drugs (e.g., stimulants or cannabinoids), being more vulnerable to addictive behaviors than general population. At the same time, individuals primarily treated for an alcohol or drug use disorder are more likely to suffer from a comorbid anxiety disorder, as a direct effect of substance use on anxiety symptoms. Comorbid anxiety and alcohol or substance use disorders represent a serious clinical challenge, influencing both treatment and prognosis.

All clinicians and mental health professionals who care people with anxiety and substance use disorders should have a comprehensive knowledge of main relevant clinical and epidemiological issues such as the following:

- Prevalence and correlates of substance use disorders among subjects suffering from anxiety disorders
- Etiological hypotheses and temporal relationships underlying this comorbidity
- Methods to assess and classify comorbid anxiety and alcohol/substance use disorders
- Specific clinical features, course and prognosis of people with this comorbidity
- Main evidence on prevention and treatment strategies

In this chapter, we provide a comprehensive overview on these issues, summarizing data derived from research that may be useful to the routine clinical practice.

92.2 Epidemiology

Comorbid anxiety and alcohol or substance use disorders are highly prevalent both in general and clinical populations. Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) on 43,093 adults shows that the 12-month prevalence of any DSM-IV substance use disorder among respondents with a 12-month DSM-IV independent anxiety disorder is 15.0% [20]. As regards specific drug use disorders involved, cannabis use was the most common (15.1%), followed by cocaine (5.4%), amphetamine (4.8%), hallucinogen (3.7%), opioid (3.2%), sedative (2.6%), tranquilizer (2.5%), and inhalant/solvent (0.6%) use disorders [16]. People suffering from any anxiety disorder had an odds ratio (OR) of 1.9 (95% CI: 1.7–2.1) for any substance use disorder and of 1.7 (95% CI: 1.5–2.0) for any alcohol use disorder. The likelihood to develop a dependence syndrome was high with ORs of 2.8 (95% CI: 2.4–3.2) and 2.6 (95% CI: 2.2–3.0) for substance and alcohol dependence, respectively [20]. Panic disorder with agoraphobia seems showing the strongest association with a co-occurring substance use disorder.

Other relevant data from North American samples, are provided by the Mental Health Supplement to the Ontario Health Survey [21], a Canadian study on 7195 individuals aged 15–64 years and interviewed using the World Mental Health Composite International Diagnostic Interview (CIDI). A lifetime alcohol abuse or dependence by diagnostic subgroup was found in 8.7% of people with any anxiety disor-

der (OR vs. healthy controls: 3.4; 95% CI: 1.6–7.1), and in 18.0% of people with comorbid anxiety and depressive disorders (OR vs. healthy controls: 7.6; 95% CI: 3.5–16.7).

Relevant epidemiological data are available also from European populations. Data from the French representative sample of the Mental Health in General Population (MHGP) survey [29] on 36,105 adults, showed a prevalence for alcohol abuse of 7.1%, 6.5%, 4.9%, and 3.6% among subjects suffering from agoraphobia, panic disorder, social phobia, generalized anxiety disorder, respectively. The results highlighted an OR of 1.7 (1.4–2.0) for alcohol abuse among people with any anxiety disorder. Similar results were found for drug addiction, with a prevalence of 6.5%, 4.4%, 3.7%, and 2.8% among individuals suffering from panic disorder, social phobia, agoraphobia, and panic disorder, respectively. Drug addiction was significantly associated with the diagnosis of any anxiety disorder, with an overall OR of 2.1 (95% CI: 1.8–2.5).

Baseline data from the Netherlands Study of Depression and Anxiety (NESDA), including 2329 subjects with lifetime DSM-IV anxiety (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) or depressive disorders and 652 controls, showed a significant association between alcohol dependence and comorbid anxiety disorder (OR: 2.4; 95% CI: 1.5–3.8) or for an anxiety disorder associated to a depressive disorder (OR: 4.3; 95% CI: 3.0–6.2) [9].

Epidemiological data are available also from the National Survey of Mental Health and Well Being (NSMHWB), a cross-sectional survey conducted in 1997 and based on 10,641 Australian adults. This study showed that the respondents with an alcohol use disorder (abuse or dependence) were three times more likely to suffer from a 12-month anxiety disorder. On the other hand, people suffering from any anxiety disorder had a prevalence of 16.0% for any past-year alcohol use disorder [13]. More recently, updated data from the NSMHWB, involving 8841 Australians aged 16–85 years, confirmed high rates of comorbidity, especially considering generalized anxiety disorder and social phobia [41].

Finally, some relevant epidemiological information is available also from Latin America. For example, a cross-sectional household survey in a sample of 2302 Brazilian adults from Bahia, Brazil [2], highlighted a prevalence of comorbid anxiety disorders and alcoholism of 14.4%, with an OR of 2.7 (95% CI: 1.7–4.2).

Generally, the comorbidity between anxiety and alcohol or substance use disorders appears a worldwide phenomenon, with similar prevalence rates and high and significant risk of co-occurrence as compared with general population.

A systematic review of 22 unique epidemiological surveys (1990–2014) confirmed the concerning interplay between anxiety and substance use disorders [28]. Relevant meta-analysis showed an association between any anxiety disorders and alcohol abuse (OR: 1.6; 95% CI: 1.3–2.0), abuse/dependence (OR: 2.1; 95% CI: 2-0-2.2), and dependence (OR: 2.5; 95% CI: 2.2–2.9), with similar effect size considering 12-month or lifetime alcohol use disorders. Consistently, anxiety disorders were associated with illicit drug abuse (OR: 2.4; 95% CI: 2.0–2.8), abuse/dependence (OR: 2.1; 95% CI: 1.2–3.9) and dependence (OR: 4.2; 95% CI: 3.4–5.1). Also in this case, no significant differences were found considering 12-month or lifetime illicit drug use disorders [28].

92.3 Etiological Hypotheses and Temporal Relationships of Comorbid Anxiety and Substance Use Disorders

The underlying mechanisms influencing the association between anxiety and alcohol/substance use disorders are unclear because of relevant clinical heterogeneity as different drugs and alcohol may not share identical relationships with different anxiety disorders. This comorbidity is a complex and heterogeneous psychopathological entity and a number of explanatory models have been proposed. Three main etiological hypotheses are worth to be mentioned.

First, an anxiety disorder may be a direct predictor of addictive behaviors. This direction of

the association is supported by evidence suggesting that some individuals may use alcohol and/or illicit substances to self-medicate their anxiety or depressive symptoms (the "self-medication" hypothesis) [26]. For example, alcohol shares several pharmacological effects with sedatives, anxiolytic, hypnotics, or anticonvulsants agents. Further scientific support for the "self-medication" hypothesis comes from longitudinal studies. Data from the NESARC on 34,653 US adults showed that those who had used alcohol or other drugs for reducing their fear, anxiety, or avoidance, had a significant risk of incident alcohol or substance dependence, with adjusted ORs of 2.6 (95% CI: 1.0–6.7) and 5.0 (95% CI: 1.7–14.2), respectively [42]. However, further findings from NESARC [32] did not support the self-medication hypothesis, highlighting that both mood and anxiety disorders may influence the transition from substance use to abuse and/or dependence rather than from abstinence to use. The representative National Comorbidity Survey (NCS) showed that a self-medication intent was present in 21.9% of individuals with any anxiety disorder, with the highest prevalence (35.6%) among people with a generalized anxiety disorder [7]. Longitudinal data seem to support the occurrence of 'primary' mood or anxiety disorders and subsequent substance use disorders among those who self-report self-medication [46]. More generally, social phobia (social anxiety disorder) has been predominantly identified as a primary disorder preceding substance use, although the temporality of other anxiety and substance use disorders is less clear. Indeed, individuals with comorbid social or specific phobia and alcohol dependence are more likely to experience anxiety disorder as primary diagnosis. On the other hand, among individuals with comorbid panic disorder or generalized anxiety disorder and alcohol dependence, it is more likely that individuals had an alcohol dependence as primary diagnosis [38]. A study based on 2801 adult Norwegian twins recently confirmed that social phobia had the strongest association with alcohol use disorder, predicting it over and above the effect of other anxiety disorders, which were better explained by shared genetic risk factors [45].

The second etiological hypothesis posits that alcohol and other substances directly promote the development of anxiety syndromes, in terms of consequences of chronic alcohol/substance use and/or related withdrawal syndromes. For example, although alcohol is a fast-acting and effective anxiolytic agent, it can also increase the levels of anxiety, when the consumption is excessive and the subjects develops withdrawal symptoms, which determine a vicious cycle between anxiety and alcohol use. Another relevant example involves early cannabis exposure that may be related to the subsequent development of an anxiety disorder. A recent study [17] on a cohort of 1756 young Australians recruited in secondary schools showed that the continuity of cannabis use from adolescence to the age of 29 was associated to a risk 3–4 times higher of having a comorbid anxiety disorder. Data from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a prospective study on 3854 adults who had no lifetime anxiety disorders at baseline, highlighted a significant association between baseline cannabis use and 3-year incidence of any anxiety disorder (especially generalized anxiety and panic disorders), after adjusting for age, gender, education, urbanicity, employment, partner status [47]. Furthermore, the existence of anxiety disorders induced by specific classes of substances, such as alcohol, cannabis, cocaine/other stimulants, and opioids, is supported by different neurobiological findings. Recent advances on the complex relationships between stress, anxiety, and alcohol use disorders, show that synaptic communication in brain regions regulating stress and anxiety-related behaviors, such as amygdale and bed nucleus of the stria terminalis, are modulated by endogenous factors like dopamine and corticotrophin-releasing factor (CRF) as well as by acute and chronic use of alcohol [44]. The CRF, a stress-related neuropeptide, has been implicated also in the anxiogenic effects of cocaine withdrawal, as well as in some of long-term effects of cocaine [18]. Cannabis, mainly through the cannabinoid type 1 (CB1) receptors, can induce biphasic responses on anxiety- and fear-related behaviors. Generally, low doses of cannabis tend to induce anxiolytic-like effects,

whereas high doses often cause an increase of anxiety symptoms [35]. Finally, as regards heroine, morphine or other opioids, it should be highlighted that the opioid system seems to play a key role in the neural modulation of anxiety. The activation of opioid system leads to anxiolytic effects both in healthy subjects and in individuals suffering from anxiety disorders since the opioid neurotransmission may serve as an adaptive mechanism addressed to blunt acute negative and distressing affective responses [15]. At the same time, blockade or down-regulation of opioid systems and second messengers is associated with the occurrence of severe anxiety, similar to opiate withdrawal [15].

The third hypothesis is that there may be an independent mediator explaining the relationship between anxiety and alcohol/substance use disorders rather than a direct causal association. Generally, studies on the common-factor models for anxiety and substance use disorders are limited, and publications directly addressing this topic are sparse and focused on alcohol use disorders. Anxiety and alcohol or substance use disorders may share genetic and environmental factors, including family history for anxiety or substance use disorders or traumatic experiences. A representative study showed that, despite it was unlikely that a family history was the third factor explaining this comorbidity, childhood trauma, at least in women, might be partially responsible for the association between these disorders [31]. Mediators of the relationship between anxiety disorders and addictive behaviors may be also some personality traits characterized by a high level of anxiety sensitivity. Individuals with increased levels of sensitivity to anxiety, and who do not have a diagnosable anxiety disorder, may be more likely to develop both anxiety and alcohol or substance use disorders. Furthermore, it has been investigated whether some molecular mechanisms could represent the common factor between anxiety and alcohol/substance use disorders. For example, it has been hypothesized that a decreased function of cAMP response element-binding protein (CREB) in the central nucleus of the amygdale might regulate both anxiety and alcohol intake via the reduced expression of neuropeptide Y (NPY), and, therefore, might provide a common link between anxiety and alcohol use disorders [39].

92.4 Diagnosis and Classification

Anxiety disorders among people suffering from substance use disorders, as well as alcohol or drug addictive behaviors among people with an anxiety disorder, remain often unrecognized and, consequently, untreated. Despite the scientific background of this comorbidity being mainly based on DSM-IV-TR criteria [3], diagnostic issues should necessarily take into account the modifications approved by the recently released DSM-5 [4]. As regards anxiety disorders, these no longer include neither obsessive-compulsive disorder (now in the chapter "Obsessive-Compulsive and Related Disorders"), nor post-traumatic and acute stress disorders (included in the chapter "Trauma- and Stressor-Related Disorders"). At the same time, DSM-5 includes several changes in criteria of the new chapter "Substance-Related and Addictive Disorders", such as the exclusion of the abuse/dependence dichotomy, the introduction of craving as a diagnostic criterion, and the dimensional classification of alcohol and substance use disorders.

Actually, all subjects suffering from any anxiety disorders should be screened for alcohol or substance use disorders at the initial assessment. Early diagnosis and treatment can improve consistently course, prognosis and treatment outcomes of both disorders. However, often it is difficult to ascertain the diagnosis and to assess whether anxiety symptoms are alcohol or substance-induced or represent signs of an independent anxiety disorder. Because of the overlapping of symptoms, a detailed interview is often a step needed to fully differentiate symptoms, which should resolve with abstinence, from anxiety and alcohol/substances use disorders. Therefore, it is important to carefully assess not only symptoms but also distinct diagnoses and clinical syndromes using standardized structured diagnostic interviews, such as SCID (Structured Clinical Interview for DSM Disorders), CIDI

(Composite International Diagnostic Interview), or MINI (Mini-International Neuropsychiatric Interview).

Observing symptoms over a sustained period of abstinence may represent the best way to differentiate substance-induced from independent anxiety disorders. Anxiety may return to baseline levels after the period of withdrawal, so clinicians should always re-evaluate and re-assess clinical features after an appropriate period of abstinence. The minimum duration of abstinence to establish the presence of an independent or substance-induced anxiety disorder is heterogeneous and based on half-life of involved drugs. For example, some benzodiazepines or methadone may require several weeks of abstinence to exclude a secondary anxiety disorder, whereas alcohol or cocaine necessitate shorter periods of abstinence to make valid diagnoses [5].

To diagnose a primary, and not substance-induced, psychiatric disorder, clinicians should verify whether (a) the onset of symptoms occurred before the substance use disorder, (b) the symptoms persist after a period of abstinence according to the characteristics of withdrawal course of each substance, and (c) symptoms exceed those produced by the specific misused substance. On the other hand, clinicians should suspect a secondary anxiety disorder if (a) the anxiety syndrome develops only during periods of active alcohol or substance misuse, (b) the symptoms are well-matched with specific symptoms of intoxication or withdrawal of the involved substance, and (c) the age at onset is atypical for a primary anxiety disorder.

Significant amounts of alcohol and substance use screening tools are available and may be helpful in detecting potential disorders. For example, the ASSIST (Alcohol, Smoking and Substance Involvement Screening Test), developed for the World Health Organization (WHO), is used to detect substance use and related problems in primary and general medical care settings [24]. As regards alcohol use disorders, AUDIT (Alcohol Use Disorders Identification Test) [43] is probably the most widely used screening tool. Relatively recent data from the NESDA [8], including 1756 individuals suffering from a past-year depressive and/or anxiety disorder, showed that AUDIT accurately detected alcohol dependence in depressed and/or anxious men and women, as compared to the gold standard of a CIDI-based diagnosis. However, the overall accuracy in detecting alcohol abuse was limited, without appropriate and identifiable cut-off scores for sensitivity and specificity.

The Addiction Severity Index (ASI) is a multidimensional and semi-structured interview used to measure substance use severity, health-related outcomes, and social problems in individuals suffering from alcohol and other drug use disorders, both at admission to treatment and at follow-up [34]. The ASI can be used appropriately for screening of anxiety disorders, since the clusters of psychological composite scores are significantly related to a current psychiatric diagnosis, especially depressive and anxiety disorders. Therefore, this instrument may be useful for both the assessment of substance use severity and the screening of patients who need an additional evaluation or treatment for their comorbid mental disorder.

However, psychometric scales and diagnostic interviews need to be always integrated with all other information sources useful to assess and differentiate primary and secondary anxiety disorders. Laboratory data, age of onset of anxiety and substance disorders, collateral information, and a family history for anxiety and/or substance use disorder, should be accurately collected.

92.5 Clinical Features, Course, and Prognosis

According to a recently published systematic review [49], anxiety, illicit drug, and alcohol use disorders accounted, respectively, for 14.6%, 10.9%, and 9.6% of overall disability-adjusted life years (DALYs) caused by mental and substance use disorders.

The comorbidity between anxiety and substance use disorders makes difficult treatment and management of both disorders, with mutual negative effects. Individuals with an alcohol use

and co-occurring anxiety disorders are significantly more disabled and use health services more than individuals without this comorbidity [13]. Furthermore, subjects with comorbid generalized anxiety and substance use disorders are more likely than those with a generalized anxiety disorder only to have a lifetime history of any psychiatric disorder, pathological gambling, and an antisocial personality disorder [1]. A severe current alcohol dependence represents an important risk factor for unfavorable course of depressive and/or anxiety disorders, with persistent and unremitted symptoms [10]. The relationship is bidirectional, since the severity of depressive/anxiety symptoms are additional independent predictors of the recurrence of an alcohol dependence [11]. Data from Wave 1 (2001–2002) and Wave 2 (2004–2005) of NESARC showed that substance users with a comorbid generalized anxiety disorder had a worse health-related quality of life, higher rates of treatment seeking, and greater self-reported drug use, supporting the need to define specific treatment options for this clinical population [30]. Similar results were found from the NCS in a variety of clinical domains, such as rates of health care utilization, additional psychiatric diagnoses, physical health problems, and interpersonal stress. Among most of comorbid individuals, social anxiety disorder onset predated that of alcohol dependence, with the former increasing the vulnerability for misusing alcohol [12].

Anxiety disorders are well-known conditions associated to suicidal behaviors. Patients with anxiety disorders are 3.0–3.5 times more likely to complete suicide, 2.5–3.0 times to have suicidal ideations, 2.5 times to attempt suicide [25]. A comorbidity for an alcohol or a substance use disorder may consistently increase this risk. Findings from NESARC study [37] highlighted that individuals with both substance use and any anxiety disorder had an OR of 3.2 (95% CI: 2.4–4.3) for suicide attempts as compared with people without these psychiatric conditions. In particular, substance users with co-occurring anxiety disorders showed a significant higher risk (OR: 1.6; 95% CI: 1.3–2.0) of suicide attempts than those without this comorbidity.

All these findings support the need of further research on innovative intervention strategies to optimally treat co-occurring anxiety and substance use disorders and to prevent clinically severe consequences.

92.6 Treatment and Management

Although several pharmacological and psychological treatments such as cognitive-behavioral therapy have been studied for treatment of anxiety disorders, there is a paucity of evidence on effective treatments for the comorbidity with alcohol or substance use disorders [33]. Furthermore, relevant management is complicated because of different patterns of anxiety and substance use disorders may interact, making difficult to generalize results [48]. New research directions for treatment of comorbid anxiety and substance use disorders are actually needed and should be focused on the following: (a) identification of specific comorbid relationships between these disorders and their underlying processes (e.g., anxiety sensitivity), (b) mechanisms that may maintain the comorbidity, and (c) well-conducted evaluations of treatments that target these mechanisms [6].

Treatment of co-occurring anxiety and alcohol or substance use disorders can be oriented either by dealing primarily with one of the two disorders (generally the more compelling in terms of severity) or, alternatively, by addressing these together. Over the past several decades, empirical studies and clinical guidelines recommendations have undergone a broad shift in approaching this comorbidity, highlighting the importance to provide simultaneous and integrated treatment for both disorders, regardless of the status of the comorbid condition [48]. However, the availability of substances but also the social contexts in terms of individual and local issues might influence treatment outcomes in different countries, where integrated models might perform differently [14]. Consistently, research conducted in this field has yielded inconsistent results, with some studies demonstrating no clear advantage for the simultaneous treatment of anxiety

disorders and addictive behaviors. For example, a meta-analysis [23] suggests that, due to the potential serious consequences of unsuccessful treatment for alcohol use disorders, an integration with interventions addressing co-occurring anxiety disorders could be important, even if the amount of absolute benefit is moderate or even smaller. Inconclusive results were shown also by a systematic review [22] analyzing integrated psychosocial treatment for substance use and comorbid anxiety or depressive disorders, as, although promising, these did not give any significant additional benefit. Generally, a potentially effective strategy may be the early treatment of the disorder the patient is ready to address, while, simultaneously, a motivational approach may be used to improve readiness to change the comorbid problem.

At the same time, there is a lack of consistent evidence for effective pharmacological interventions for both anxiety and substance use disorders, whereas only sporadic interventions studies are available from the scientific literature, e.g., for alcohol use disorders. Selective serotonin reuptake inhibitors (SSRIs) seem effective in reducing and preventing anxiety symptoms, but there is a lack of clinical trials assessing their efficacy in comorbid patients. Among them, paroxetine may be effective for co-occurring social anxiety and alcohol dependence [19]. In addition, preliminary data are available for buspirone in comorbid anxiety and alcohol use disorder [19]. Relevant studies have shown mixed results on comorbid generalized anxiety and alcohol use disorders, but no significant improvement in anxiety or substance use outcomes among subjects with opioid dependence receiving methadone maintenance treatment [5, 33]. Despite benzodiazepines are effective in the treatment of anxiety disorders, their use in individuals with current or lifetime alcohol or substance use disorders may be complicated by their potential for abuse and dependence. More generally, although the use of medications for comorbid psychiatric disorder is encouraged, it is still unclear whether a full detoxification should be achieved before starting psychopharmacological treatment [48].

Finally, use of agents specifically addressed to substance use disorders in individuals suffering from comorbid anxiety disorders is underexplored [5]. In one randomized study conducted at three Veterans Administration outpatient clinics on 254 patients with mental disorders and alcohol dependence, the efficacy of disulfiram and naltrexone, or their combination, was investigated. Subjects treated with an active medication showed more consecutive weeks of abstinence and less symptoms of craving than those treated with placebo, but there were no significant differences in other measures of alcohol consumption. Furthermore, subjects treated with disulfiram experienced significantly fewer obsessive-compulsive and phobic symptoms over time, whereas no clear advantage of combining medications was observed [40].

A secondary analysis of a study evaluating efficacy of naltrexone in veterans suffering from alcohol dependence, showed that among subjects taking antidepressant medications for mood and anxiety symptoms, those randomized to naltrexone had significantly smaller percent drinking days than those receiving placebo. On the other hand, for patients not on antidepressant medication the difference between naltrexone and placebo was not significant [27].

92.7 Conclusions

The dual diagnosis between anxiety and co-occurring alcohol or substance use disorders is a common and serious clinical issue. This comorbidity tends to complicate treatment, management, and prognosis of both disorders. Clinicians face a number of heterogeneous combinations of anxiety and substance use disorders. The prevalence of alcohol or substance use disorders among subjects with anxiety disorders is high worldwide. Etiological links and temporal relationships of this comorbidity are still unclear and, probably, multi-factorial. Individuals may misuse alcohol and substances to self-medicate their anxiety and avoidant and phobic symptoms, although these symptoms often remain unrecognized and untreated. Clinicians should assess this

comorbidity using structured diagnostic interviews, and observing symptoms over a sustained period of abstinence to differentiate substance-induced from independent anxiety disorders. A comprehensive diagnostic evaluation should include also alcohol and substance use assessment. While some pharmacological and psychosocial treatments have shown effectiveness for separate treatment of anxiety and substance use disorders, there is a lack of evidence on treatments addressed to both disorders as dual diagnosis label means more complex needs rather than two distinct problems.

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The Comorbidity of Post-traumatic Stress Disorder (PTSD) and Substance Use Disorders

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Kathleen T. Brady, Jenna L. McCauley, and Sudie E. Back

Contents

Abstract

Post-traumatic stress disorder (PTSD) and substance use disorders (SUDs) frequently co-occur. Among individuals seeking treatment for SUDs, it is estimated that 30–50% meet criteria for lifetime PTSD. Epidemiologic surveys demonstrate that individuals with PTSD are 4–5 times more likely to have a SUD at some point in their lives compared to individuals who do not have PTSD. Self-medication and susceptibility are two hypotheses that have been proposed to help explain the etiological relationship between PTSD and SUDs. It is also possible that common factors, such as genetic, neurobiological, or environmental factors, contribute to the high rate of PTSD-SUD co-occurrence. Integrated psychotherapeutic approaches for the treatment of patients with both disorders show promise. There are also a number of pharmacotherapeutic agents that have demonstrated preliminary efficacy in the treatment of co-occurring PTSD/SUD, but further investigation is needed. This chapter reviews these and other advances in the study of comorbid PTSD and SUDs, and suggests areas for future research and clinical activity.

Keywords

Post-traumatic Stress Disorder · Comorbidity
Trauma · Exposure Therapy

K. T. Brady (✉)
Department of Psychiatry and Behavioral Sciences, Addiction Sciences Division, Medical University of South Carolina, Charleston, SC, USA
e-mail: bradyk@musc.edu

J. L. McCauley · S. E. Back
Medical University of South Carolina, Charleston, SC, USA
e-mail: mccaule@musc.edu; backs@musc.edu

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93.1 Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that occurs after exposure to an event (experienced or witnessed) involving actual or threatened death, serious injury, or threat to the physical integrity of oneself or others. The traumatic event must be followed by at least 1 month of symptoms, such as intrusive recollection, avoidance or emotional numbing, and hyperarousal, which interfere with the individual's ability to function. Substance use disorders (SUDs) commonly co-occur with PTSD. Moreover, comorbid PTSD/SUD is associated with a more complex and costly clinical course when compared with either disorder alone, so identification and treatment of both illnesses in individuals with comorbidity is essential to optimize clinical care.

Discussions of international issues in co-occurring PTSD and substance use are complicated by a number of factors. Definitions and experiences of trauma are culturally bound and in many countries can be connected with issues of politics and social justice. There is also debate about the cross-cultural application of the DSM-defined PTSD criteria. Modifications of the DSM criteria and textual modification have been suggested to improve cross-cultural applicability [47]. Similarly, patterns of substance use and definitions of SUDs also occur in cultural contexts that can tremendously alter the perspectives of acceptable use and willingness to honestly report use. In addition, we do not have accurate estimates of prevalence of either SUDs or PTSD alone or the comorbidity in many areas of the world. Thus, in the sections that follow, much of the data that is presented is based on studies conducted in a few countries. However, the diagnostic, phenomenologic, and neurobiologic underpinnings of the relationships and treatment options for PTSD and SUDs discussed are likely to apply broadly.

93.1.1 Epidemiology of PTSD/SUD Comorbidity

93.1.1.1 United States

Prevalence estimates for PTSD, SUD, and comorbid PTSD/SUD among US adults are primarily garnered from three sources: national epidemiological surveys and Veteran and treatment-seeking populations. Early estimates were provided by the National Comorbidity Survey (NCS; *N* 8098), conducted from 1990 to 1992, indicated a 7.8% lifetime prevalence for PTSD and a 26.6% lifetime prevalence for SUD among the general population (aged 15–54), [54]. Individuals with PTSD were between two and four times more likely to meet criteria for an SUD than those without PTSD. A decade later, the National Comorbidity Survey – Replication (NCS-R; *N* 5692) indicated a 6.8% lifetime prevalence of PTSD and 35.3% lifetime prevalence of any SUD [55]. The 2010 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; *N* 34,653) estimated that 6.4% of the population met lifetime criteria for PTSD, more than one in five (22.3%) of those with PTSD met criteria for drug abuse or dependence, and nearly half (46.4%) met criteria for any SUD [71]. The most recent NESARC interviews, conducted between 2012 and 2013, found a 29% lifetime prevalence of AUD [42]. Approximately 69% of respondents had experienced a PTSD qualifying event and 9% of this group met criteria for PTSD. Individuals with PTSD were 1.5 times more likely to meet criteria for SUD as compared to those without PTSD [40].

Veterans constitute a population of particular interest due to their increased risk for developing both PTSD and SUDs in comparison to the general population [79]. Post-deployment prevalence rates have been estimated at approximately 21% for SUDs and between 15% and 20% for PTSD among Veterans of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) [92]. Severity of combat exposure has been directly linked to risk for development and chronicity of PTSD symptoms and misuse of substances [82]. Administrative data from the Department of Veterans Affairs indicate that among Veterans serving in the Vietnam era or later, almost half (41.4%) with an SUD were also diagnosed with PTSD [69]. Conversely, a recent study followed a large cohort of Veterans diagnosed with PTSD (*n* 272,509) over a three-year timeframe and found that nearly one in five (19.33%) were diagnosed with a comorbid SUD and presence of a comor-

bid SUD was positively associated with mortality at follow-up (hazards ratio 1.70; [17]).

Treatment-seeking individuals have rates of comorbid PTSD and SUD that are consistently higher than the general population. Patients seeking treatment for PTSD are up to 14 times more likely than patients without PTSD to have an SUD [38]. Conversely, among patients seeking treatment for SUDs, lifetime PTSD rates range from approximately 30% to over 60% [20]. Finally, a multimodal assessment of comorbidity among patients at a level I trauma surgery center indicated that 79% had one or more SUD and/or PTSD comorbidity; three in four (74%) met criteria for an SUD, whereas one in four patients endorsed symptoms consistent with PTSD [100]. Variations in prevalence estimates among treatment-seeking populations are most likely attributable to methodological differences, including differences in patient populations sampled and measurement techniques.

93.1.2 International Prevalence Estimates

As mentioned above, we do not have accurate prevalence estimates of the rates of either PTSD or SUDs in much of the world. While the World Health Organization (WHO) has sponsored a series of international studies of mental health disorders, the complexity of the trauma questions used, cultural differences in the definition of trauma, and reluctance to discuss traumatic events likely led to underestimates of PTSD prevalence [53]. In general, the estimates for lifetime PTSD prevalence range from a low of 0.3% in China to 6.1% in New Zealand [32]. The International Consortium to Predict PTSD (ICPP) [29, 93, 9, 23] compiled data from 13 longitudinal studies of acute trauma performed in six different countries found a wide range in baseline PTSD (3.1–61.6%; [75]). As might be expected, some evidence suggests that the risk of PTSD is higher among people from less developed countries who have been exposed to prolonged traumatic experiences associated with wars and political and ethnic violence. For example, 65% of Bosnian refugees resettled in the United States have PTSD [96] and 73% of Palestinian children exposed to war trauma experienced PTSD [91]. In a recent WHO survey, disability from common mental and physical disorders was assessed in nationally representative samples from 26 countries [22]. While physical disorders were considerably more common than mental disorders, there was more disability associated with mental disorders as compared to physical disorders at an individual level. Of all physical and mental disorders, PTSD was associated with the highest level of disability.

While little is known about the prevalence of PTSD in many countries, even less is known about the prevalence of co-occurring PTSD and SUDs. An epidemiologic survey conducted in Australia in 2007 found that the 12-month prevalence of PTSD was 6.4%, higher than the prevalence of any other anxiety disorder [66]. SUDs were much more common in individuals with mental illness as compared to those without mental illness, and nearly 40% of those with anxiety disorders reported daily drug misuse. Data for PTSD specifically was not presented. In a 2004 analysis of a survey of the general population in six European countries, individuals with PTSD were twice as likely to have alcohol abuse and three times as likely to have alcohol dependence [3]. This suggests that the common co-occurrence of PTSD and SUDs, which has been found in the United States, exists in other countries. However, in an investigation of the prevalence of psychiatric disorders in South Africa [88], the authors note that local factors such as poverty and lack of access to substances may change the occurrence of certain psychiatric disorders and comorbidities.

93.2 Etiologic Relationship Between PTSD and SUD

93.2.1 Self-medication Hypothesis

A number of theories have been posited to explain the etiology and functional associations between PTSD and co-occurring SUDs. The most prominent theory is the *self-medication hypothesis* [56]. According to the self-medication

theory, substance use is negatively reinforced when it alleviates PTSD symptoms, such as sleep impairment, intrusive memories, nightmares, hyperarousal, and feelings of estrangement. In support of this theory, Saladin et al. [80] compared individuals with PTSD only vs. PTSD/SUD and found that hyperarousal and avoidance symptoms were more severe among the comorbid PTSD/SUD group. Laboratory-based findings also provide support for the self-medication model. One study examined responsivity to trauma cues (i.e., presentation of personalized trauma narrative) and found that individuals with comorbid PTSD/SUD demonstrate increased craving for substances in response to the trauma cues [24]. Moreover, research has shown that trauma cue-elicited craving is significantly reduced following exposure therapy for PTSD [25]. Finally, increases in craving have been shown to be positively correlated with severity of PTSD symptoms [81].

Among patients with PTSD/SUDs, the drug of choice (e.g., central nervous system depressant or stimulant) may reflect an attempt to alleviate a particular cluster of symptoms. For example, Saladin et al. [80] found that PTSD/SUD individuals with more severe hyperarousal symptoms (Criterion D) were more likely to be dependent on alcohol than cocaine. Likewise, PTSD/SUD individuals with more severe avoidance (Criterion C) and flashback symptoms (Criterion B) were more likely to be dependent on cocaine. More recently, Tull et al. [95] observed a significant relationship among PTSD hyperarousal symptoms and dependence on heroin, as opposed to crack/cocaine and alcohol dependence. In addition to self-medication of PTSD symptoms, individuals with PTSD/SUDs may also use substances to self-medication withdrawal symptoms, which may mimic symptoms of PTSD. For example, withdrawal from alcohol or drugs may result in sleep disturbances, difficulty concentrating, irritability and anger, and feeling "on edge." Thus, withdrawal symptoms may contribute to a reinforcing cycle of self- medication among individuals with PTSD/SUD.

Research examining the temporal order of onset of development of PTSD and SUDs also provides some insight with regard to etiology. In the majority of cases, the development of PTSD precedes the development of the SUD [10, 51]. Furthermore, PTSD and SUD symptoms have been shown to covary over time. For example, Ouimette et al. [68] tracked weekly fluctuations in PTSD and SUD symptoms among 35 PTSD/SUD outpatients for the self-medication hypothesis and showed that increases in PTSD symptoms were associated with increases in SUD severity. More recently, Simpson et al. [85] used daily interactive voice response (IVR) to examine the relationship between PTSD symptoms and same-day as well as next-day alcohol craving among 29 outpatients entering SUD treatment (26/29 had PTSD). The findings showed that greater PTSD severity was associated with greater alcohol craving and greater hyperarousal symptoms were particularly associated with craving. Next-day craving was predicted by nightmares the previous night, emotional numbing, and hypervigilance. Finally, several studies investigating civilian and Veteran patients' perceptions of the interrelationship of PTSD and SUD symptoms demonstrate support for the self-medication hypothesis [10]).

The *high-risk hypothesis* [1] posits that the lifestyle of an individual with an SUD increases the likelihood of being exposed to a traumatic event and subsequently developing PTSD. For example, individuals with SUDs often spend time in dangerous environments and engage in high-risk behaviors associated with obtaining or using substances (e.g., prostitution, theft) that may put them at risk for experiencing a Criterion A event. The *susceptibility hypothesis* posits a biological vulnerability to developing PTSD among individuals with SUDs. Individuals who engage in chronic substance use often experience anxiety and arousal and exhibit poor coping skills (e.g., more avoidant or emotion-focused coping vs. problem-focused coping) [87]. Lastly, there is some evidence that other common factors, such as genetics, common neurophysiologic systems, described below, and prior exposure to traumatic events, may play a role in the etiology of comorbid PTSD/SUD [67, 89].

93.2.2 Neurobiology

A growing body of evidence from basic science and translational studies implicates common neurobiologic pathways and abnormalities involved in anxiety disorders and SUDs. One of the bridging neurobiologic constructs between anxiety disorders and SUDs involves the role of stress. Corticotrophin-releasing factor (CRF), one of the key hormones involved in the stress response, has been implicated in the pathophysiology of anxiety, affective, and addictive disorders. Stress stimuli that activate CRF circuits are also known to potentiate mesolimbic dopaminergic reward pathways in laboratory animals. Similarly, human laboratory studies have shown that emotional stress and negative affect states increase drug craving in drug- and alcohol-dependent individuals. Animal models indicate that early-life stress and chronic stress result in long-term changes in stress responses, which can alter the sensitivity of the dopamine system to stress and increase susceptibility to self-administration of substances of abuse. While it is difficult to systematically delineate the specific neural basis of comorbidity, these studies provide potential pathways to explore in attempts to understand the well-established relationship between early-life adversity, PTSD, and SUDs in adolescents and adults [19, 90].

93.3 Assessment

Symptom assessment is critical to the effective treatment of PTSD/SUD and should ideally encompass detection of trauma exposure and substance misuse, evaluation of diagnostic criteria for PTSD and SUD, and monitoring of symptom severity [94]. Historically, instruments assessing PTSD and SUD were predominantly developed for use with in English-speaking, westernized cultures. However, in 1990, recognizing the need for cross-cultural assessment of mental illness, the World Health Organization (WHO) developed a tool that addressed criteria for both the American Psychiatric Association's Diagnostic and Statistical Manual and the International Classification of Disease (ICD). The resulting Composite International Diagnostic Interview (CIDI; [77]) was a comprehensive, structured, modular interview designed to assess mental disorders – including but not limited to PTSD and SUD. As of 2011, versions of the CIDI have been translated into approximately 25 languages for use in at least 20 countries [99]. Recognition of the important roles that culture and language play in the conceptualization, experience, and expression of PTSD and SUD is increasing [48]. Consequently, increased efforts have been made to translate and adapt a range of instruments previously validated with English-speaking populations (e.g., [2]) as well as to develop culturally specific instruments, to screen, diagnose, and monitor symptoms of PTSD and SUD in a variety of international populations (e.g., [57]).

Regardless of cultural context, there are several general constructs relevant to the assessment of PTSD and SUD. These constructs include determination of the presence, order of onset, frequency, duration, and severity of symptoms, as well as the degree to which symptoms interfere with or impair daily functioning, employ- ment, and interpersonal relationships (for review, see [78]). Several reviews of PTSD assessment (e.g., [78, 98]), SUD assessment [35], and PTSD/SUD assessment (e.g., [51]) are available in the extant literature. When assessing comorbidity, special consideration should be given to the relationships between symptoms, including PTSD symptoms as potential motivators for substance misuse. Validated self-report, semi-structured, and fully structured interview instruments are available to assist with (1) screening for trauma exposure, (2) screening for PTSD/SUD symptoms, (3) determining diagnosis, and (4) monitoring symptom change over time. Table 93.1 presents a sampling of validated measures frequently used in the assessment of PTSD and SUD.

In addition to self-report and interview, biological testing is recommended in assessing SUD and may overcome some of the culture-bound limitations of self- report and clinician-administered assessments. Urine drug screening (UDS) is the

Table 93.1 Assessment and screening instruments

Screening		
Measure	Source reference	Language/Country of origin
Trauma life events questionnaire	Kubany et al. [58]	English
Short post-traumatic stress disorder rating interview (SPRINT)	Connor and Davidson [26]	English
PTSD checklist – civilian version, short form	Lang and Stein [59]	English
Trauma Screening Questionnaire (TSQ)	Brewin et al. [21]	English
Primary Care PTSD Screen (PC-PTSD)	Prins et al. [74]	English
Alcohol Use Disorders Identification Test (AUDIT	Saunders et al. [83]	English
Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)	Humeniuk et al. [49]	English
CAGE	Cooney et al. [27]	English
Drug Abuse Screening Test (DAST)	Gavin et al. [39]	English
Davidson Trauma Scale (DTS)	Ali et al. [2]	English
	Davidson et al. [31]	Urdu/Uganda
HADStress	Gulden et al. [43]	Ethiopia
Diagnosis		
Clinician-Administered PTSD Scale (CAPS)	Blake et al [15]	English
Alcohol use disorders and associated disabilities interview schedul	Grant and Hasin [41]	English
Anxiety Disorder Interview Schedule for DSM-IV (ADIS)	DiNardo et al. [33]	English
Composite International Diagnostic Interview, version 3.0	Robins et al. [77]	English, German, French, Dutch, Chinese, others
Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I	First et al. [34]	English
Mini-International Neuropsychiatric Interview (MINI)	Sheehan et al. [84]	English
Self-Report Inventory for PTSD (SRIP)	Kok et al. [57]	Dutch
Post-traumatic stress disorder interview for Vietnamese refugees	Dao et al. [30]	Vietnamese
Symptom monitoring		
Impact of events scale	Weiss and Marmar [97]	English
PTSD Checklist (PCL)	Blanchard et al. [16]	English
PTSD Symptom Scale (PDS)	Foa et al. [36]	
Addiction Severity Index (ASI)	McLellan et al. [62]	English
Timeline Follow-Back (TLFB)	Sobell and Sobell [86]	Universal
Symptom interaction		
Inventory of drinking situations	Annis et al. [5]	English
Drinking motives questionnaire	Cooper [28]	English
Inventory of drug-taking situations	Annis and Martin [4]	

most common and preferred method for detecting illicit drug use given that it is cost effective and minimally invasive and provides a quantitative means for measuring the use of substance.

Additional biological assessment options exist for use as either adjunctive or alternative assessments of SUD: testing of bodily fluids, such as blood and saliva, breathalyzer analysis for recent alcohol use, hair analysis techniques, and a blood- based testing method known as percent carbohydrate-deficient transferrin [6]. These methods are less frequently used due to higher cost, increased invasiveness, false positives, and/or narrow detection windows [52].

93.3.1 Psychotherapeutic Treatment

Historically, psychosocial treatment approaches for individuals with PTSD and SUDs have adhered to the *sequential treatment model*, in which the SUD is treated first and trauma work is deferred until a period of sustained abstinence (e.g., 3–6 months) has been achieved. This generally entails two separate providers (i.e., one provider addresses SUD and another addresses PTSD) in two separate clinics with little cross-communication. Proponents of the sequential model state that (a) continued substance use will impede therapeutic efforts and/or (b) trauma-focused work may increase risk for relapse [72]. However, there is little empirical data to support these concerns. Given the high co-occurrence of PTSD and SUDs, the covarying interrelationship between PTSD symptoms and substance use severity, as well patients' preferences for treatment (e.g., less than 30% of patients prefer sequential treatments; [10]), recent advances in psychosocial treatments have focused on the development and testing of *integrated treatment models*. In contrast to sequential treatments, integrated treatments are provided by the same clinician and address both the SUD and PTSD concurrently. The integrated model posits that addressing the PTSD symptoms early in treatment will likely improve recovery from SUDs, particularly if substances are being used to self-medicate trauma-related symptoms [7, 45, 63].

Compelling support for the integrated model is provided by recent investigations examining the temporal course of symptom improvement among PTSD/SUD patients. Among 94 outpatients with alcohol dependence and PTSD, improvements in PTSD symptoms had an impact on improvements in alcohol-dependence symptoms, but decreases in drinking did not impact PTSD symptoms [10].

Hein et al. [45] replicated these findings using data from a larger sample (*N* 353) from a National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) study. For every unit of PTSD improvement, the odds of being a heavy substance user at follow-up decreased more than fourfold [45]. A growing body of literature examining the tolerability and efficacy of addressing PTSD among SUD patients demonstrates that substance use typically decreases significantly and does not increase with the addition of trauma-focused interventions [11, 45, 63].

Prolonged exposure (PE; [37]) therapy has been deemed one of the most effective treatments available for PTSD [50], but there is limited research exploring its efficacy in substance-abusing populations. PE involves having the patient revisit the traumatic memories (i.e., imaginal exposures) and approach safe but anxiety-producing situations in real life that are avoided by the patient (e.g., in vivo exposures). A recent meta-analysis demonstrated large effect sizes for PE in comparison to control conditions [73]. Furthermore, a longitudinal study conducted among 65 patients 5–10 years after receiving PE demonstrated maintenance of effects with only 17.5% of patients meeting diag- nostic criteria for PTSD [76]. PE has demonstrated effectiveness in addressing PTSD among a variety of traumatic stress populations, including victims of rape, physical assault, refugees, motor vehicle accidents, combat, terrorism, childhood abuse, and mixed trauma types [37, 64, 76]. Despite that fact that PE is one of the most effective treatments for PTSD, the majority of integrated treatment interventions developed to date generally do not include PE components. Rather, treatment tends to focus on psychoeducation, exploring the relationship between PTSD symptoms and substance use, self-management of symptoms and negative emotions, and devel- opment of cognitive behavioral coping skills [61].

One of the most widely used and investigated integrated treatments to date is *Seeking Safety* (SS), a non-exposure-based 24-session manualized therapy that prioritizes establishing and maintaining safety [65]. Other key concepts include anticipating dangerous situations, setting boundaries, anger management, and affect regulation. In a study of 107 women comparing SS to relapse prevention [44], both treatments resulted in improved substance use and PTSD severity; however, no significant between group

differences in PTSD or SUD symptoms were observed. In a larger national multisite community study, SS was compared to a women's health education (WHE) group [46] in 353 women. Both SS and WHE resulted in significantly improved PTSD symptoms; however, neither group resulted in a significant reduction in abstinence rates over time. Of interest, modified versions of Seeking Safety have been used successfully to treat intergenerational trauma in Aboriginal peoples in Canada [60].

Back and colleagues developed an exposure-based, manualized cognitive behavioral therapy for PTSD/SUDs [8] called *COPE* (*Co*ncurrent Treatment of PTSD and Substance Use Disorders Using *P*rolonged *E*xposure), which combines evidence-based cognitive behavioral therapy for SUDs with the key components of prolonged exposure for PTSD [37], and includes both in vivo and imaginal exposure techniques. COPE was initially trialed as a 16-session, individual intervention and tested in an uncontrolled psychotherapy development study among patients (*N* 39) presenting with comorbid PTSD and cocaine dependence [18]. In this study, no signs of increased substance were observed with the inclusion of PE. Treatment completers demonstrated significant improvements in all PTSD symptom clusters and a significant reduction in cocaine use from baseline to end of treatment (Brady et al. 2001). Reductions in PTSD and SUD symptoms were maintained at six-month follow-up. Mills et al. [63] recently completed a randomized control trial of COPE plus treatment as usual (TAU) vs. TAU alone. Participants were 103 patients (62.1% female) with civilian PTSD and SUDs in Sydney, Australia. For this trial, COPE consisted of 13, individual sessions. From baseline to nine-month follow-up, significant reductions in PTSD symptom severity were found for both groups; however, the COPE group demonstrated a significantly greater reduction in PTSD symptom severity (mean difference − 16.09) and lower rates of PTSD diagnosis as compared to the control group (56.4% vs. 79.2%). No significant between-group differences in rates of abstinence, number of SUD dependence criteria met, or retention were found. The findings suggest that integrated PTSD/SUD treatments employing PE techniques for PTSD can be used safely without an increase in substance use, can lead to sustained improvements across various domains (e.g., depression), and produce greater improvements in PTSD than TAU. Currently, COPE is being evaluated as a 12-session intervention in a randomized controlled trial among Veterans, and the preliminary findings are positive [11]. Recently, prolonged exposure has been incorporated into existing residential SUD treatment with promising preliminary results supporting its safety, feasibility, and efficacy [14].

93.3.2 Pharmacological Treatment

A recent review pharmacotherapeutic treatment for co-occurring PTSD and alcohol use disorders (AUDs; [70]) found nine double-blind, placebo-controlled trials; three focused on medications to treat PTSD (serotonin reuptake inhibitors); three focused on agents to treat AUD (naltrexone and disulfram); three used agents targeting both disorders (topiramate, alpha-adrenergic agonists; neurokinin-1 receptor antagonist) and one study with a medication to treat PTSD and a medication to treat AUD (naltrexone and sertraline). All but one of the studies found that PTSD symptoms and drinking outcomes improved significantly over time and there was not one agent with clear evidence of efficacy in this comorbid group. In general, there was evidence to suggest that individuals with comorbidity can be safely prescribed medications generally used to treat either PTSD or SUDs and evidence to support the use of medications to treat AUD among those with comorbid PTSD. Two pilot studies of glutamatergic agents targeting both PTSD and AUD have shown promise. Batki et al. [13] found that topiramate (300 mg/day) improved drinking outcomes and reduced hyperarousal symptoms in 30 veterans with co-occurring PTSD/AUD. Back and colleagues et al. [12] found that N-acetylcysteine (2400 mg/day) improved PTSD symptoms and decreased craving but not alcohol/drug use in

35 veterans with PTSD/SUD. While these studies show promise, clearly more work needs to be done to explore pharmacotherapeutic treatments of co-occurring PTSD/SUDs.

93.4 Conclusion

In summary, while we do not have information about the international prevalence estimates of co-occurring PTSD and SUDs, many studies suggest that these two disorders commonly co-occur. A number of theories have been posited to explain the functional relationship between these disorders, and there are clear neurobiologic connections. Medication treatments have shown some promise, but more investigation is needed. In terms of psychotherapeutic approaches, integrated treatment has been accepted as a safe and effective model of treatment. Although non-trauma-focused treatments offer some PTSD symptom reduction, data suggests that trauma-focused, exposure-based treatment offers greater symptom reduction than non-exposure-based treatment in SUD treatment programs. There are promising pilot developments in the pharmacotherapy of PTSD/SUD, but more work needs to be conducted before there is a significant clinical impact. Recent evidence demonstrates that improvement in PTSD positively impacts substance use outcomes, clearly supporting a more rigorous approach to the assessment and treatment of PTSD among patients with SUDs.

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Psychotic Disorders and Substance Use Disorders

94

Daniele Carretta, Francesco Bartoli, and Giuseppe Carrà

Contents

Abstract

The comorbidity of psychotic and substance use disorders (SUDs) is a major issue in mental health, because of its high frequency and poor prognosis. Moreover, it is often neglected both for the difficulty to assess SUDs in psychotic patients and for scarce attitude to evaluate and treat substance misuse by psychiatric services staff. On the other hand, patients with psychosis and SUDs can receive inadequate treatment for psychosis by SUDs services, for similar reasons.

D. Carretta (✉)
Department of Mental Health and Addiction, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

F. Bartoli · G. Carrà
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
e-mail: f.bartoli@campus.unimib.it

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Assessing and treating this comorbidity requires the knowledge and the integration of specific tools and interventions, which should be tailored towards patients' clinical condition and that can be difficult to manage in daily clinical practice.

94.1 Introduction

Since the 1980s, a strong literature evidence has shown that psychotic disorders are frequently associated with substance consumption or clinically relevant substance use disorders (SUDs), namely alcohol use disorders (AUDs) or drug use disorders (DUDs).

This comorbidity contributes to the definition of "dual diagnosis", known as the simultaneous presence of a mental disorder and a substance use disorder.

Psychotic disorders typically arise at young ages, when people are laying the foundations of their own life, often seriously compromising the process, leading to unfavourable social, residential and occupational outcomes. SUDs are frequently associated with these disorders, generally with a further pejorative effect on the prognosis [1].

94.2 Epidemiology

94.2.1 The United States of America

The past-year prevalence of schizophrenia and other psychotic disorders among adults (age of 18 or older) in the United States (US) is estimated to be 0.3%, while the lifetime prevalence is about 0.5% [2].

SUDs are more common than psychoses. The third National Epidemiologic Survey on Alcohol and Related Conditions (NESARC III), carried out between 2012 and 2013 among US adults according to the definitions of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), shows prevalence rates of 13.9% for AUD in the past year and 29.1% for AUD lifetime [3], as well as 3.9% for other DUDs in the past year and 9.9% lifetime [4].

A great part of the evidence about prevalence of dual diagnosis among people with psychotic disorders in the US general adult population comes from three large studies, the Epidemiologic Catchment Area (ECA) Study, the National Comorbidity Survey (NCS) and the already cited National Epidemiological Survey of Alcohol and Related Conditions (NESARC). These studies confirm the high prevalence of alcohol and substance misuse among people affected by psychoses. Moreover, psychotic disorders are more frequent among alcohol and substance misusers than in general population, even if prevalence rates are lower than observed for alcohol and substance consumption in psychoses.

The ECA study was carried out between 1980 and 1984 on a sample of more than 20,000 subjects aged over 18 years, and found that, among individuals with schizophrenia, SUDs had a prevalence of 47% (odds ratio = 4.6, $p < 0.001$). Indeed, 34% of subjects had an AUD (OR = 3.3, $p < 0.001$), and 28% a DUD (OR = 6.2, $p < 0.001$). Conversely, comorbid schizophrenia was found in 3.8% of subjects with an AUD and in 6.8% of those with a DUD [5]. The NCS study was conducted between 1990 and 1992 on a sample of approximately 8100 individuals between 15 and 54 years of age, and found a prevalence of SUDs of 44.8% among those suffering from chronic psychotic disorders [6]. Finally, the NESARC study interviewed more than 40,000 non-institutionalised adults in 2000–2001, finding that psychotic disorders have a prevalence of 1.5% among people affected by AUDs and of 4.2% among people affected by DUDs [7].

The high prevalence of SUDs among people suffering from psychotic disorders is confirmed by a meta-analysis that pooled the results from ECA, NCS and NESARC with those from other smaller studies, all published from 1990 to 2017. The authors report an overall prevalence of SUDs of 41.7%, a prevalence of 30% for AUDs and a prevalence of 33% for DUDs [1].

94.2.2 Europe

European evidence about psychotic and substance use disorders show prevalence rates in the general population of about 1% and between 0.3% and 3%, respectively [8, 9]. In Europe, unlike the USA, there are no studies that routinely and comprehensively investigate the prevalence of dual diagnosis across all the countries [10]. However, the European Schizophrenia Cohort (EuroSC), a multicenter prospective study carried out in Europe on a cohort of 1200 patients with schizophrenia, found a prevalence rate of 24% for comorbid dependence from alcohol or other substances, mostly due to alcohol, albeit with some differences between countries where the study was carried out. Dual diagnosis had a prevalence rate of 35% in the UK, 21% in Germany and 19% in France [11]. Smaller studies have shown similar prevalence rates across European countries. Moreover, according to various local studies, psychotic disorders have a prevalence of about 5–15% among individuals affected by SUDs [12, 13].

In summary, in Europe prevalence rates of substance misuse among people with psychotic disorders seem lower than in the USA [11]. The differences between USA and Europe may, at least partly, depend on important differences in lifestyle and care pathways of the surveyed populations. Thus, there is the need of a prudential approach, as the epidemiology of dual diagnosis depends upon many factors, which may vary across different countries. Evidence must be interpreted considering local settings' features.

94.2.3 Critical Issues of Dual Diagnosis Epidemiological Studies

Most of the studies on the comorbidity of psychotic and substance use disorders deal only with schizophrenia, neglecting other psychoses, so very scarce evidence is available for the latter [8]. Furthermore, most of the evidence on dual diagnosis comes from the USA, which limits its generalisability, because of the specific features of their health care system.

Moreover, available epidemiological studies on dual diagnosis have shown various methodological limitations. First, it must be considered that recruitment of people with dual diagnosis may not be so obvious: the assessment techniques show variable validity [14]. Secondly, the DSM-5 merged alcohol and substance "abuse" and "dependence" in a unique category, which may bring an increase in the prevalence of these disorders [15]. This may be useful to elicit attention to the problem, but will make difficult to make comparisons between studies based on DSM-5 and those based on its previous editions, even if many studies used to merge the categories of abuse and dependence [16].

There are also issues regarding sampling: convenience samples help to ascertain and explain the critical aspects of treating specific populations, but they may provide misleading findings about the real prevalence of dual diagnosis. It is well known that dual diagnosis is significantly more common among some special populations, e.g., patients admitted to acute psychiatric settings, the homeless and users of the criminal justice system [17]. Finally, two interrelated problems must be considered: the spread of polysubstance abuse, including alcohol, and the difficulties in ascertaining a problematic substance use. Polyabuse is particularly common among patients suffering from psychotic disorders [16, 14, 18], so each patient might have more than one SUD, making almost impossible distinguishing them. However, patients often deliberately hide their consumption of substances, leading to an underestimation of their prevalence [19].

As a whole, the epidemiological research about dual diagnosis shows many uncertainties, partly due to organisational problems and partly due to the very nature of the patients. In fact, psychotic disorders and SUDs are severe illnesses, and suffering from these conditions makes people exposed to several confounding factors, which can hamper validity of correlations and

causal links. However, an epidemiological understanding is needed to implement appropriate treatment programmes.

94.3 Potential Aetiological Relationships Among Psychotic and Substance Use Disorders

Substance use and psychotic disorders seem to be linked by a mutual risk relationship [20]. Their strong epidemiological, biological and clinical association has worked as a springboard for a large number of research initiatives aimed at understanding the aetiology of this association. The efforts have been mainly directed in ascertaining if one has a significant role in the aetiology of the other. Furthermore, some authors have hypothesised that both these disorders may be due, at least partly, to a common cause [21]. However, there are no firm conclusions about any etiological links between SUDs and psychosis, but various risk factors for dual diagnosis have been found and some aetiological models have been developed.

94.3.1 Correlates and Risk Factors for Dual Diagnosis

Psychotic disorders and alcohol and substance use disorders seem to share many genetic and psychosocial risk factors [21] that seem to promote the development of both conditions. Moreover, the risk factors associated with dual diagnosis are largely similar to those for substance misuse found in the general population [22]. In this paragraph, an overview of them will be presented.

94.3.1.1 Genetics

Both SUDs and psychotic disorders have their own genetic risk factors, namely a polygenic inheritability with multiple genes giving each one a small contribute to the global risk of developing these diseases [23].

Until a few years ago, it was thought that vulnerability to SUDs and psychosis depended on distinct mechanisms of inheritance [24]. However, more recently some genes have been identified contributing to the pathogenesis of both disorders, with many of them involved in brain development and neuronal plasticity, such as the genes for neuregulin-1 (NRG1), neurexins (NRXN1 and NRXN3), the cathecol-O-methyl transferase (COMT) and the monoamine oxidase A (MAOA - 21).

94.3.1.2 Male Sex and Young Age

These characteristics are strongly associated with comorbid psychotic and SUDs, regardless of the substance considered or setting [1, 19]. This is probably due to the propensity of young men in experimenting risky behaviours, while females tend to take alcohol or substances to self-medicate stress, depressive or trauma-related symptoms [1].

94.3.1.3 Low Educational Level and Unemployment

These factors seem associated with both conditions [21], probably because they favour drift towards social relationships and situation with high risk of substance consumption [25].

94.3.1.4 Substance Availability and Attitude Towards Substance Consumption

Living in social contexts characterised by high availability of substances and belonging to a social network familiar with consumption seems to favour its spread among individuals with psychotic disorders [19].

94.3.1.5 Personality and Neurodevelopmental Disorders

Personality disorders are relevant risk factors for SUDs, as they can be found in up to 50% of problematic alcohol or drug users. Antisocial and borderline personality disorders are the most exposed ones, because of their diathesis to risky behaviours, impulsive search for gratification and inability to make long-term plans [10].

Attention Deficit Hyperactivity Disorder (ADHD) is a risk factor for SUDs, with prevalence rates of 5–33% among users seeking treatment for these conditions [10], and is frequently associated with schizophrenia, posing an even greater risk for SUDs [26]. Even Autism spectrum disorders (ASD) are often comorbid to schizophrenia [26]. They have been considered protective towards alcohol and substance use disorders, because of the limited social relationships of the affected individuals. However, prevalence of alcohol and substance consumption among individuals with ASD varies from 0.7% to 36%, being more common than expected [27].

In summary, ADHD and ASD are frequent comorbidities of schizophrenia, and ADHD is by itself a well-recognised risk factor for alcohol and substance misuse. Therefore, AUDs and SUDs should be assessed in presence of a psychotic disorder associated to a neurodevelopmental disorder.

94.3.1.6 Early Onset of Illness and Good Premorbid Functioning

Individuals with good premorbid functioning and earlier onset of schizophrenia are more prone to AUDs and SUDs. As a good premorbid functioning usually correlates with later onset of illness, the anomaly of earlier onset of psychosis has been explained with the hypothesis that using alcohol or illicit drugs may have anticipated the emergence of schizophrenia [14].

94.3.1.7 Subthreshold Psychotic Symptoms

Subclinical psychotic symptoms, typical of prodromal manifestations of psychotic disorders, are risk factors for both subsequent onset of psychotic disorders [28] and for alcohol or substance consumption [23].

94.3.2 Etiopathogenesis: Models and Evidence

It is not known why AUDs and SUDs are so common among people suffering from psychotic disorders. Various etiopathological models have been proposed and will be presented below.

94.3.2.1 The Self-Medication Model

The self-medication model is a long-standing hypothesis. In its original shape, it claims that alcohol or other substances should be chosen by individuals affected by psychosis to counteract specific symptoms of this disorder or side effects of the pharmacological treatment [23, 14]. This model is supported by numerous research results that show how the toxicodynamic properties of various substances of abuse may compensate dysfunctions in the neuronal circuitry of affected patients [21, 17].

The self-medication model should imply a correlation between certain symptoms or pharmacological side effects and specific patterns of substance consumption, but research evidence has refuted this model showing that substance consumption patterns among individuals suffering from schizophrenia are similar to those shown in general population of the same environmental context [25, 24]. Furthermore, it has been argued that if drugs of abuse improved symptomatology, probably the prognosis of patients with dual diagnosis would be better, but the literature is almost unanimous in affirming the contrary [25], and some experimental results have questioned the effectiveness of some substances in relieving symptoms of psychotic disorders [23].

Some evidence, however, supports a less mechanistic form of the self-medication hypothesis. According to this one, substance consumption in psychosis is interpreted as an attempt to get high or relieve dysphoria, anxiety or depressive symptoms, similarly to what happens in general population, rather than as a way to medicate specific psychotic symptoms [24, 14]. The long-term counterproductive effect of substance consumption seem to be a consequence of patients' choice of the temporary benefits at the expense of a broader and less immediate negative impact on their lives, maybe sustained by the deficit in planning long term actions in schizophrenia [29].

94.3.2.2 Environmental Stress Vulnerability

According to this model, the problematic substance use would be one of many factors that can precipitate the development and exacerbation of psychotic disorders in susceptible individuals [17]. Even if alcohol, cannabis and methamphetamines have been proved capable of causing persistent psychoses, along with transient psychotic syndromes [30], this model seems simplistic, as several studies have reported that psychotic disorders are not merely caused by SUDs, given the mutual risk relationship that seems to bind these two syndromes [21].

94.3.2.3 Vulnerability to Comorbid Dependence

In this model, suffering from a psychotic disorder is per se a risk for substance use disorders, as both illnesses may share various biological substrates. The model is supported by evidence at various levels.

From a psychosocial point of view, the cumulative risk factor hypothesis motivates the vulnerability seen in schizophrenia to SUDs with the cumulative effects of marginalisation, exposure to deviant environments and poor cognitive and social skills, a lacking that hampers both the capability of avoiding drugs offers and the capacity of anticipating and counteracting the negative consequences of substance consumption [23, 25, 19].

From a neurobiological point of view, the primary addiction or reward deficiency syndrome hypothesis suggest a role for a deficit in the reward system and related neuronal networks. The reward system consists of the dopaminergic neurons that project their axons from the mesencephalic ventro-tegmental area (VTA) to the nucleus accumbens (NA), located in the ventral striatum. In schizophrenia, functional magnetic resonance imaging studies have shown a deficit in the activity of the reward circuit coupled with hypersensitivity to substance-related cues. These findings may explain both the attempt of patients to self-medicate the dysfunction of the reward circuit and the diathesis to the development of an alcohol or substance use disorder. The dysfunction of the reward system may in turn be due to developmental abnormalities in hippocampus and frontal cortex [23].

All these hypotheses about the etiopathogenesis of dual diagnosis probably describe only some of its facets, so they should not be conceived as mutually exclusive. For instance, attempts to self-medicate psychotic or unspecific symptoms could be reinforcing elements for substance consumption, and people with schizophrenia may be highly vulnerable to such reinforcement. It is also possible that pathogenesis mechanisms shared by all or most of drugs of abuse coexist with mechanisms related only to specific psychotropic substances [21].

94.3.3 Cannabis and Psychotic Disorders

Cannabinoids are both the most used illicit substances in the world and a source of possible pharmacological treatments for several conditions, including chronic pain, multiple-sclerosis and Parkinson Disease [31]. Cannabis contains more than 100 phytocannabinoids, of which the most abundant and studied are (−)-trans-Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is considered the main responsible for the psychoactive effects of cannabis, while CBD seems to reduce them. THC acts as a partial agonist on the cannabinoid receptors CB1 and CB2, whose major endogenous ligands are arachidonylethanolamine or anandamide and 2-arachidonylglycerol [32, 33]. CB1 seems the only one involved in the psychoactive effects of cannabis [31]. CBD seems to act as an allosteric negative modulator of CB1, a reuptake and hydrolysis inhibitor of anandamide and an agonist on 5HT1A, α1 and μ receptors [32].

Many countries have shown a tendency towards cannabis legalisation, both for pleasure and medical purposes, so contributing to the already ongoing increase in its consumption [31]. However, since the 1960s, there has been a growing concern about its impact on mental health, including its role in the onset and exacerbation of psychotic disorders [32].

Research evidence show that cannabinoid consumption can induce acute psychotic episodes, as well as clinical exacerbations of already existing chronic psychotic disorders [34]. A still debated question is the capability of cannabinoids of causing schizophrenia or other chronic psychotic disorders.

The epidemiological data elaborated by various meta-analyses show that there is a dose-dependent correlation between cannabinoid consumption and the onset of chronic psychotic disorders, whose age of onset is significantly earlier among cannabis users. Cannabinoids also seem to erase the gender differences in the onset of these disorders, which typically arise in men before than in women [32, 23].

Clinical research has confirmed that, despite robust epidemiological evidence, the correlation between cannabis consumption and psychosis is complex: for instance, various cross-sectional studies report that it seems mediated by comorbid psychopathology [28].

From a neurobiological perspective, cannabis exposure and psychotic disorders share many neurobiological features, widely described in several reviews. For instance, cannabis use has been correlated to an increase in striatal levels of dopamine, similarly to what happens in acute psychosis. Moreover, chronic cannabis consumption has been correlated to a reduction in dopamine synthesis and release, which has been associated to impairment of executive functions and negative symptoms. Cannabinoids can reduce the activity of the inhibitory interneurons that use γ-aminobutyric acid (GABA) as a neurotransmitter, including those located in hippocampus and prefrontal cortex, two regions in which there have been found several structural abnormalities in schizophrenia. In these two regions, moreover, cannabinoids can induce a reduction in glutamate levels, similarly to what is seen in schizophrenia [31].

Bossong and Niesink formulated two hypotheses about the role of cannabis in psychotic disorders. The former starts from the evidence that the CB1 receptor has a role in the brain development, both in prenatal age and in adolescence. Adolescence is crucial for the development of the superior brain functions, so heavy exposure to exogenous cannabinoids may disturb this process, causing alterations that might result in schizophrenia [34]. This hypothesis is sustained by various studies showing that heavy cannabis users may present hippocampal and amygdalar atrophy and several alterations in neural connectivity, as well as, from a functional point of view, alterations in cognitive and emotional processing. Taken together, all those structural and functional alterations show similarities to findings related to schizophrenia, so suggesting an etiopathological role in its development [32]. The latter hypothesis speculates that cannabinoid consumption, altering perception and memory, might alter the perception of exogenous stimuli, relevant for brain maturation in adolescence [34].

Despite the consistent neurobiological evidence correlating cannabis consumption and chronic psychosis, several experimental results have not been unanimously replicated, probably because of methodological heterogeneity and the role of unknown confounding factors [31]. Therefore, Bloomfield and colleagues have speculated that cannabis may cause chronic psychotic disorders in two not mutually exclusive ways: catalysing the same etiopathological pathway that leads to idiopathic chronic psychotic disorders and through alternative ways that lead to a similar syndrome [32].

Altogether, the research results about the link between cannabis and chronic psychotic disorders point out that cannabis consumption seems to be neither a necessary nor a sufficient cause for the onset of chronic psychotic disorders. It is one of the many factors, partly known and partly unknown, that interact to give each person a specific risk for chronic psychosis, but its contribution in the genesis of the disorder may be bonded to the presence of other factors.

Two additional sources of complexity are the proportions of exogenous cannabinoids contained in cannabis products and the role of synthetic cannabinoids. The cannabis products sold in the legal and illegal market contain different amounts of THC and CBD, so adding heterogeneity to epidemiological and clinical findings. Moreover, the last 20 years have shown an

increase in the concentration of THC, both in USA and Europe, from about 4% to about 12–13%, as well as an increase in the THC/CBD ratio [33]. Given the psychoactive role of THC and the opposite effects of CBD, this variation, besides representing a public health concern, makes difficult to make comparisons among the oldest and the most recent research results.

Synthetic cannabinoids are another source of concern, both from a medical and from a research point of view. They appeared in the European market in 2006, and then their consumption has progressively grown. They are sold as a mixture of different compounds, generally with a stronger agonist activity on CB1 receptor than THC. Besides their capability of inducing acute psychosis and acute recurrences of chronic psychotic disorders, they seem capable of inducing chronic psychotic disorders by themselves, although with the uncertainties described above [35]. However, their high potency legitimates the suspicion that they may represent, from a toxicodynamical point of view, a menace even higher than the one posed by phytocannabinoids.

Taken together, all these research results suggest that preventing or reducing the use of both phytocannabinoids and synthetic cannabinoids may be useful to delay or maybe avoid the onset of psychotic disorders, especially in people at high risk. This is important especially in the age of development, so health education interventions are highly appropriate especially for pregnant women and adolescents. In fact, even if the onset of psychosis were inevitable, delaying the onset could allow many patients to reach a developmental level sufficient to have a decent life.

94.4 Clinical Features, Course of Illness and Diagnosis

94.4.1 Clinical Features and Course of Illness

After tobacco, the most frequently used substances among people suffering from psychotic disorders are alcohol, cannabis and, slightly less frequently, cocaine or amphetamines [23, 10, 19], similarly to what happens in the general population [31].

Clinical pictures of comorbid psychotic and substance use disorders may be complex, as they often appear as a mixture of signs and symptoms of acute or chronic psychosis, intoxication, withdrawal, and chronic substance use, which may involve multiple substances. The clinical picture may be further complicated by a substance-induced psychosis, namely a psychotic syndrome due to substance intoxication or withdrawal [10, 19].

Any substance, if taken in large quantities and over a long enough period can induce a psychotic state, as well as a relapse of a chronic psychotic disorder. The clearest psychotogenic effect has been shown for stimulants (e.g., amphetamines and cocaine), cannabinoids and NMDA receptor antagonists (e.g., phencyclidine and ketamine). Lysergic acid diethylamide (LSD) and 3,4-methylenedioxy-N-methylamphetamine (MDMA or ecstasy) can cause hallucinations, but usually only during acute intoxications. Alcohol and benzodiazepines can induce psychotic symptoms only in acute withdrawal states, while opiates and nicotine have not clearly shown psychotogenic properties. Acute presentations of schizophrenia and substance-induced psychoses may be indistinguishable. The main instrument to differentiate them is longitudinal observation, as substance-induced psychoses usually remit after days or weeks after the cessation of substance consumption [36]. However, some psychotic disorders may last for several months, years or also lifelong even after cessation of the substance use [30].

Endogenous psychoses in people who misuse substances may be different from the abstinent ones in frequency and intensity of positive, negative and cognitive symptomatology. There is evidence about a higher frequency of positive symptoms, with less negative and cognitive ones, in those with substance use disorders [19, 14].

In terms of clinical course, each disorder can worsen the other, and both may be exacerbated by environmental stressors [30, 21]. Moreover, dually diagnosed people are prone to adverse outcomes in several domains. They have a high risk

of treatment noncompliance, poor clinical response, more frequent psychotic relapse and hospitalisation, violent behaviour, suicide attempts and medical problems, such as infectious diseases, so being frequent users of emergency services. They also face some adverse social and economic outcomes. They are in fact more at risk of victimisation, housing instability and homelessness, unemployment, poverty and committing offences with related criminal justice issues. Besides, dual diagnosis imposes a high emotional and economic burden on families and friends of patients, increasing the risk of social drift [1, 30, 19].

94.4.2 Assessment

An adequate assessment starts from clinical suspicion. Cues of a history of substance abuse can be found in risk factors described above or in a childhood history of ADHD [10]. Moreover, because of the high prevalence of comorbid severe mental illnesses and substance use disorders, the presence of one of them should be considered by itself a reason to search for the other [30, 20].

The assessment can be difficult for various reasons, especially in emergency settings. Patients' clinical conditions may be complex and their cooperation is not warranted, for instance, because of agitated or violent behaviour, disorganised speech, high sedation or paranoid psychotic symptoms, and acute or chronic cognitive impairment. The patient may not want to talk about his symptoms or his substance use because of embarrassment, fear of negative responses or scarce insight [19]. Therefore, it could happen that the clinician has to achieve a diagnosis based only on scarce and fragmentary data. The most reliable approach consists in combining data from more sources, namely clinical history, physical examination, clinical interview, laboratory tests and neuroimaging [30].

Firstly, it is essential to establish a positive therapeutic alliance with the patient, setting a non-judgemental and trustful relationship [37, 18]. The clinical history can be evaluated asking the patient. It is important to ascertain if he has ever attended psychiatric services, received a psychiatric diagnosis or the prescription of a psychopharmacological treatment. The clinician must ask about any psychotropic substance consumption, substance use disorder or related treatment. If the patient assumes substances, it is important to know what substances, or at least what substances the patient believes to have assumed, as well as quantity and frequency of consumption [20]. The patient's last drug consumption time is very important for diagnostic assessment, especially in case of emergency [38]. Patients' collaterals, such as family members, friends or partners may be a source of reliable information. However, even patients' collaterals can be unreliable, for various reasons. They may be interested in hiding the patients' drug consumption, for example because of legal reasons, or they simply may not know how the patient lives.

The clinical interview can be integrated with structured interviews or questionnaires. They have been found to produce highly reliable diagnoses [14], but they must be tailored toward the patient's clinical conditions. For example, for patients with higher functioning and less severe mental illness the Addiction Severity Index (ASI), the Drug Abuse Screening Test (DAST) and, for alcohol, the CAGE and the Alcohol Use Disorders identification Test (AUDIT) have shown adequate reliability [30, 20]. However, these instruments may not be reliable for patients with the most severe mental illnesses, for two reasons. First, these tools focus on substance related dysfunction, of which the most severely ill patients could be unaware. Secondly, they may not be sensitive to the cognitive impairment common among the most compromised patients [30]. Two screening tools developed for such patients are the Dartmouth Assessment of Lifestyle Instrument and the Substance Use Event Survey for Severe Mental Illness. Regardless of the chosen screening tool, it is important to verify if it can be easily administered to a patient and if it has been validated for dually diagnosed populations [39]. Furthermore, these instruments should be used when the patient is stabilised and self-report tools should not be too lengthy. Repeating

the administration of these tools may help to assess variations in the clinical course [18].

During the physical examination, every sign or symptom must be evaluated [36]. Its main purpose, besides looking for any condition that deserves medical or surgical treatment, is to search for the physical stigmata of a drug use disorder or of a mental illness. Cues of a substance use disorder can be signs of intoxication, withdrawal or chronic use, but they can overlap each other and with signs of comorbid physical illnesses and unspecific vegetative symptoms (i.e., tachycardia and diaphoresis because of anxiety [20]). Signs and symptoms of intoxication and withdrawal by psychotropic substances are described elsewhere in this book. Here it will be stressed only the importance of evaluating if the patients' behaviour suggests delusions or hallucinations, and if there are physical signs of activation or inhibition, including pupils' diameter. A horizontal, vertical or rotary nystagmus can suggest an intoxication by NMDA receptor antagonists, such as phencyclidine or ketamine [36, 30]. Further, the chronic stigmata of a substance use disorder must be searched for, such as signs of cirrhosis or of intravenous drugs use [30]. A poor nutritional state could be observed both in case of a SUD and of different severe mental disorders.

Laboratory tests provide objective evidence of substance consumption, as well as signs of medical illness or somatic consequences of drug use. Urine tests are a cost/effective tool to assess drug consumption. They usually detect drugs taken in the previous 48 hours. THC is an exception: due to its lipophilic structure, it can be stored in fat cells, and found in urine samples for up to 6 weeks after consumption. Other instruments include breath analysis for alcohol, which can detect consumption only in the last few hours before the test, and plasmatic blood levels, useful to detect many substances of abuse. Blood cells, liver function and carbohydrate-deficient transferrin (CDT) are indirect measures of alcohol consumption [30, 18]. In addition, the hair radioimmunoassay can be useful [30].

Structural neuroimaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), could be useful to exclude an organic aetiology of neuropsychiatric signs and symptoms [36].

In summary, differentiating a primary psychosis, a psychosis due to substances or organic disease or a condition with comorbid psychosis and SUDs can be challenging. It requires a holistic, integrated approach that must be tailored toward patients' conditions, setting and available tools.

Overlooking one of these conditions or incorrectly assuming multiple diagnoses can respectively affect the prognosis or lead to unnecessary treatment and iatrogenic harm [30].

94.5 Treatment and Prognostic Issues

Treating people with comorbid psychosis and substance related disorders can be very difficult. It can follow a sequential, parallel or integrated approach. The sequential treatment takes care of one disorder at a time, from the first to the second once that the former is stable or in remission. In the parallel treatment psychosis and the substance abuse disorders are treated simultaneously but separately. It is mostly up to the user to follow and coordinate both of them. The integrated model of treatment provides that treatment for both the disorders is provided by the same team [40].

The sequential and parallel treatment have often been proven to be unable to meet users' needs, especially because of the lack of coordination [41]. Thus, patients may be referred from one service to another and users can be treated only for one of their two disorders. They may also receive incompatible or inconsistent and fragmented treatment. It is also possible that, facing many difficulties and seeing their needs unmet, they give up both treatments [42].

The integrated model is designed to reduce the gap between mental health and substance misuse services [40]. However, in many countries it is hard to be implemented because national health systems keep this services separate, and unifying them would implicate complex political choices and administrative efforts [38, 19]. Thus, manualised integrated treatment, with one team look-

ing after both disorders, is difficult to be broadly implemented. Furthermore, evidence about the efficacy of integrated treatment models is inconclusive, partly because of several methodological issues of research on this topic [43]. However, many authors have observed that integrated treatment, although not harmful, might not be more effective than standard care 40,43). Indeed, even if there is uncertainty about its effectiveness, it is reasonable to implement part of its philosophy to counteract daily practice problems. In fact, many obstacles due to the services' dichotomy can be managed establishing a strong synergy between them [38].

The aim of ensuring a good quality of care to dually diagnosed individuals should start with setting formal collaboration protocols between local services. For each patient with dual diagnosis they should set out their respective responsibilities, first of all agreeing on which are patients' main needs and which service has to coordinate treatment interventions [41]. In case of psychosis, the British National Collaborating Centre for Mental Health states that coordination should be kept by psychiatric services, due to the complex care needs of psychosis. Second, services have to regularly communicate and share information, to reduce redundant interventions and to fill care gaps. Similar agreements and collaborations should be set with other services and institutions involved in patient's life, such as assisted housing institutions or the judiciary system [38, 19].

Besides organisational aspects, an appropriate treatment strategy should consider two further issues, i.e., the stage of patients' motivations and coexisting physical, social and financial problems [41, 44]. People suffering from severe mental disorders have commonly low motivation to change. This is partly due to low self-esteem, low tolerance of frustration, and scarce social skills. Positive, cognitive and negative symptoms of psychosis and being in contact with a substance-promoting social context are all factors that may further limit motivation [41]. It is important to consider the role that the substance consumption has in patients' life, keeping in mind that different substances can have a different functional meaning in patients' life (e.g., cocaine against depressed mood and cannabis to facilitate socialisation), and to evaluate patients' opinions and emotions about their personal situation and the treatment course, given that motivation can be hampered by many factors, including social and financial problems [37].

Although treatment interventions in dual diagnosis are the same used for substance misuse and severe mental disorders, it is paramount to coordinate the efforts and to tailor care programs according to patient's characteristics. Irrespective of which of the two disorders may have supposedly come first, they should be treated simultaneously as for people with a single disorder [44].

94.5.1 Pharmacological Treatment

Pharmacological treatment of dual diagnosis involves treatment for both psychosis and substance use disorders. The risk of pharmacokinetic and pharmacodynamic interactions should not be overlooked. There is currently poor evidence to support one antipsychotic over another or first versus second generation antipsychotics when treating schizophrenia with comorbid harmful substance use, abuse or dependence, either in relation to superiority in reducing substance use or improving psychiatric symptoms. However, a recent systematic review with meta-analysis on this topic reported that clozapine and risperidone may have better efficacy in reducing substance use and craving, and that clozapine, olanzapine and risperidone performed better than other antipsychotics in reducing the symptoms of psychosis [45].

Mood stabilisers can be useful in case of schizoaffective disorders. Valproate has been proven to be effective in comorbid AUDs, and carbamazepine in DUDs. The efficacy of lithium among other drugs is scarcely known and controversial [46, 38].

Methadone brings some risk of interactions. It is metabolised by the CYP3A4 cytochrome, so inductors of this cytochrome, such as barbiturates, carbamazepine, phenitoine, rifampicine may decrease its serum level, which may result in a withdrawal syndrome. Cannabinoids, grapefruit

juice, SSRIs and other drugs may inhibit this cytochrome, thus increasing methadone's serum levels [38]. There is also risk of interaction with antiretroviral therapy for HIV infection. For the evaluation of the risk of pharmacological interactions, it can be useful to consult the summary of product characteristics (SPC) of the involved pharmacological treatments.

Lastly, is important to pay attention to prescribing anticholinergics for extrapiramidal side effects and benzodiazepines, as they can be abused for their stimulating and sedative effect, respectively [47].

94.5.2 Psychological and Psychosocial Interventions

It is difficult to state which types of psychological and psychosocial interventions are more effective for comorbid substance use and psychotic disorders [40]. Patients' stage of motivation it is fundamental to tailor the intervention [44]. A rationale framework for treatment includes several phases, i.e., engagement, motivation, active treatment and relapse prevention [41, 44]. Engagement means establishing a trustful relationship between the clinician and clients. In this phase is important to pay attention to the social and cultural background of users and to work for their gradual involvement, being flexible in interacting with them. Outreach interventions can be useful in this phase [44]. About motivation to treatment, motivational interviewing is the instrument of choice, especially in the early stages of treatment, to explore and try to modify the actual availability of clients to be engaged in treatment. Typical psychosocial interventions include cognitive-behavioural psychotherapy and contingency management, namely setting rules about facilities and penalties depending on treatment compliance and substance consumption [41]. Motivational interviewing, cognitive-behavioural therapy and contingency management have been largely tested in dually diagnosed patients, but for now, there is no evidence to claim that one intervention is better than others or than treatment as usual. Several trials have shown initial benefits of these interventions when compared to standard care, but the benefits were lost in a short time after the end of the trial. It is possible that these interventions, developed for people not affected by severe mental illness, may need to be specifically tailored to those suffering from the most disabling mental disorders [48].

Treatment can be delivered in group form or in residential settings. On group approaches, they are mainly derived from cognitive-behavioural therapy, and have proven to be useful across several types of populations, maybe depending on nonspecific factors such as education, skills building and peers support [41]. However, not all group interventions may be suitable for people with psychosis. 12-step programs may be unhelpful, because patients' limitations in emotional expression and low social skills could hamper adherence, as this approach requires some introspection, and talking about several intimate aspects of one's life [41].

Residential treatment may be useful for dually diagnosed people, as it provides a protected context in which therapeutic interventions are not hampered by an uncooperative environment [38].

94.5.3 Admission to Psychiatric Wards

People with comorbid psychotic illness and SUDs have more frequent hospital admissions and use of emergency services. Thus, it happens quite frequently that they need to be admitted to a hospital ward, often a psychiatric one, for a psychotic relapse or for an intoxication syndrome [20, 25]. However, they could be difficult to be managed because of their craving for substances or for drug or alcohol trafficking, violent or manipulative behaviour or for inappropriate relationship with other inpatients. Indeed, psychiatric and substance misuse services, being a sort of safe and non-judgmental environment, can become a favourable setting for substance consumption, dealing and related issues [49]. Therefore, it is important that some rules are set about their hospitalisation, especially regarding visits arrangements, search procedures and other security

issues. Drug tests should be part of the routine. The aim is to have an environment free from drugs and alcohol, and these procedures should be explained to patients and their families. Treatments proven to be effective in outpatient settings are to be continued during the admission [38].

94.5.4 Prognostic Factors and Course

Dually diagnosed patients usually make slower progresses and have higher dropout rates [41]. To deliver an effective treatment, it is important to frequently monitor patients' stages of motivation, and to monitor retention in treatment as this is directly related to psychosocial outcomes [41, 37].

Factors that may affect outcomes include dissatisfaction for quality of life, peer pressure, lack of an alternative daily occupation or of a satisfying social network once attained abstinence. All of these can make patients relapse into consumption [37]. Positive prognostic factors include availability of regular and interesting activities (other than substance consumption), a decent housing, a loving, caring relationship with someone sober and sensible about patient's mental illness and a positive relationship with a mental health professional. Negative prognostic factors are related to patient's history, especially having experienced dire poverty, violence or abuse and being grown up with someone in the family or in the household affected by a SUD or a severe mental illness [37].

Treatment of dual diagnosis challenges what we know about treatment of both SUDs and psychosis. It needs great efforts and even greater flexibility. Nonetheless, treatment needs of the comorbid population need to be met to guarantee a subjective quality of life at least as high as that of their nondependent counterparts.

94.6 Conclusions

The aim of this chapter was to give a brief overview of the epidemiological relevance, the main clinical features and the treatment options of the comorbidity of psychotic disorders and substance use disorders. However, a large proportion of the etiology and physiopathology of these two syndromes is still unknown, and recent progresses in the knowledge of their neurobiology have a scarce impact on clinical practice.

Actually, the cornerstone of dual diagnosis treatment seems to be the coordination in the treatment of psychosis and substances consumption. A bulk of evidence has shown that this strategy is crucial for the efficacy of various treatment options, with great relevance both at health delivery and at individual level. An effective coordination should be achieved first of all in physicians' and other professionals' minds.

Besides the need of coordinated treatment, it is important that every person involved in the care of dually diagnosed individuals understands the role of substance consumption in patients' life, as treatment should be tailored to give patients the opportunity to conceive and live a reliable alternative to drug abuse.

However, the need for further knowledge in this field cannot be quenched. Evidence about treatment outcomes in substance consumption are still scarce and partly contradictory, mainly because of methodological issues and, probably, because of the effect of undetected confounders.

Therefore, the comorbidity of psychosis and SUDs is a largely unexplored field, in which the clinical practice greatly relies on experience, flexibility and common sense, but such a situation must be an even stronger trigger to the development of methodologically reliable scientific evidence.

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Attention Deficit/Hyperactivity Disorder & Substance Abuse in Adults & Children

95

Naomi Dambreville, Mariely Hernandez, and Frances Rudnick Levin

Contents

Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD), often diagnosed in childhood, is a neurodevelopmental disorder characterized by disruptive symptoms of inattention and/or hyperactivity/impulsivity and is associated with significant impairment across several domains, particularly when untreated. ADHD can often persist into late adolescence and adulthood, conferring an increased risk of co-occurring psychiatric problems such as alcohol and substance use disorders (AUDs, SUDs). This chapter reviews the etiology of ADHD, risks and outcomes across the lifespan, prevalence and diagnostic challenges of co-occurring ADHD and SUDs (ADHD+SUD), and pharmacological and non-pharmacological treatment approaches for this challenging population.

N. Dambreville · M. Hernandez
The City College of New York, CUNY, New York, NY, USA

The Graduate Center, CUNY, New York, NY, USA
e-mail: Mhernandez1@gradcenter.cuny.edu

F. R. Levin (✉)
Columbia University Medical Center, New York State Psychiatric Institute, New York, NY, USA
e-mail: frl2@cumc.columbia.edu

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95.1 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder associated with impairing symptoms of inattention, impulsivity and/or hyperactivity across multiple settings [2]. Often persisting into adulthood, those with ADHD are at greater risk of developing an alcohol or substance use disorder (AUD or SUD) when compared to their non-ADHD peers [34]. Further, those with ADHD often initiate alcohol and/or substance use at an earlier age, escalate their use at a faster rate, are more likely to engage in polysubstance use, and have higher rates of relapse in treatment settings [15, 26, 34]. Individuals with co-occurring ADHD and SUD (ADHD+SUD) present a uniquely challenging clinical population to both identify and treat given the numerous overlapping symptoms and the effects one diagnosis has on the presentation of the other. Etiology, phenomenology, risk factors, and outcomes in the ADHD+SUD population will be reviewed. Clinical approaches for screening, diagnosing, and treatment for ADHD+SUD will be discussed, including pharmacotherapy and psychosocial treatments.

95.2 ADHD & SUD Prevalence Rates

According to the *Diagnostic and Statistical Manual of Disorders – 5th Edition* (DSM-5), Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder distinguished by symptoms of inattention and hyperactivity/impulsivity, across multiple settings, and often associated with impairment and/or reduced functioning in academic, social, or vocational domains [2]. In children and adolescents, the estimated worldwide prevalence of ADHD is 5.29% [37], based on a meta-analysis spanning three decades and including data from non-Western regions. In the United States (US), the prevalence of pediatric ADHD diagnoses is higher at 9.4% [10].

For many individuals, ADHD symptoms can remit over time, although up to 65% of those diagnosed in childhood have reported symptoms in adulthood [13]. The estimated global prevalence of ADHD in adults is 3.4%, with significant variation between countries (e.g., 1.2% in Spain, 7.3% in France) [16]. In the US, the estimated prevalence of adult ADHD diagnoses ranges from 2.5% to 4.4% with up to 40% of these adults presenting as "severe" [24]. Importantly, even for those who may not meet full DSM-5 criteria for persistent ADHD in adulthood, these individuals experience significant impairment [13]. Lastly, the variety in estimated ADHD prevalence rates across countries may not be indicative of the true percentage of affected individuals as much as it may reflect the mental health resources available to identify, diagnose and treat individuals with ADHD.

ADHD is associated with a number of adverse health and functional outcomes in adolescence and adulthood, including an increased risk for an alcohol use or substance use disorder (AUD or SUD) [7]. This risk is largely attributed to shared genetic vulnerabilities and/or environmental influences, some which increase the likelihood of delinquency in adolescence [33].

The prevalence of co-occurring ADHD and SUD can vary significantly by country and treatment setting. Among substance use populations, rates of co-occurring ADHD can range from 7.6% (Hungary) to 32.6% (Norway) [45]. High rates of ADHD have been observed in both treatment and non-treatment seeking SUD populations, with an estimated prevalence of 25.3% (C.I. 20.0–31.4%, $I^2 = 93.2\%$) in adolescent and 21.0% (C.I. 15.9–27.2%, $I^2 = 91.3\%$) in adult populations [46]. While identifying ADHD can pose its own challenges, as symptoms of inattention and hyperactivity can change in presentation over time, diagnosing ADHD in substance use

populations presents perhaps a greater challenge due to neural changes in attention, inhibitory control, motivation, and reward pathways associated with both acute and prolonged alcohol and/or substance use.

95.3 ADHD Diagnostic Criteria & Phenomenology

ADHD is a neurodevelopmental disorder with considerable heterogeneity in its presentation. Persistent symptoms can evolve over the course of development and manifest differently in children, adolescents, and adults. Continued research has resulted in modifications to the DSM diagnostic criteria for ADHD in the DSM-5 [2]. Criterion A is largely unchanged; the authors have added additional behavioral examples of how symptoms may manifest in adolescence and adulthood, as well as reduced the minimum number of symptoms required in each domain for older adolescents and adults, from six to five [11]. Age of onset, or Criterion B, was changed from before the age of 7 to before 12 years old. This was to account for several factors that resulted in cases of ADHD not identified until adolescence or early adulthood. For example, some individuals with ADHD may not experience significant impairment due to highly structured environments. Then, when their academic and/or organizational demands exceed their resources, the ADHD symptoms become more prominent and adversely affect academic performance, prompting clinical intervention.

Criterion C was modified such that the requirement of "evidence of impairment" was changed to "evidence of symptoms" in two or more settings. The criterion for "clinically significant" impairment (Criterion D) was also updated so that individuals must instead indicate that their symptoms have reduced the quality of their psychosocial, academic, and vocational functioning [2, 11]. Criterion E was adjusted so that Autism Spectrum Disorder (ASD) was no longer exclusionary to an ADHD diagnosis, given clinical and research evidence that these two disorders can co-occur. Lastly, rather than "subtypes," the different specifiers for ADHD are called "presentations," to reflect how ADHD symptom manifestations can evolve over the course of development (e.g., a child with ADHD may grow into a less hyperactive but more inattentive adult) [2, 11]. In summary, children and adolescents must display at least six symptoms of inattention and/or six or more symptoms of hyperactivity/impulsivity such that they cause distress and/or reduce functioning in at least two settings. At least some of these symptoms must have been present before the age of 12. For older adolescents and adults, only five symptoms in one or each category is required for a diagnosis of ADHD [2].

95.3.1 ADHD in Childhood

Symptoms of ADHD can look different across developmental stages due to a confluence of biological maturation and environmental factors. Children, who are physically and mentally immature, require significant adult supervision and scaffolding, with parents, caretakers, and/or authority figures structuring their schedules and keeping track of personal belongings and important dates. Thus, inattention in young children may not be as evident until academic demands exceed their capacity and they begin to struggle in keeping up with lectures, making careless errors in their schoolwork (not checking answers, not writing their name or the date), forgetting important dates, misplacing assignments, losing notebooks, jackets, and daydreaming. Inattentive children are easily distractible, have difficulty following multi-step instructions, and often take longer to complete assignments. They may need things repeated multiple times, have trouble being ready on time, and have messy rooms and/or desks or bookbags. Many parents of children with ADHD may deny that their children have these symptoms until queried about how much they are involved in structuring the lives of their children. Parents find themselves breaking down complicated tasks into smaller, more manageable ones, frequently checking in, communicating often with teachers, constantly reminding their

child of important dates/assignments, scheduling play dates, and more, past the age when this is typically necessary. Other symptoms of inattention include avoiding tasks that require a lot of concentration, such as reading and/or writing. Children with ADHD symptoms of inattention may also be easily distracted by external stimuli and may have difficulty following along in classes unless they are seated in the front of the class.

Children with symptoms of hyperactivity/impulsivity are probably the most easily identifiable early on, as they tend to require more supervision and engagement than their peers. While more severe cases may be referred for an evaluation in Pre-K or Kindergarten, typically hyperactive children have difficulty with the transition to the more structured and sedentary classroom experience of elementary school and beyond. Children with hyperactivity/impulsivity often stand when they should sit, run instead of walk whenever possible, grab at items without asking, interrupt others and blurt out answers, have difficulty waiting their turn in games or even for the bathroom or water fountain. They may have trouble playing quietly, such that they are one of the loudest voices you would hear on the playground. Children with hyperactivity/impulsivity often talk a lot and can be distracting to their peers. They have trouble controlling their impulses and regulating their emotions compared to their peers, so they present as emotionally immature, which can make socializing a challenge. Novelty and sensation-seeking behaviors with poor consideration of adverse consequences or even the desire for social acceptance can result in older children and adolescents experimenting with alcohol and substances at an early age.

95.3.2 ADHD in Adolescence & Adulthood

Physiological and neurological changes coupled with increasing social and academic demands play significant roles in how ADHD symptoms manifest across the lifespan. The Diagnostic Interview for ADHD in adults, 3rd edition (DIVA-5) is a semi-structured interview used to diagnose ADHD in adults based on DSM-5 criteria [25] and provides useful examples of ADHD symptom presentations in childhood and adulthood. While children are frequently supervised and follow structured schedules, academic and social demands increase as they get older.

Adolescents are physically more mature and typically enjoy a greater degree of independence than children. Therefore, with less scaffolding, impairment related to symptoms of inattention may become more evident. As academic demands become greater, teens with ADHD may struggle with meeting deadlines and completing assignments. They may forget test dates, misplace handouts, and/or complete assignments incorrectly. Adolescents may engage in truancy due to boredom, avoidance of tasks they find challenging, and/or difficulty sitting still in lectures, placing them at risk for delinquency [33]. Although they have more autonomy, adolescent brains undergo an important period of neural development that can result in more impulsive, risky behaviors [3]. Those with ADHD are at an increased risk for poor, impulsive decision-making without considering negative consequences of their behavior. Thus, adolescents with ADHD may have poor sleeping and eating habits, engage in thrill-seeking behaviors such as risky sex practices, reckless driving, and experimenting with drugs and alcohol.

By late adolescence and adulthood, individuals with ADHD have likely found ways to adapt to their cognitive and behavioral limitations, so the symptoms may look different from those observed in childhood. For example, an adult who has a history of making careless mistakes may work slowly on detailed tasks to avoid making errors, although others may still miss details or make errors when working too hastily on a task. Other examples of inattention symptoms in adults include difficulty sitting through a film or reading a book (unless the topic is of particular interest), trouble following lectures or conversations and/or changing the topic of conversation, asking questions that have already been discussed, difficulty completing administrative tasks, struggling to finish a task through to the end without being distracted and/or

initiating a new task before the first is completed. For example, someone may forget to put wet laundry in the dryer after becoming engaged in another activity.

Additionally, adults with inattentive symptoms have difficulty with planning and time management. They may often arrive late, double-book events, have difficulty meeting deadlines, and/or have a messy or disorganized space. Adults with inattentive symptoms may also avoid doing tasks that require a great deal of concentration or organization or that they may find dull, such as completing reports, reading, and administrative tasks. Those who are forgetful often misplace items such as keys, wallets, glasses, etc. They spend a great deal of time looking for items and often leave personal items behind. They may also frequently forget appointments and can be late in paying bills and running household errands.

Hyperactivity in adults also looks different than in children, particularly since adults have more autonomy. For example, those who have difficulty sitting still for long periods of time may take frequent bathroom breaks during meetings, fidget with their hands and/or feet, or skip lectures and long meetings altogether. Restless adults may often appear that they are in a hurry, due to trouble relaxing and feeling like they always need to do something. Some adults often have trouble doing activities quietly and speak loudly at inappropriate times and settings. Those who talk excessively find it difficult to stop talking, do not provide space for others to participate in the conversation, and often use more words than necessary to communicate. Adults with hyperactive/impulsive symptoms often interrupt others, finish another's sentences, answer questions before the person is finished asking, may be tactless and say what they are thinking. Adults who are impatient and/or have difficulty waiting in lines may struggle during delays and traffic congestion. They may avoid driving altogether due to this frustration. Additionally, they may leave places where there is a long wait for the bathroom or for service. These individuals may have frequent job changes and numerous short-term relationships because of impatience.

In both children and adults, these symptoms are not only disruptive in school, work, and social settings, but they can make it difficult to maintain jobs and interpersonal relationships, place individuals at risk for physical accidents (such as driving offenses) and mental health disorders such as depression, anxiety, and substance use problems [7, 33].

95.3.3 Etiology of ADHD

Research on the etiology and phenomenology of ADHD is ongoing, although studies have supported a combination of environmental and genetic risk factors contributing to the likelihood of an ADHD diagnosis.

Twin and familial risk studies have long established that ADHD is an exceedingly heritable and phenotypically diverse neurodevelopmental disorder. Familial risk studies have shown that having a first-degree relative with ADHD greatly increases one's odds of developing the disorder [51]. Depending on the methods, used, the heritability of ADHD is estimated at 76% based on a meta-analysis of 20 twin studies [14], or between 77% and 82% in a sample of 1,480 prospectively followed Swedish twins [6].

95.3.4 Neural Correlates of ADHD

Continued research on the phenotypically observed symptoms of inattention, impulsivity, and hyperactivity characteristic of ADHD has sought to identify corresponding cognitive impairment, structural and functional abnormalities, and associated neural pathways. Neuropsychological studies, particularly in children, have been inconsistent, in part due to the varying rates of prefrontal brain maturation. Broadly, neuropsychological deficits in areas of attention and executive function, memory, motivation and reward systems, timing, and inhibitory control have been implicated [1]. Structural imaging studies comparing individuals with and without ADHD have found reduced overall brain volume and 3–5% reductions in gray matter in

both pediatric and adult ADHD groups [5], specifically in frontal, parietal, striatal, and cerebellar regions, areas associated with attention and executive function [9].

Functional imaging and positron emission tomography (PET) studies have linked these structural differences between ADHD and control groups to variations in connectivity between neural networks and to cognitive performance in neuropsychological tasks. Dopamine pathways have been a primary focus of neural models and dopamine transporters targets for genetics studies. Aberrant connectivity between striatal pathways involved in attention and executive function, and alterations top-down connectivity from the pre-frontal cortex (PFC) to sub-cortical areas involved in reward and motivation have been observed [9].

Pathways originating from the pre-frontal cortex have been a focus in structural and functioning imaging studies because of its role in attention, executive function, motivation, and other cognitive processes. It is important in ADHD phenomenology as well as in addiction and compulsive behavioral disorders (such as gambling).

Different regions of the PFC have been conceptualized as "hot" executive function (EF) or "cool" EF processes. Accordingly, PFC regions associated with planning, attention, inhibition, cognitive flexibility, and working memory (dorsolateral prefrontal cortex and inferior frontal cortex), represent the "cool" EF pathways whereas regions associated with reward-based tasks and motivation (ventromedial prefrontal cortex and the orbitofrontal cortex), are considered the "hot" EF pathways [1, 9]. Following the hot/cool EF systems framework, researchers propose that cognitive impairment and impulsive behaviors characteristic of ADHD are the result of failures in top-down regulation of "hot" EF functions by the "cool" EF processes of inhibitory control and attention regulation. Another possibility is that *both* "hot" and "cool" EF systems are affected by inadequate connectivity between regions, such that heightened sensation-seeking and reward salience regulated by the mesoaccumbens region overwhelms an underdeveloped PFC, resulting in poor planning and inadequate inhibitory control [44].

95.3.5 SUD Diagnostic Criteria & Risk

The DSM-5 modified its diagnostic criteria for alcohol and substance use disorders in several important ways. First, rather than distinguishing between substance-specific abuse and dependence, individuals are diagnosed with an alcohol (AUD) or substance use disorder (SUD), with the substance or class of substance specified. Severity of the presentation is determined by the number of symptoms out of a total of 11, such that the presence of two to three symptoms indicates a mild presentation, four to five symptoms is moderate, and six or more symptoms denotes a severe presentation [2].

To receive a diagnosis of a SUD, an individual must present with a problematic pattern of alcohol or substance use resulting in significant impairment or distress as evidenced by the presence of at least two of the following symptoms during a 12-month period:

1. Use more than intended
2. Repeated failed attempts to reduce or limit use
3. Increased time spent obtaining, using, or recovering from effects of substance
4. Craving
5. Less time meeting occupational, social, or personal responsibilities because of use
6. Continued use despite problems with family and/or others
7. Use of substance in risky situations
8. Continued use despite worsening psychological or physical problems
9. Giving up occupational, social, or recreational activities in favor of substance use
10. Tolerance, as indicated by requiring a greater amount to have the same effect or having a reduced effect with the same amount
11. Withdrawal (symptoms vary by substance, but typically manifest as physiological and/or psychological changes)

Thus, to meet diagnostic criteria for a SUD, individuals must experience repeated negative consequences in multiple settings due to their use. Individuals with ADHD with poor planning and time management skills, sensation seeking temperaments, and problems with inhibitory control may be more likely to experience these adverse outcomes despite comparable rates of drug and/or alcohol use as their peers.

95.4 ADHD & Co-occurring Substance Use

This theoretical model of the neural underpinnings of ADHD is an important one to consider in terms of vulnerability to developing an SUD in adolescence. Adolescence marks an important period in neural development, specifically one in which the PFC lags behind subcortical brain regions in maturation [3]. Thus, adolescents can exhibit poor planning, impulsive and risky behavior typically characteristic of ADHD. This also marks a vulnerable period in adolescents who initiate drug and alcohol use, as excessive use of these substances can have a lasting impact on neural development [3]. Children and adolescents with ADHD may then have an increased risk of drug and alcohol use initiation and escalation due to already vulnerable brain connectivity in regions regulating attention and reward. Individuals with ADHD are at an increased risk of developing an SUD [7], with longitudinal studies consistently finding that individuals with ADHD tend to initiate drug and/or alcohol use earlier and escalate their use faster than their non-ADHD peers [34]. Although some studies have suggested that this risk is mediated by a co-occurring conduct disorder [33], others have shown that ADHD confers a risk for an SUD or AUD independent of conduct problems [41].

One of a number of diagnostic challenges with co-occurring ADHD and SUD is determining whether alcohol or substance use exacerbate pre-existing ADHD symptoms or whether symptoms of inattention and/or hyperactivity/impulsivity were caused by prolonged use of psychoactive substances. Individuals with co-occurring ADHD and SUD are at an increased risk of adverse consequences, particularly with alcohol. A 2012 study on college students with and without ADHD showed that those with ADHD reported similar rates of alcohol consumption but greater alcohol-related impairment than their non-ADHD peers [39]. One compelling study of alcohol effects on inhibitory control in a go-no-go task found that adults with ADHD were more sensitive to the disinhibiting effects of alcohol, thus putting them at increased risk for impulsive, reckless behavior when intoxicated [48]. However, this study was limited by a small, largely male sample. Thus, additional research is needed.

95.4.1 Assessment and Diagnosis of Co-occurring ADHD & SUD

The diagnostic assessment of ADHD is challenging, as it requires a systematic review of symptoms and impairments across one's lifetime and the clinical presentation of ADHD itself may interfere with the evaluation process [19]. The diagnostic complexities increase when screening and assessing co-occurring SUD in individuals with ADHD and vice versa.

Guidelines for evaluating ADHD+SUD [8, 28, 29] note that a standardized diagnostic clinical interview should be conducted by a clinician with training in addiction, differential diagnoses of ADHD, and the specific population (pediatric vs. adult). In addition to toxicological assessments and common substance use screening measures, feasible and reliable ADHD screening instruments have been used in ADHD+SUD populations with good sensitivity and specificity [8, 28]. The most commonly used screening measures include the Adult ADHD Self-Report Scale Short Version (ASRS-SV), the Conners' Adult ADHD Rating Scale (CAARS), and the Wender Utah Rating Scale (WURS) that assesses childhood ADHD.

A comprehensive evaluation with the patient and collaterals (i.e., family or partner) aims to obtain the history of ADHD symptoms before the initiation of substance use and the presence

of ADHD symptoms during periods of abstinence across multiple settings [8, 29]. Available diagnostic interviews include the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) - the gold standard for assessing co-occurring ADHD and SUD, the Structured Clinical Interview for DSM-5 (SCID-5), and the Diagnostic Interview for ADHD (DIVA), which has yet to be validated in SUD populations [8]. For clinicians, under- and over-diagnosing ADHD in SUD population is a concern given the tendency for individuals to minimize or inaccurately recall substance use patterns and periods of abstinence as well as recall childhood history and underreport current ADHD symptoms, potentially due to low self-awareness, a diminished ability to perceive impairments as related to ADHD symptomology, or due to the acute and/or chronic effects of substance use [8, 26, 28]. One study found that individuals with AUD and co-occurring ADHD seemed to underreport symptoms on ADHD self-report measures [26]. Recent or current substance use can also confound the diagnostic process. Research notes various options: one can initiate the evaluation once serious intoxication and withdrawal symptoms cease or allow a 2 to 4-week period of abstinence [8]. The setting of the evaluation will also play an important role, as abstinence may be difficult to achieve in outpatient treatment. Additionally, while neuropsychological assessments measuring attention, planning, organization, and memory capacities may not be able to diagnosis ADHD [36], they can help provide additional information about core ADHD-related dysfunctions [19, 29, 36].

Mental, physical, and psychosocial functioning should be assessed to understand the impact of ADHD and SUD impairments, independently and when they co-occur. Many educational and professional consequences associated with ADHD (e.g., inconsistent performance, difficulties with tasks that challenge executive function capacities) can also be found in SUD populations. Notably, compensatory strategies have often been used by patients and others for many years across multiple settings to address and ease ADHD symptoms, thus obscuring the clinical picture. A medical examination should also be incorporated to evaluate potential somatic conditions (i.e., neurological, endocrine and metabolic disorders) that may mimic ADHD symptoms and to assess for contraindications related to pharmacological ADHD+SUD treatments [29]. Lastly, Matthys and colleagues [29] highlight the need to account for differences in gender, socioeconomic status, and culture when evaluating and diagnosing ADHD and SUD.

95.5 Pharmacological Treatments for ADHD+SUD

Psychopharmacotherapy, in the form of psychostimulant and non-stimulant medication, is the first-line treatment for ADHD and has been proven efficacious in reducing symptoms and associated problems in children and adults. In SUD individuals, clinicians often raise valid concerns regarding prescribing medications in the context of addiction, given the potential risk for abuse, difficulties with medication compliance, and the higher tolerance that may require doses higher than those administered in clinical trials [27]. Yet, evidence shows initiating psychostimulant treatment of ADHD earlier in childhood can reduce the risk of subsequent substance use compared to those who begin treatment at a later age [38]. Early identification and treatment of ADHD in childhood appears to be protective against substance use escalation and poor outcomes [20, 32]. When addressing ADHD+SUD in SUD treatment settings, additional challenges arise that affect treatment adherence and potentially increase rates of relapse: poly-substance use, riskier drug use behaviors and more severe SUD symptoms than their non-ADHD peers, as well as additional psychiatric comorbidities [27, 50]. Furthermore, SUD individuals are often excluded from ADHD studies and practitioners may be hesitant to treat and prescribe ADHD medications due to fears of misuse. Research has largely shown psychostimulants to be safe and effective in treating ADHD symptoms in SUD populations, with low abuse potential, particularly for longer acting formulations [4, 8, 12, 17, 28, 29].

95.5.1 Stimulant Medications

Amphetamine (AMP) is a potent central nervous system stimulant whose primary mechanism of action is to stimulate neurotransmitter release and block the reuptake of dopamine [17, 28]. Amphetamine analogues are available and widely used as an ADHD treatment although one, methamphetamine, is rarely prescribed due to concerns of non-medical use and diversion. Lisdexamfetamine (LDX) is an efficacious, US Food and Drug Administration (FDA) approved AMP analogue ADHD stimulant treatment (30–70-mg per day dosage) that remains a therapeutically inactive molecule until after oral ingestion and is associated with a longer duration of effect and reduced abuse potential in individuals with a history of stimulant abuse [17, 23].

Methylphenidate (MPH), another AMP analogue psychostimulant, is available in immediate and extended-release formulations for the treatment of ADHD. This drug allows for increased dopamine and norepinephrine availability, which have been shown to impact brain regions associated with cognitive, executive functions, risky decision making, and regulation of reward processes in preclinical and human studies [17, 28]. Common side effects of AMP and MPH are mostly related to their stimulant properties and include insomnia, palpitations, increased heart rate and elevated blood pressure, nervousness, emotional lability, and gastrointestinal disturbances such as nausea and vomiting. Rare but serious adverse effects include severe hypertension, seizures, psychosis, and myocardial infarction. Active substance users pose an additional challenge when treating the effects of ADHD. In ADHD+SUD populations, oral MPH has shown efficacy in treating ADHD symptoms without producing significant effects of euphoria in intravenous cocaine and methylphenidate users [27]. A recent systematic review of RCT's for DSM-IV ADHD and co-occurring stimulant dependence [49] note that Osmotic-Release Oral Systems (OROS)-MPH, a long-acting formulation of MPH, in higher than usual doses (e.g., up to 180-mg per day) for longer durations can effectively treat ADHD and lessen use in amphetamine users. For adolescents known to misuse stimulants or suspected of selling or diverting medication, research suggests prescribing a long-acting stimulant, such as OROS-MPH or LDX, given its lower abuse potential [20, 23]. Results from two national CTN studies found no differences in subjective levels of euphoria with OROS-MPH, or in patterns of medication misuse in adolescents with and without SUD [27]. While these findings are promising, there is a need for clinical and dosing guidelines specific to ADHD and SUD populations. One study of Swedish adult ADHD patients treated with MPH found those with co-occurring SUD were prescribed 40% higher doses 2-years into treatment than their non-SUD peers [43]; those using stimulants or diagnosed with co-occurring DUD and AUD had a significant increased risk of exceeding the FDA recommended maximum dose of 72-mg per day (up to 360-mg of MPH daily).

The FDA has approved a transdermal methylphenidate system (MTS) for ADHD treatment. This drug-in adhesive matrix patch (available in varying sizes and corresponding dosages) delivers a once-daily MPH dose over the course of 9-hours [17, 30]. Research has found the MTS to be safe and efficacious in children and adolescents across multiple settings and well received by parents; in adults, it was found effective in treating ADHD [17, 30]. For individuals who have previously used oral MPH medications, have difficulty swallowing pills, or have concerns about competitive metabolism of other medications, MTS appears to be an effective alternative. Adverse reactions to MTS include mild dermal or application site reactions, decreased appetite, and headaches but are otherwise similar to those of other MPH formulations. One study of adults with ADHD and a history of illicit stimulant use found MTS to be safe and effective at reducing ADHD symptomology and stimulant use over 8 weeks, although participants did consume other drugs [30].

Lastly, Modafinil is an FDA-approved stimulant drug that acts as an histamine, unlike typical stimulants. Modafinil primarily promotes wakefulness and treat sleep disorders; its utility in treating ADHD lies in its ability to boost cogni-

tive functions while improving the symptoms of ADHD without resulting in hyperarousal [31]. While Modafinil RCTs have only shown slight efficacy for children and adults, its lack of activation in regions that mediate the reward system and its single route of administration (oral) results in a low abuse potential, allowing it to serve as an alternative, second line treatment for ADHD, particularly in SUD populations [31]. Modafinil has demonstrated reductions in substance use in cocaine and methamphetamine dependent individuals [31].

95.5.2 Nonstimulant Medications

ADHD symptoms have also effectively been treating with nonstimulant medications. With the exception of atomoxetine, a first line FDA approved nonstimulant ADHD medication, nonstimulants are considered off-label, second-line ADHD treatments [12, 17, 28]. In ADHD+SUD adults, nonstimulant medications have shown efficacy in reducing ADHD symptoms, with mixed results in reducing substance use.

Atomoxetine (ATX) increases norepinephrine and dopamine in the frontal cortex to effectively treat inattention and impulsivity symptoms in children, adolescents, and adults with ADHD [4, 12, 17, 49]. The therapeutic effects of ATX are produced more gradually than with stimulants, often taking several weeks to manifest. Furthermore, ATX may be used with individuals who are unresponsive to or have difficulty tolerating stimulants [17]. Common side effects of ATX include sedation, appetite suppression, nausea, vomiting, and headache. Rare but serious side effects reported in children and adolescents include increased suicidal ideation and hepatotoxicity. ATX has no known non-medical use potential and is less vulnerable to abuse and diversion, compared to stimulants, so it is an appealing medication option in the treatment of ADHD+SUD. Although published data are limited, the pharmacology of ATX can be associated with improved ADHD symptoms and reduced substance use [49]. An RCT comparing the efficacy of ATX versus placebo in cannabis dependent individuals found that ATX in combination with Motivational Interviewing (MI) was effective at reducing some ADHD symptoms, but did not significantly reduce substance use [12]. Similar results were seen in an open-label trial of ATX in adults with ADHD and cocaine dependence [29]. Another RCT of ATX versus placebo in ADHD+SUD adolescents found no significant differences between groups on these factors of interest [12].

Antidepressants have been considered for off-label treatment of ADHD. Bupropion, a dopaminergic antidepressant tricyclic antidepressant, which blocks the reuptake of norepinephrine, demonstrated less effectiveness than stimulants and evidenced no benefit over placebo in SUD patients [4, 8, 28]. In an adolescent sample with ADHD+SUD and co-morbid mood diagnoses, sustained-release bupropion reduced ADHD symptoms and substance use [29]. Of note, monoamine oxidase inhibitors (MAOIs) are contraindicated in SUD populations given the potential for hypertensive crises associated with tyramine-containing foods and medications, limiting their utility [28].

Guanfacine extended release, a norepinephrine alpha-2 agonist, is another non-stimulant medication shown to be nearly as effective as stimulants in improving ADHD symptomology in children and adolescents after just 1-week of administration [22, 28]. While guanfacine has limited findings in adult populations, it has demonstrated an ability to further reduce ADHD symptoms when co-administered with stimulants among children and adults who have had a limited response to stimulants alone [22]. Common side effects of guanfacine include somnolence, headaches, sedation, and hypotension. Lastly, extended release Clonidine, a non-stimulant molecularly similar to guanfacine, evidenced a reduction in ADHD symptoms for those with only a partial response to stimulants [28]. However, it is generally less effective than stimulant and other FDA-approved nonstimulant medication [28]. Side effects include sedation, dry mouth, depression, confusion, electrocardiographic changes, and hypertension with abrupt withdrawal.

Luo and Levin [27] suggest computational modeling as a method to identify clinical, genetic and biological markers that support patient-treatment matching and precision addiction medicine, facilitating individually tailored treatment ADHD+SUD patients. Similarly, research has assessed whether the development of a risk score can help clinicians select individualized ADHD treatment options based on patient and diseases characteristics [40]. Indeed, findings from numerous studies suggest certain treatments are optimal for specific subpopulations. OROS-MPH was found effective at reducing substance use in adolescents with co-occurring CD [4] and revealed improved nicotine abstinence in combination with a nicotine patch for adults with more severe ADHD [27], while ATX may be particularly beneficial in ADHD and AUD populations [8, 12]. In patients with high-risk scores of OROS-MPH failure, characterized by older age, higher scores on ADHD rating scales, and longer duration of symptoms, the benefit of LDX was more pronounced than the average benefit of LDX over OROS-MPH observed in the overall population [40]. Developing a risk score to guide optimal treatment for ADHD+SUD individuals would be very beneficial given the varied clinical presentations and patterns of substance use in this population.

95.5.3 Psychosocial Interventions for ADHD+SUD

Challenges for clinicians working with ADHD+SUD individuals include deciphering between symptoms associated with ADHD and those with SUD and developing a patient's capacity to link the two to support, integrate, and optimize long-term treatment outcomes. Evidence-based psychosocial substance use treatments, such cognitive behavioral therapy (CBT) and relapse prevention (RP), emphasize the identification of beliefs and behaviors that trigger and maintain substance use. ADHD psychosocial treatments include specific psychoeducation and/or CBT that focus on manualized skills training targeting executive functions, regulating emotions, impulsive behaviors and prosocial competence as well as negative cognitive schemas that maintain poor self-efficacy, avoidance, procrastination, and psychological mood symptoms [25]. Psychosocial treatments for ADHD have demonstrated effectiveness at reducing ADHD symptoms, its related functional impairments in daily living, and associated cognitive distortions and emotional dysfunctions [25].

There is a lack of research assessing the efficacy of psychosocial treatments for ADHD+SUD. Given that ADHD-related impairments in cognitive processes can affect gains made in psychosocial SUD treatments, integrating interventions for ADHD+SUD populations that target cognitive and executive functioning deficits may support progress and success in skills-based behavioral interventions, particularly for adolescents. A recently published RCT compared CBT for SUD only and Integrated CBT in 119 Dutch ADHD+SUD individuals receiving SUD treatment [47]. Integrated CBT consisted of 15 weeks of individual sessions employing motivation enhancement, relapse prevention, and coping skills to target SUD and planning skills, problem-solving skills and managing emotions for ADHD. With an additional five sessions, results showed a reduction in ADHD symptoms post-treatment; as these participants were predominantly not on ADHD medication, these findings hold promise for the efficacy of specific evidence-based psychosocial ADHD+SUD interventions.

For ADHD individuals, coaching offers a collaborative/mentoring approach to providing support and feedback for implementing ADHD skills and improving functioning in daily living; uncontrolled studies assessing its clinical efficacy have found preliminary evidence for positive outcomes [25]. Additionally, Dialectical Behavior Therapy (DBT) and mindfulness-based therapies (MBT) have been used to address ADHD symptomology and its associated dysfunctions [25]. Group DBT was modified to address ADHD+SUD in Swedish men in compulsory care for severe SUD [35]. Results showed that while low treatment acceptability and feasibility was low compared to outpatient studies, likely due to the more

severe clinical characteristics and inpatient setting, patients reported increased general well-being and decreased ADHD symptoms and externalizing behaviors [35]. A meta-analysis of nine RCT studies assessing Mindfulness-Based Relapse Prevention (MBRP), an intervention that integrates traditional substance use treatment with meditation practices to target the psychological distress associated with craving, withdrawal, and/or encountering triggers that leave individuals vulnerable to relapse, in adults with SUD did not find that it improved long-term substance use outcomes or have a greater clinical effect beyond comparable treatments, such as CBT and RP [18]. However, given the presence of target symptoms, mindfulness and MBRP may be an area of future exploration for co-occurring ADHD+SUD.

Reviews and census statements on treating ADHD and ADHD+SUD recommend a multimodal approach, thus psychosocial treatments are best used in conjunction with pharmacotherapy [25, 29]. Results from an RCT examining the efficacy of CBT or relaxation with educational support for adults with persistent ADHD on medication show this intervention reduced ADHD symptoms and maintained gains 12-months post-treatment [12]. A 16-week, multi-site, RCT of OROS-MPH + CBT for ASU versus CBT for ASU + Placebo in adolescents demonstrated overall comparable significant decreases in ADHD symptoms and drug use, but the combined active treatment group had better secondary outcomes, greater drug use reduction, and greater self-reported improvements in problem-solving abilities and focused coping skills [4, 27, 49]. Involving supportive family/partners is an important component of ADHD treatment, particularly for adolescents. Family-based ADHD interventions for adolescents have been developed and appear promising for treating ADHD+SUD in a developmentally appropriate manner. The Medication Integration Protocol (MIP) integrates medication into behavioral treatment planning for adolescents with ADHD and is therefore a useful tool for ADHD+ SUD populations [21]. The MIP includes ADHD and medication psychoeducation, reframing patient issues into family problems with potential family solutions, and medication management to enhance adherence. Supporting Teens' Academic Needs Daily (STAND), another psychosocial ADHD treatment that has yet to be used with co-occurring adolescent SUD but may be applicable in this population, is an 8 to 10-week protocol integrating behavioral management and academic training to emphasize organization skills, parenting skills, and family problem solving [42].

95.6 Conclusions

Independently, ADHD and SUD are associated with a number of adverse health and functional outcomes in adolescence and adulthood. Research shows that ADHD confers significant risk for PSUDs and is overrepresented in SUD populations; thus, ADHD+SUD are at significant risk. Yet, individuals with this comorbidity are underserved and present diagnostic and treatment challenges due to shared cognitive, emotional, and behavioral features of both disorders. Validated screening instruments are useful in identifying probable ADHD and SUD, as patients often underreport symptoms and/or lack insight into associated problems, and should be followed by a thorough clinical or diagnostic interview to better assess the impact of ADHD symptomology on SUD and tease out the effects of active or chronic SUD on ADHD and general functioning. While pharmacological treatment, primarily psychostimulant medication, is the first line and most effective treatment for ADHD, clinicians may be reluctant to prescribe them to individuals with co-occurring SUD due to fears of non-medicinal use, abuse, and diversion. Published findings on the efficacy of stimulant and non-stimulant medication in adolescents and adults with ADHD+SUD demonstrate multiple options available that reduce ADHD and/or SUD symptoms and improve functioning. Psychosocial and combined interventions for ADHD+SUD have also been shown to be effective at targeting the emotional and behavioral difficulties associated with this comorbidity. In conclusion, a review of research and interventions regarding treating

ADHD+SUD populations underscore the need for additional research, potential revisions of dosing guidelines, and further development of diagnosis specific and individualized treatment options.

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Personality Disorders and Addiction Disorders

96

Ronald Fraser, Lori Isaif, Debora Teles, and Lise Laporte

Contents

R. Fraser (✉)
McGill University, Montreal, QC, Canada
e-mail: ronald.fraser@mcgill.ca

L. Isaif · L. Laporte
McGill University Health Centre, Montreal, QC, Canada

D. Teles
Personality Disorder Program, McGill University Health Centre, Montreal, QC, Canada

Abstract

Addictive disorders and personality disorders (PD) have been connected since the early days of psychiatry to such an extent that initially substance use disorders (SUD) were conceptualized as personality pathology rather than distinct disorders in and of themselves. Admittedly, these two sets of disorders have

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many common features and indeed frequently co-occur in the same individual. Similarly, the presence of one disorder significantly impacts prognosis of the other disorder. Individuals with comorbid PD and SUD usually present with an earlier onset, an increased addiction severity, and greater impairment in functioning, and failure to accurately diagnose PDs could have an impact on their recovery and clinical prognosis. Severity of symptoms, resistance to treatment, and increased risk of relapse can potentially result in the presence of a comorbid personality disorder in individuals with addictive disorders. There is only a small amount of data available on treatment approaches for co-occurring addiction and PDs, but it seems that these patients are likely to respond to structured integrative psychosocial care and evidence-based relapse prevention pharmacotherapy for addiction. This chapter explores the interface between addictive disorders and personality disorders, attempting to highlight the complex interaction of the respective disorders and how this might inform treatment choices, specifically the need for comprehensive approaches for patients suffering from PDs and addiction, who tend to be stigmatized and marginalized.

Keywords

Personality disorders · Addiction
Comorbidity · Assessment · Treatment
Risk factors

96.1 Introduction: Conceptualization and Evolution of Personality Disorders

The initial Diagnostic and Statistical Manual of Mental Disorders (DSM) was conceptualized and actualized in 1952. Upon the DSM's inception, psychiatrists were generally consigned to hospitals and asylums for the severely mentally unwell and the focus was generally pragmatic rather than academic. There was minimal interest in nosology beyond practical uses. Classification of mental disorders was inclined to be broad and fluid. Consequently, there was much overlap of diagnostic groupings and radical differential diagnoses from one psychiatrist to the next. With the introduction of mental disorder classifications in the DSM, psychiatry began to have statistics. This brought into awareness prevalence rates, demographic patterns, disease courses and as a result, mental health public policy and increased funding came into play [9]. From this, professionals began to be able to better screen, assess, treat and monitor people who met criteria for psychiatric diagnoses. Initially, the DSM-I defined alcoholism as a form of sociopathic personality disturbance. The first actual mention of personality disorders (PDs) was in the DSM-II (1968) and at that time substance abuse was defined as a personality disorder [15]. In DSM-III (1980) and the successive DSM III-R (1987) and DSM-IV (1994), PDs were defined as distinct types, assembled into three clusters, positioned on different axis (Axis II). This categorical approach was in step with the medical model previously brought forth by Emil Kraepelin. Borderline and narcissistic PDs, which came into play in the DSM-III, were revised from psychoanalytical concepts [15]. With the introduction of the DSM-5, the multi-axial classification was dropped as it had become apparent that rather than allowing diagnoses on Axis II to receive the attention necessary by highlighting them as originally intended, the system had inadvertently resulted in even further marginalization of these diagnoses. By eliminating the Axis I and II dichotomy it was hoped to reverse this trend and promote a sense of equal legitimacy between various diagnoses.

96.2 DSM-5 Personality Disorders

The DSM-5 outlines the diagnostic criteria for a general personality disorder, and later provides the diagnostic criteria for the ten principal personality disorders. In general, an individual who has a personality disorder dem-

onstrates a long-standing pattern of thinking, behaving and emotional expression that is not consistent with what would be expected from within that individual's cultural background. Personality disorders develop in adolescence or early adulthood and must be pervasive in multiple domains leading to either significant clinical distress or functional impairment [2]. Typically, personality psychopathology involves four key components:

1. Cognition – the manner in which the individual conceptualizes themselves, others in their social sphere, and the world around them differs from the perceptions of their peers; for example, the individual with paranoid personality disorder would be perceived by others to be overly suspicious and distrustful without good reason.
2. Affective expression – the individual demonstrates emotional range, reactivity, intensity and appropriateness that is markedly different from what would be expected; for example, the individual with antisocial personality disorder would be observed to be overly aggressive and potentially explosive.
3. Interpersonal functioning – the individual has interpersonal relationships that are potentially chaotic and unstable, or simply not as satisfying in nature as might be expected by others in their community; for example, the individual with schizoid personality disorder who does not desire interpersonal contact with others including romantic or sexual relationships.
4. Impulse control – this can either be present as a lack of impulse control or as excessive behavioral inhibition; for example, the patient with BPD may exhibit tremendous self-destructive impulsivity in the form of substance misuse, shoplifting, self-injury or binge eating, whereas individuals with avoidant personality disorder may present as so inhibited that they are unable or unwilling to initiate simple social interactions.

DSM-5 divides the personality disorders into three Clusters and in two other categories [2]:

- *Cluster A – "Odd and Eccentric"* – consists of Paranoid Personality Disorder (PPD), Schizoid Personality Disorder (SPD), and Schizotypal Personality Disorder (STPD).
- *Cluster B – "Dramatic, Emotional, and Egocentric"* – consists of the most clinically prominent personality disorders, and includes Antisocial Personality Disorder (ASPD), Borderline Personality Disorder (BPD), Histrionic Personality Disorder (HPD), and Narcissistic Personality Disorder (NPD).
- *Cluster C – "Anxious and Fearful"* – includes Avoidant Personality Disorder (AVPD), Dependent Personality Disorder (DPD), and Obsessive Compulsive Personality Disorder (OCPD).

Other Personality Disorders (OSPD) and Unspecified Personality Disorder (UPD) are probably the two most common diagnosed personality disorders in the general population. They are diagnosed when individuals present with general features of the personality but do not meet the more specific diagnostic criteria for one of the ten major categories or there is insufficient clinical information to determine which specific personality disorder they have at the time of assessment.

96.3 Personality Disorders and Addiction: A Common Comorbidity

It is estimated that, in 2017, 14.8% of Americans aged 16–23 years and 6% of those over 26 years struggled with a substance use disorder [58] and approximately 10% of the general population have a personality disorder [61], with this rate being much higher (50%) in those receiving psychiatric treatment [7]. Among individuals who suffer from either of these mental illnesses, the lifetime joint comorbidity is very high. Adults diagnosed with these two disorders are a greatly impaired subpopulation and present significant challenges for addiction rehabilitation services [12].

96.3.1 Prevalence of Personality Disorders Among Individuals with SUDs

According to different systematic reviews, personality pathology is present in 5–91% of individuals with SUDs [45, 64]. Among individuals treated for their addiction, which represent only a small proportion of individuals with SUDs [20], the probability of co-occurring personality disorder is much higher. The overall prevalence of PDs among patients in treatment ranges from 35% to 73% (median of 56.5%) in Verheul [67] and from 33% to 91% in Casadio et al. [12].

Such significant variations across studies in reported rates of comorbidity between PDs and SUDs suggest the presence of large differences in the methodology used. Differences in the assessment procedures (standardized diagnostic tool vs. self-report vs. chart review, current vs. lifetime prevalence, drug abuse vs. dependence, etc.) as well as in the sampling (inpatient, outpatient, community, selective inclusion of gender, small sample size, etc.) have strong effects on observed prevalence [12, 48, 68]. Furthermore, large variations in reported prevalence rates reflect the fact that many studies have not investigated the full range of PDs. For these reasons, all prevalence rates should be interpreted with caution as should be ranking attributed to the most commonly detected PDs [51]. Nonetheless, all studies consistently report evidence of high comorbidity between these two disorders. They also highlighted that some types of PDs are more prevalent in SUD population, while some forms of SUD are more often associated with specific personality disorders.

96.3.1.1 Cluster B

Most research investigating the presence of PDs among individuals with SUDs, has focused on Cluster B PDs with the strongest and most consistent association found with BPD and ASPD [29], regardless of whether participants were from inpatient, outpatient, or community settings [64]. In a systematic review of 70 articles in 2018 [62] and a meta-analysis of 26 studies in 2000 [64] found a weighted prevalence of respectively 27.4% and 22% of patients in addiction treatment met BPD criteria. The literature further suggests that BPD is present in 24% of individuals with alcohol dependence, and in 46% of those with drug dependence [24]. ASPD is also highly comorbid with SUDs with reported rates ranging from 14% to 27% (review by [12, 68]). These figures are even more remarkable when one realizes that BPD and ASPD has a prevalence of only 1–2% in the general population.

These two PDs are prevalent among individuals who use a variety of addictive substances. Individuals with ASPD often report alcohol misuse [21] while patients with either of these PDs often have problems with illegal drugs, mainly cocaine [41, 29]. Finally, as patients with BPD often display chronic pain syndromes and might be prescribed opioid medications, they are more likely to misuse medication and at risk of developing opioid use disorder; in an outpatient buprenorphine maintenance clinic, 44% of those in treatment had BPD [53]. The incidence of cocaine, opioid, or alcohol use disorder is markedly high in patients with BPD [62].

A small number of research studies have looked at other Cluster B PDs with a suggested 12.4% lifetime prevalence of Narcissistic PD among individuals with alcohol dependence and 22% lifetime prevalence among those with any drug dependence (NESARC; [57]). Verheul [68] study reported a 12% rate for Histrionic PD. These PDs are often linked with alcohol misuse.

96.3.1.2 Cluster C

Studies of the association between Cluster C PDs and SUDs have extended the possible comorbidities beyond the focus on Cluster B [21, 51]. Results from the Wave 1 NESARC epidemiologic survey [24] reported a prevalence of 25.2% of OCPD among those with any drug dependence and of 15.9% among individuals with alcohol dependence. Casadio et al. [12], review of articles on substance-addicted patients, report prevalence rates varying from 0.7% to 26% for OCPD, from 2% to 35% for DPD and from 2% to 27.4% for AVPD. In a clinically large sample of individuals seeking treatment, Roncero

et al. [51] noted that Cluster C PDs was present in 18.5% of those in treatment for benzodiazepines (the most common substance for consultation), 9.4% of individuals in treatment for alcohol abuse, in 6.1% of those treated for opioids, in 9.7% for cocaine and 12.2% for those in treatment for cannabis. Patients who consumed benzodiazepines presented mainly with DPD while the presence of OCPD was more common among patients who consumed alcohol, opioids, cocaine, and cannabis.

96.3.1.3 Cluster A

Very few articles present rates of comorbidity between SUD and Cluster A PDs. Casadio et al. [12] reported prevalence rates varying from 0.9% to 7% for SPD and from 3% to 26.7% for PPD. In the NESARC survey [50], presence of STPD among participants with any drug dependence was 19.4%.

96.3.2 Prevalence of SUDs Among Individuals with Personality Disorders

As seen in the previous section, numerous studies have demonstrated that the prevalence of PDs among patients with SUDs is substantial. The opposite is also true. However, this has been established by a smaller number of studies [67], and has focused mainly on BPD and ASPD [48], the two PDs most likely to be diagnosed in clinical settings. In two systematic review articles examining the lifetime prevalence of SUDs in PD patients, Newton-Howes and Foulds [46] and Guy et al. [27] reported a similar pooled estimate of around 60%, while a register-based study of all people in Denmark treated for a PD in a 44-year period reported a 46.4% prevalence of any SUD [60].

The extent of comorbid addiction disorders among individuals with PDs varies according to types of PD [27]. A comprehensive overview provided by Trull et al. [62] on the co-occurrence of BPD and SUDs across different settings reported that 75% of participants with BPD received a lifetime unspecified SUD diagnosis and 59.5% a lifetime AUD diagnosis. Results from the NESARC study reported a very similar lifetime prevalence of 73% for substance use disorder for people with BPD [24], while review from Guy et al. [27] suggested a lower average prevalence rate of 52%. Using a strict diagnosis rule for diagnosing PDs, Trull et al. [63] reported high comorbidity rates of lifetime alcohol dependence for individuals with ASPD (52%) while comorbidity rates for lifetime drug dependence was 27%.

Minimal research exists on other personality disorders and addiction. In Guy et al. [27] review, lifetime prevalence of SUD in PDs other than BPD and ASPD, was 39% (29–49%). NESARC study reported a lifetime SUD prevalence of 64% for individuals with NPD [57] and of 68% of any SUDs for individuals with STPD [50]. Trull et al. (2010) reported high comorbidity rates of lifetime alcohol dependence for individuals with HPD (49.8%), while comorbidity rates for lifetime drug dependence, was 29.7%.

To summarize these data, there is extensive comorbidity between many PDs and a variety of SUDs regardless of whether the samples originate from a population of patients with PDs or conversely from a population of patients with SUDs.

96.3.3 Prevalence of Personality Disorders Among Individuals with Gambling Disorder

Literature has shown that there is high prevalence of personality disorders in individuals with gambling disorder. Some studies that have looked specifically at the prevalence of PDs in the general population of pathological or problem gamblers report a prevalence of around 42% for any PDs (Pietrzak et al. 2007 in [8, 65]) and a prevalence 28.8% specifically for comorbid ASPD (review article by [38]).

A review conducted by Brown et al. [11] reports that 43% of treatment-seeking problem gamblers met criteria for a PD. Another sys-

tematic review and meta-analysis among this population revealed a similar weighted average estimate of 47.9%, ranging from 12% to 93% for any PDs [18]. This review suggested that Cluster B PDs are the most prevalent with a mean of 17.6% with the highest prevalence for Narcissistic (16.6%), followed by Antisocial (14.0%) and Borderline (13.1%) PD. There was also a weighted mean effect of 12.6% for Cluster C PD (12.6%) with both AVPD and OCPDs at a prevalence of 13.4% and a mean effect of 6.1% for any Cluster A PDs with the highest.

96.4 Risk Factors for Persistent SUDs in Individuals with PDs

The presence of a PD seems to be a significant risk factor for persistent substance abuse issues, as illustrated in Table 96.1. Over a three-year period, ASPD, BPD and STPD consistently predicted persistence of alcohol, cannabis, nicotine, and drug disorder (cannabis, other illicit substances, and/or nonmedical use of prescription drugs) controlling for demographics and concurrent Axis I and II disorders. Among PD traits that influenced the persistence of SUD, deceitfulness

Table 96.1 Personality disorders as risk factors for persistent substance use disorders over a 3-year course

	Alcohol dependence[a] ($n = 1172$)		Cannabis abuse/dep.[a] ($n = 454$)		Nicotine dependence[a] ($n = 4017$)		Drug use disorder[b] ($n = 613$)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Cluster B								
Antisocial	**3.51*****	**1.74–7.08**	**2.46***	**1.05–5.73**	**3.19*****	**1.64–6.18**	**2.75***	**1.27–5.99**
Borderline	**2.52*****	**1.64–3.85**	**2.78****	**1.40–5.50**	**2.04*****	**1.56–2.68**	**1.91***	**1.06–3.45**
Narcissistic	**1.96****	**1.32–2.91**	1.32	0.63–2.74	1.22	0.92–1.61	1.55	0.84–2.84
Histrionic	0.96	0.57–1.60	1.10	0.46–2.65	1.10	0.76–1.59	1.10	0.58–2.07
Cluster A								
Schizotypal	**3.36*****	**1.98–5.72**	**5.90*****	**2.68–13.00**	**1.65****	**1.19–2.28**	**2.77****	**1.42–5.39**
Schizoid	1.10	0.59–2.06	0.80	0.33–1.97	**1.47***	**1.08–2.01**	0.60	1.28–1.29
Paranoid	1.18	0.72–1.95	0.83	0.40–1.73	0.99	0.73–1.35	0.86	0.48–1.56
Cluster C								
OCD	0.89	0.57–1.38	0.91	0.44–1.87	**1.40***	**1.06–1.85**	1.05	0.54–2.03
Avoidant/dependent	0.92	0.49–1.74	0.73	0.29–1.83	1.02	0.69–1.51	0.75	0.37–1.52

Modified from [a][28] and [b][20]

Studies based on DSM-IV. Data from National Epidemiologic Survey on Alcohol and Related Conditions (NESARC/USA)

Odds ratios were controlled for demographics, axis I and II, as well as other factors depending on the study

OCD – Obsessive-compulsive disorder; Drug use disorder – abuse and dependence assessed in ten classes: cannabis, cocaine, inhalants, hallucinogens, heroin, opioids, stimulants, tranquilizers, sedatives, and other drugs

$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.0001$

and lack of remorse (antisocial traits), identity disturbance and self-damaging impulsivity (borderline traits) and ideas of reference and social anxiety (ST traits) were the strongest predictors.

96.5 Screening and Assessment

Standardized clinical semi-structured interviews are regarded as the most reliable and valid assessments for PDs. Self-report questionnaires may have poor specificity and may be rather tiring for patients as they require significant concentration. Cooperatively, one could administer a short semi-structured interview in conjunction with a brief screening tool. A study completed by Gonzalez [23] described the use of two quick screening instruments for PDs: the self-report Standardized Assessment of Personality – Abbreviated Scale (SAPAS-SR) [44] and the Iowa Personality Disorder Screen (IPDS-SR) [33]. The study involved screening 53 inpatients dependent on drugs or alcohol, with a 42% prevalence of a personality disorder [23]. Both instruments were found to be quick and easy to administer, taking approximately 2 minutes to complete, and were deemed satisfactory to be used in clinical practice.

The Standardized Assessment of Personality – Abbreviated Scale [44] consists of an eight yes/no items screening questions focused on personality features interview, taken from a much more comprehensive the opening section of an informant-based semi structured interview (Standardized Assessment of Personality (SAP). It produces a dimensional score that signifies the probability that an individual has a PD in general and does not screen for any specific PD [43]. Please see Fig. 96.1.

The Iowa Personality Disorder Screen (IPDS) is a brief interview-based measure developed from the DSM III version of the Structured Interview for Personality Disorders (SIPD). This screen takes approximately 5 minutes to complete having 11 items to evaluate whether a PD is present. It was designed for use in out-patient settings. Most of the items have supplementary questions totaling 19 potential questions. The

Standardised Assessment of Personality – Abbreviated Scale (Moran)

Please ask your patients the following questions. Only tick a response if the patient thinks that the description applies *most of the time* and *in most situations*.

1.	In general, do you have difficulty making and keeping friends?	☐ **Yes**	☐ No
2.	Would you normally describe yourself as a loner?	☐ **Yes**	☐ No
3.	In general, do you trust other people?	☐ Yes	☐ **No**
4.	Do you normally lose your temper easily?	☐ **Yes**	☐ No
5.	Are you normally an impulsive sort of person?	☐ **Yes**	☐ No
6.	Are you normally a worrier?	☐ **Yes**	☐ No
7.	In general, do you depend on others a lot?	☐ **Yes**	☐ No
8.	In general, are you a perfectionist?	☐ **Yes**	☐ No

Responses in bold should be scored as 1, those not in bold as 0.

A total score of 3/8 or more indicates personality disorder is likely. (A score of 3 or more on this tool correctly identied 90% of psychiatric patients with DSM-IV personality disorder. Sensitivity 0.94 and specificity 0.85).

Fig. 96.1 The Standardized Assessment of Personality – Abbreviated Scale (SAPAS). (Reproduced from [44])

IPDS can be simply incorporated into standard diagnostic clinical interviews and primary validation research supports that it is satisfactory in detecting people necessitating additional testing to conclude if they meet criteria for a PD [33].

96.6 Treatment of Comorbid Addictions and Personality Disorders

96.6.1 The Role of Integrated Treatment

Historically, clinical wisdom held that patients needed to get their addiction successfully treated to subsequently be suitable to receive treatment for their mental health issues, or to receive therapy for their personality disorder before receiving addictions treatment. Patients were often bounced from one service to another because they did not meet specific inclusion criteria and therefore did not receive treatment. This approach is suboptimal and generated a great deal of frustration among clinicians, patients and their families. Resulting from this has been advocacy for the idea of integrated treatment where one clinical team provides treatment for both PD and SUD concerns [32].

For instance, the isolated treatment of SUD in patients with BPD might contribute to the rise of compulsive behaviors in other areas, such as for eating or for sex, while on the other hand, the sole treatment of BPD focusing on self-harm might increase substance misuse. Indeed, it is not possible to assume that substance use is an epiphenomenon that will resolve with remission of symptoms related to the PD. Apart from the limitations of the treatment diagnoses in isolation, another concern pertains to treatments that are held in parallel, as it may not provide a coherent whole and optimal cohesion among service providers and result in unintended mixed massaging.

On treatment modalities, psychotherapy is considered the most effective treatment for PDs, with pharmacotherapy having a possible adjunctive role for specific symptoms, while for SUD combined psychotherapy and pharmacotherapy is the most indicated approach. As for dual diagnosis, different treatment modalities should be offered when possible, considering individual, group and family therapy, medication, and involvement in peer support groups as they may all be useful at different points in the recovery [19]. Current analyses of available studies offer no clear guidelines of which therapy to prefer, and the core feature seems to be a systematic and integrative approach of treating the PD simultaneously with the SUD [31].

When one disorder is treated without addressing the other, the likelihood of suboptimal treatment outcomes dramatically increases. Decrease in symptomology of one, may positively impacts the other. Treatment success increases motivation for continuing treatment and moving towards recovery. Treatment frequently has common foci independently of the origin of symptoms (from addiction or PDs).

96.6.2 The Role of Medication

There are no approved medications with the indication for the treatment of personality disorders. However, medications from all psychotropic classes are frequently used in an attempt to address certain specific symptomatology such as affective instability, anxiety, impulsivity, dissociation, and quasi-psychotic symptoms. This is often in spite of an absence of evidence of pharmacological effectiveness and unfortunately often results in polypharmacy with minimal benefits and potentially significant side effects (particularly metabolic syndromes), as additional medications are often added to earlier medications that were insufficiently effective. Whenever possible, one should strongly consider removing an ineffective earlier medication before initiating a trial of another medication. Also, one should strive to avoid prescribing medications with abuse or dependence potential, such as psychostimulants, opioids, and sedative hypnotics [5]. Instead, in individuals with co-occurring PD and SUD, one should give emphasis to the addiction pharmacotherapies that have quite robust evi-

dence of effectiveness and target the individual's substance use disorder, for example using opioid substitution therapy in opioid use disorder, various anti-craving medications for alcohol use disorder or potentially an opioid antagonist for gambling disorder.

96.6.3 The Role of Psychotherapy

The most effective treatment for individuals with PDs is psychotherapy, with most of the evidence relating to treatment of people with BPD [5]. Studies investigating psychotherapeutic models of intervention for patients with PDs and SUD are limited. Even in the field of PDs, evidence-based treatments are lacking for most disorders outside of BPD, and the level of evidence accumulated so far is not robust. Clinical trials often have limitations such as small sample sizes, and provide variable outcomes [32]. The knowledge on the field is largely empirical. It is not possible to have a definitive postulate of the preferred therapy so far and further research is urgently needed to show which treatment approach is effective for the treatment of PD and SUD [31].

96.6.3.1 Cluster B

Cluster B is the most prevalent and studied group of PDs in association with SUD. As such, most of the psychotherapeutic models for concurrent PD and SUD were tailored for individuals with Cluster B pathology. BPD and ASPD were the conditions most explored in scientific studies so far with some incipient evidence about treatment efficacy.

Borderline Personality Disorder

The few studies that evaluated the efficacy of models to treat both BPD and SUD don't allow for meta-analytic reviews, and the narrative reviews sometimes indicate slightly different conclusions from the same studies [31, 35, 48, 49]. Further research is definitely needed to determine which treatment approaches are effective for these co-occurring diagnoses. Models tested had a treatment length of approximately 1 year and some degree of integration with the current most widespread approaches specific to SUD.

Table 96.2 Hierarchy of targets in DBT-SUD [17]

1st: Reduce behaviors that are imminently life threatening (e.g., suicidal)
2nd: Reduce behaviors that interfere with treatment (e.g., not attending therapy)
3rd: Reduce behaviors that decrease quality of life (e.g., substance abuse)
4th: Increase behavioral skills

Dialectical Behavior Therapy (DBT) for Substance Abusers (DBT-SUD; [36]) is an adapted version of DBT, an evidence-based treatment for patients with BPD [37], developed specifically for patients with both BPD and SUD. In this model, BPD or drug abuse is viewed as attempts to regulate aversive emotions. The goal of DBT-SUD is to both encourage abstinence but also minimize the duration and severity of any potential relapses. Like other DBT approaches, therapeutic goals have a hierarchy of priorities to optimize treatment outcomes (see Table 96.2).

Overall, DBT-SUB studies were felt to be of good quality and demonstrated good clinical outcomes and effectiveness [35]. The first clinical trial of DBT-SUD showed positive results, but medication was a confounding variable. The second trial was better delineated to control for medication and to balance the number of activities and the resemblance between the conditions. The model tested consisted of weekly individual therapy focused in DBT; psycho-educational skills group that comprised mindfulness, emotion regulation, distress tolerance and interpersonal effectiveness; phone coaching for patients; and consultation for therapists, aiming at keeping capability and motivation in the face of intense emotions. The control adopted in this second trial was very rigorous and the results came out mixed; there was a higher likelihood of decreased opiate use after 12 months in the DBT group, but not at 16 months, and no change was observed in the use of other drugs comparing both groups. Also, there was higher dropout in the DBT group [49]. Although results of outcomes studies are not always robust, DBT-SUD has been recommended

as a potentially beneficial treatment for patients with co-occurring BPD and SUD by many authors [32, 35, 48].

Finally, the similarities of DBT-SUD to specific therapies for SUDs such as motivational interviewing and relapse prevention might favor its acceptability among SUD clinicians. For instance, the model proposes a dialectical approach to abstinence, encouraging the patient to stop all harmful substance misuse and adopting abstinence, while also accepting that any relapse that should occur is not indicative of treatment failure and that abstinence is not possible. In this approach, the appropriate level of abstinence for each patient is determined by: (1) targeting the primary drug of abuse (the substance causing the most significant problems); (2) targeting other substances that lead to the use of the primary drug; (3) making sure that the treatment goals are attainable, which might mean gradual goals [17]. Patient will be helped to "fail well", which means learn from the incident through behavioral analysis. Thus, the philosophy of dialectics will play a role to counteract previously held rigid and extreme response patterns.

Another treatment model, Dual-Focus Schema Therapy (DFST), has been adapted from Schema-Focused Therapy [70]. This psychotherapy is not restricted to BPD but can be used for all PDs. The core principle of this approach is that PDs result from early adopted faulty schemas that are a response to failed attempts to satisfy important basic needs, resulting in harmful coping strategies. Maladaptive coping attempts to avoid or compensate for the activation of the schemas are seen as important triggering factors for patients with PD and SUD in this model. While Ball et al. [4] suggest that working on these triggers would be beneficial for the treatment of both PD and SUD, Lee et al. [35], states contrarily that DFST did not appear to be effective and demonstrated limited benefits.

Deconstructive Dynamic Psychotherapy (DDP; [26]) is a model based in psychodynamics developed for treatment-resistant patients with BPD, including those with a concurrent SUD. The goal of this treatment is to activate the ability "to form associations between different aspects of affective experience, to provide integrated attributions to those experiences, and to assess the accuracy of those attributions" [26]. This psychotherapy showed overall good outcomes, especially in reducing alcohol use and suicidal behavior. However, it is not possible to draw firm conclusions from these results due to the small number of studies, with small sample sizes, all from the same research group [32, 35]. These results would need replication. Furthermore, when DDP was studied in patients suffering only from BPD, it performed poorly [47].

Finally, Mentalization-Based Therapy (MBT) has shown efficacy for the two conditions separately, however, it was not tested for concurrent BPD and SUD [40]. Specific evidence on the efficacy of Transference Focused Therapy (TFT), Cognitive-Behavioral Therapy (CBT), 12-Steps programs (12S) or Motivational Interviewing (MI) was not found for this subpopulation of patients. It is also noteworthy that there is some evidence against long-term residential treatments, such as a therapeutic community for substance dependence, for BPD patients due to the high dropout rates [52] (Table 96.3).

Table 96.3 Clinical tips in treating individuals with ASPD and SUD [19]

Substances use may offer a way of coping with both physical and psychological distress
Self-injurious behavior can evoke strong feelings in clinicians, such as anxiety and anger
Dissociation is common
Under significant stress these individuals regress in functioning and become much less adaptable
A crisis management plan developed in collaboration is recommended
Clinicians should develop the professional support structure for both skill development and psychological wellbeing
Responses of clinicians may polarize between over-involvement believing they can "rescue" the patient versus resignation with a growing of a self-protective distancing, with excessive detachment counterproductive for therapy
In self-help recovery groups (12-steps, AA, NA) it may be beneficial to encourage selection of sponsors that are not likely to be potential romantic partners as it might pose a difficulty for the patient dealing with the proximity and the boundaries of these less formal helping relationships

Antisocial Personality Disorder

ASPD is associated with considerable personal, familial and societal adverse consequences. It is linked to poor occupational productivity and increased criminal justice costs, resulting in extensive economic impact. Consequently, the identification of interventions that could reduce these impacts should be a major research priority [22]. Prevention and intervention efforts of both antisocial syndromes and SUD can benefit from integrated approach, and programs that focus on adolescents are particularly indicated as a way to reduce later substance use disorders [14]. Unfortunately, there is scarce research and little good quality evidence as to what might (or might not) be effective for this condition. The Cochrane systematic review and meta-analysis conducted by Gibbon et al. [22] investigated psychological interventions for ASPD. The majority of the included studies were trials with a focus to reduce substance misuse, and ASPD was a subsample studied. Consequently, the interventions applied were not specifically focused on treating the ASPD, as was the case for BPD, where treatments originally tested for BPD were adapted into the scope of dual diagnose with SUD.

Gibbon's study observed some evidence that contingency management plus standard maintenance is effective in reducing substance misuse in ASPD and improving attendance in sessions (not interfering in dropout rates), while the aspects related to the symptoms associated to the personality were not measured. Noteworthy, the attractiveness of the positive reinforcements in contingency management seem to have a weight on the success of the intervention, such as providing high value vouchers [22].

A multi-component intervention utilising motivational interviewing principles plus incarceration [69] was superior to treatment as usual (incarceration alone) on number of drinking days and on consumption quantity in prisoners sentenced for driving whilst intoxicated for individuals with ASPD. Interestingly, the ASPD subgroup had heavier and more frequent drinking but showed significantly greater declines in drinking from intake to post-treatment assessments. Thus, it seems that non-confrontational treatment could be an option to enhance outcomes for individuals with ASPD.

The role of a psychoeducational approach for individuals with ASPD has been explored in one RCT showing some benefit regarding compliance and retention in SUD treatment [48]. The six sessions of the manualized impulsive lifestyle counseling focused on: (1) impulsivity, goals and life dreams, (2) behaviors, consequences, and triggers, (3) streetwise pride and crime, (4) values, and (5) social support. The style is non-confrontational, and the patient is invited to consider whether the themes are relevant to his or her life. Homework, handouts and worksheets are also used [59]. Results of the study suggest an increase inpatients' self-rated perceived help for their personality disorder, which was in turn associated with more days of abstinence, higher treatment satisfaction, and reduced risk of dropping out of treatment [59]. This single study suggests that psychoeducation could be beneficial for the treatment of individuals with SUD and ASPD.

Therapeutic community (TC) treatment is a psychosocial intervention for reducing substance use [16] which has been utilize with individuals with ASPD. It has been developed to the intertwined personality and behavioral issues that are found in severe ASPD and substance misuse. Results from the literature have provided mixed findings. Samuel et al. [52] suggest that the ASPD traits might lead to difficulty accepting the rules and regulations of a well-controlled long-term rehabilitation treatment center at first, and once the initial orientation period is over, those same traits might equip the individual for success within (or at least tolerance for) the confrontive atmosphere of this modality of treatment.

ASPD is also highly prevalent among problem gamblers, and is associated with elevated gambling disorder symptoms. An exploratory study suggested that this subgroup may benefit from specific behavioral therapies targeting the underlying neurocognitive dysfunctions of increased impulsivity, and impaired cognitive flexibility and executive planning [10] (Table 96.4).

Table 96.4 Clinical tips in treating individuals with *ASPD* and SUD [19]

They may be distrustful and entitled, and not show appreciation for the services received. These characteristics may result in clinicians distancing themselves or conversely relaxing boundaries in an attempt to demonstrate the willingness to help
ASPD patients can be seductive and persuasive, and clinicians may find themselves positively responsive to their charm
ASPD patients are likely to push for special treatment or softening of rules, be aggressive and intimidating, and may seek to exploit vulnerabilities in the clinician or the system
Clinicians should demonstrate determination, strength, and incorruptibility. Individuals with ASPD respect power, tough-mindedness and a clear consistent stance, and do not relate well to clinicians that they perceive to be powerless
Major consideration should be given for the safety of the staff and other clients
Recovery should be presented as a road to freedom, reflecting on how antisocial behavior is disadvantageous in present and future, specially focusing on the lack of autonomy and mastery, such as not being able to sustain a job, a relationship, or being in difficulty with the law
Highlight the fact that the strengths inherent in their personality can make recovery possible or can worsen addiction and its consequences. Help them to see clearly potential outcomes

Table 96.5 Clinical tips in treating individuals with NPD and SUD [19]

Clinician's should strive to self-monitor impatience, indignation, counter-arrogance, as these responses are counterproductive. Team consultation or supervision can help support the therapeutic approach
Clinicians can model learning to tolerate one's own faults and frailties
Patients can utilize the motivation to look strong to lead to acceptance of recovery activities
Peer support groups might be beneficial for both SUD and NPD, as they may come to better understand and respond to the needs of others

Narcissistic Personality Disorder

Presently, there is no specific evidence-based treatment for NPD, such that there is also no treatment that has been developed for individuals with NPD who also present with SUD. The patterns of grandiosity, need for admiration, lack of empathy, and fantasies of being the smartest and feeling entitled to special privileges are known to cause negative reactions in therapists, thus challenging the therapeutic alliance and may negatively impact treatment efforts [19]. Stinson et al. [57] hypothesize that "SUD may reflect attempts on the part of men with NPD not only to re-establish or maintain grandiosity, but also to defend against the negative affect accompanying dysthymic disorder that often accompanies aging and life's inevitable limitations" ([57], p. 1042). The NPD cognitive pattern of self-indulgence is seen as characteristic that make them vulnerable to SUD [6]. Helping NPD patients to recognize these patterns and motivations may potentially assist them in their recovery from SUD (Table 96.5).

96.6.3.2 Cluster A

There is a lack of well organized randomized controlled trials of treatment for people with Cluster A personality disorders [5], while specific treatment for the dual disordered have not been developed and tested. Consequently, there are no evidence-based interventions to recommend for those with co-occurring Cluster A PDs and SUD. Some clinicians theorize that Cluster A personality disorders would be better conceptualized as subsyndromal disorders better conceptualized as part of the schizophrenia spectrum, and as such might have better outcome in programs developed for concurrent psychotic disorders and substance abuse, which often focus more on practical skills.

Schizotypal Personality Disorder

STPD differs from other Cluster A personality disorders in that social aversion is accompanied by more behavioral eccentricities and lapses in their sense of reality (dissociation and derealization). Empirical evidence suggests that cognitive therapy can promote change in both the cognitive and social disabilities of patients with STPD [5].

Cannabis has a high prevalence and persistence of use in people within the schizophrenia-spectrum. While the association between cannabis use and schizotypal symptoms is well

known, only one study addressed time order and found that the schizotypal symptoms preceded cannabis use [28], meanwhile the symptoms cannot be fully explained by STPD [1]. Cannabis users are significantly more prone to cognitive and perceptual distortions, and also to disorganization [54].

It is believed in the clinical field that STPD are inclined to use alcohol and other drugs to either manage their anxiety or connect socially, escaping from feeling odd and unaccepted, which needs to be considered to pace the treatment according to the need of the patient. Service providers who do not recognize the cost of abstinence may push too hard without considering their interpersonal losses [19]. Assisting with the development of social skills training and alternative anxiety management techniques may provide the STPD patient with an alternative to substance use (Table 96.6).

96.6.3.3 Cluster C

PDs in Cluster C are characterized by being anxious and fearful and may not be at elevated risk for developing SUD. Hasin et al. [28] demonstrated the odds of persistent SUD for PDs within this cluster as being statistically the same as for the general population. PDs in the cluster characterized by being anxious and fearful are not a major concern for developing SUD. The odds of persistent SUD for PDs within this cluster are statistically the same as for the general population, as can be observed in the data brought by Hasin et al. [28]. Exception should be made for OCPD, which was associated with persistent nicotine dependence [28] and weak evidence suggest associations with any substance and alcohol disorders [24]. Also, individuals with problematic gambling that had OCPD showed lower severity of gambling symptoms and treatments focusing on social support and skills to cope with stress and finances could be more effective to this comorbidity [42]. Specific treatments for Cluster C in association with SUD were not specified. As with Cluster A, unfortunately there are no robust studies demonstrating effective treatment modalities for Cluster C PDs alone, let alone with co^{m}-morbidities. Intuitively, clinicians have focused on traditional evidence-based treatments for addiction, emphasizing those that target anxious affect as a risk factor for use and relapse. Helping individuals develop skills such as distress tolerance, general stress management, relaxation exercises and self-soothing all may be potentially beneficial but any quality studies of efficacy remains lacking.

Table 96.6 Clinical tips in treating individuals with STPD and SUD [19]

Clinicians should be emphatic and show acceptance in face of surprising statements and peculiar ideas, as a trusting therapeutic relationship will allow for reality testing
Clinicians must sustain appropriate involvement in treatment, as STPD clients might elicit boredom or anxiety
Treatment is most effective when structured, supportive, and focused on the teaching of social skills
Group settings are valuable for potential growth, while 12-step groups that meet in mental health centers can often deal with more acceptances with the unusual behaviors, attitudes, or beliefs that may be expressed

96.7 Barriers and Challenges to Treatment

96.7.1 Stigma

It is well documented that individuals with SUD, as well as those with PDs, notably BPD and ASPD, experience stigma, both from family members and society, and from health professionals) [3, 66]. Despite recent advances in the neurobiology of these disorders, SUD continues to be viewed as a result of moral weakness [12], whereas PDs are simply people behaving badly due to character flaws [55]. Thus, according to these societal views, these disorders have not been viewed as requiring "treatment" in the medical sense.

Treating patients with comorbid disorders can be extremely challenging as the behaviors common to both conditions can elicit strong emo-

tional reactions from therapist and the change of rigid patterns can be a slow process.

Patients with concurrent PD and SUD can experience a double stigmatization, with associated multiple negative consequences, including exacerbation of symptoms and reduction in healthcare utilization and treatment adherence [56]. These individuals can also experience difficulties in accessing treatments that are made available to other individuals because of systemic prejudices denying them these appropriate therapies. Stigmatization can also stem from the use of a certain language by health professionals. Research has showed that an individual referred to as 'a substance abuser', as 'an addict' or as 'a PD' instead of individual having a "substance use disorder" or having a "personality disorder" has been judged by service providers as less deserving of treatment [30]. Individuals with SUD and PDs, notably BPD, are also very vulnerable to self-stigma, a 'maladaptive process in which individuals accepts societal prejudices and integrate this evaluation into their self-concept" [25], which result in further discrimination.

As stigma is often based on preconceived ideas and collective myths, and rarely on facts, it is possible to alter negatives attitudes and beliefs from the general population with effective education and with more familiarity with mental illnesses [56]. Stigma can also results in rejection and discrimination on the part of health professionals. This can be changed with knowledge and skills, and could begin with the identification of negative countertransference reactions.

96.7.2 Countertransferential Challenges

A positive therapeutic relationship is central to the management of individuals with PDs and SUDs and mental health professionals, who have negative attitudes toward this clientele and are judgemental and rejecting, make engaging and maintaining an effective therapeutic alliance extremely difficult [39]. It is important for all therapists to recognize their negative countertransference and how it might impact their treatment or their responses to crisis [39]. In her book on PDs and addiction, Ekleberry [19] describes well what it takes to work with dual disordered clientele:

> The work requires uncompromising integrity, a strong commitment to ethical practice, continuous learning, interpersonal skills, personal resilience, and a unyielding honesty about feeling, reactions, and behaviors elicited from interacting with these individuals. (page 207)

On the other hand, many authors also describe the many rewards of working with this clientele [19], which is not often the focus of articles on clients with SUDs or PDs. Choi-Kain and Gunderson [13] describes that the work with a difficult clientele can foster personal growth and can be seen as a "highly personal, deeply appreciated, life-changing role".

Working effectively with this dual disordered population often requires openness on the part of the clinician to receive regular supervision, even if only in the form of peer support. Consulting with colleagues can help tremendously in the challenges that arise from working with these complex clinical cases, and such professional support is often essential in preventing burnout and fostering personal and profession resilience [34, 19]. As the most studied PD, data derived from evidence-based treatments for BPD have in common the characteristic of maintaining regular supervision of therapists. Clinicians discuss cases, including personal reactions, with others professionals [5]. The DBT model have treatment interfering behaviors as the second most important target of treatment, just behind life threatening behaviors. It includes behaviors from both clients and therapists, as they might be highly deleterious of treatment efficacy and contribute to early termination of therapy. In this model, clinicians work as a collaborative team and have weekly consultation meetings to focus on therapist's emotional reactions and motivation to treat patients, sustained in principles like non-judgement and acceptance, in an effort to diminish defensiveness and increase effectiveness [37]. Therefore, self-monitoring and peer-supervision or consultation should be part of

Table 96.7 Strategies to work with negative countertransference [39]

To receive clinical or collegial supervision
To share the responsibility of client management with a team of service providers
To seek external consultation when necessary
To put in place policies to manage difficult behaviors
To seek support from colleagues to "review treatment plan, help identify blind spots, offer alternatives, validate efforts, and hold hope for changes" (p. 378)

treatment when looking for best practices for dual disordered populations.

In this light, some strategies to work with negative countertransference were suggested by experts (see Table 96.7) and are important to consider in working with this clientele.

96.8 Conclusion

Addictive disorders and personality disorders frequently co-occur and the presence of one significantly impacts the expression and prognosis of the other. There is a greater likelihood that people with a PD will use multiple substances at a younger age, as well as having an increased compulsive and severe substance use pattern. They are also more likely to become physiologically dependent, more susceptible to relapse, and more resistant to collaborating with treatment. Individuals with PDs who misuse substances results in an increase their personality disturbance and have reduced treatment outcomes. PDs raise the susceptibility to SUDs while SUDs reduce willingness to adapt for PDs, while both disorders are heavily stigmatized and the combination of the two only worsens this. Recognizing the coexistence of SUDs and PDs early on in treatment allows the opportunity to optimize treatment outcomes by offering structured comprehensive integrated treatment for both disorders concurrently. It is essential that clinical staff have training and supervisory support in dealing with this challenging patient population.

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Part IX

Special Interest Populations

Giuseppe Carrà and Nady el-Guebaly

Special Populations: An Introduction

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Giuseppe Carrà and Nady el-Guebaly

The challenge of this section is to select special populations with special needs not otherwise covered by the rest of the textbook. Six such groups are highlighted.

The first chapter addresses the special needs of women. We recognize the awkwardness of addressing half of humanity as a "special population," and indeed, a separate section can be devoted to women in future editions. Drs. Moran-Santa Maria and Brady present a masterful synopsis of the scientific endeavors focusing on women. Remaining gender disparities in research are acknowledged. The prevalence difference of various substance use disorders between men and women across the life cycle is outlined. These data for a number of African and Asian countries remain unavailable. This part of the chapter also addresses the increased exposure of female sex workers. While the "telescoping course" of females addicted to alcohol and the related biologic causes are well known, the chapter also addresses parallel reactivity to other drugs as well as areas for further study. The treatment section describes different responses to pharmacotherapy as well as the barrier encountered in the design of gender-specific programs and the parameters of improved outcome.

The second chapter describes the special needs of seniors, soon to become a quarter of humanity but with disproportionately higher service needs as compared to other age groups. Dr. Rao summarizes the available prevalence figures of older people with substance use. The related costs to a developed community are outlined. Distinctive issues in substance use among the elderly provide a window on the higher comorbid health conditions. This perspective leads to a thorough consideration of the issues central to the assessment of older people: the barriers to detection and the benefits and limitations of the available screening instruments in this population. A paucity of data addresses the disproportionate need for pharmacological and psychological treatments. Among clinical trials, there remains a lack of evidence about safety issues in this age group. There are few trials of psychological treatment despite the observation that older people may in fact do better than their younger counterparts. Effective ingredients of comprehensive service programs and models are becoming identified.

The chapter by Dr. McSweeney describes how "drug-related" offending continues to be a significant driver of global prison populations and its associated costs. While a growing number of

G. Carrà (✉)
Department of Medicine and Surgery,
University of Milano-Bicocca, Milan, Italy

Division of Psychiatry,
University College of London, London, UK
e-mail: giuseppe.carra@unimib.it

N. el-Guebaly
Division of Addiction, Department of Psychiatry,
University of Calgary, Calgary, AB, Canada

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countries have implemented alternative policy innovations for dealing with drug-using suspects, defendants, and convicted offenders using forms of depenalization, diversion, or decriminalization, most continue to incarcerate and criminalize people for the possession or use of illicit drugs and rely on punitive sanctions, such as imprisonment, as the default response to "drug-related" crime. This chapter draws upon international evidence for the effectiveness of "coerced" and mandated forms of treatment (which are ordered, motivated, or supervised by the CJS) as a response to "drug-related" offending. It also highlights what this evidence base tells us about how different contexts and mechanisms for implementation and delivery can hinder or enhance the effectiveness of these approaches.

Inevitably, the illness of addiction impacts on the criminal justice system, and in recent years, there has been considerable progress in moving addiction treatment forward into settings outside of those directed specifically at treatment, i.e., prison settings and forensic applications as drug courts, described in the fourth chapter by Dr. Marlowe.

The fifth chapter focuses on the health of physicians with implications for other caregivers as a special group. The chapter by Drs. Braquehais and Casas et al. is based on the experience of the Galatea Clinic in Barcelona. A review of the literature concerning prevalence, possible causes, and drugs of abuse in various medical careers on both sides of the Atlantic is presented. The Physician Health Programs have attracted attention in the field due to their demonstrated excellent outcomes. These programs have evolved from a culture of denial and unrealistic expectations in the medical community to the development of successful strategies aimed at protecting patients and helping the physician recover back to the practice of medicine. Key factors for prevention and treatment of physicians with substance use disorders are identified including, among others, confidentiality, specialized staff training, group approaches, and lengthy monitored follow-up.

The last chapter deals with populations not commonly covered in our textbooks, but appearing regularly in our global media. Dr. Ezard and colleagues report on the staggering 45 million people currently displaced by conflicts across the world, two-thirds of whom are in a "protracted situation" of more than 5 years. Patterns of substance use reflect a combination of predisplacement patterns, host population patterns, and substance availability. The experience of various displaced groups, and they are unfortunately many, is described. While experiences of interventions to reduce substance-related harm among refugees are limited, a harm reduction approach is recommended from thiamine provision for heavy alcohol users to more structural interventions including community mobilization, alternate income strategies, and equity-based initiatives. Quantitative evaluations may be difficult to conduct, and qualitative ones may be more realistic with common end points such as violence prevention.

Women and Addiction

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Kathleen T. Brady and Jessica B. Lydiard

Contents

Abstract

Over the last 25 years, awareness of the significance of gender differences in addiction has grown exponentially in the United States. International studies of gender differences are scarce but growing in number. Understanding gender differences in epidemiology, etiology, risk and protective factors, clinical presentation, psychiatric comorbidity, course of illness, and treatment outcomes of substance use disorders (SUDs), particularly in developing countries, is critical to the implementation of effective treatment and prevention strategies.

K. T. Brady (✉)
Medical University of South Carolina, Charleston, SC, USA
e-mail: bradyk@musc.edu

J. B. Lydiard
University of Miami, Miami, FL, USA

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98.1 Introduction

The definition, prevalence, assessment, and management of addictive disorders are dramatically influenced by social, ethnic, and cultural contexts. This is particularly true for addictive disorders in women. Women from various cultures maintain diverse roles in society which can lead to a variety of coping mechanisms and behavioral adaptations that influence the prevalence and presentation of mental health problems and substance use–related issues. In this chapter, we present an overview of SUDs in women with an emphasis on international issues including social and cultural influences.

98.2 Overview of Epidemiology

The number of published research reports from the United States examining multiple aspects of SUDs in women and gender differences has risen in the last 25 years. These studies have provided critical insights into the epidemiology, etiology, risk and protective factors, clinical presentation, psychiatric comorbidity, course of illness, and treatment outcomes. While the number of international studies of SUDs among women is increasing, there are still significant disparities in our understanding of gender differences in SUDs at a global level. In addition, as acknowledgment of the importance of sexual orientation on behavioral health has broadened, the body of knowledge concerning addictions in sexual minorities is growing.

98.2.1 United States

The evolving opioid epidemic that has impacted the United States over the last 20 years has been particularly problematic for women. Between 1999 and 2015, prescription opioid overdose increased 471% in women vs. 218% in men. Between 2002 and 2013, heroin use increased 100% in women vs. 50% in men, and between 1999 and 2015, there was an 850% increase in synthetic opioid-related deaths in women [20]. Consistent with this, data from 2012 to 2013 suggest no difference between men and women with nonmedical prescription opioid use disorder (NMPOUD) as compared to the 2001–2002 survey which found a higher rate of NMPOUD in men vs. women [68].

In 2013, approximately 20.6 million Americans 12 years of age or older met the *Diagnostic Statistical Manual of Mental Disorder* (DSM-IV) criteria for current substance/drug abuse or dependence [72]. The prevalence of SUDs in men (10.8%) was significantly higher than for women (5.8%). In addition, the prevalence of current illicit drug use in men (11.5%) was significantly greater than in women (7.3%). Compared with women, men were more likely to use marijuana (9.7 vs. 5.6%), cocaine (0.8% vs. 0.4%), and hallucinogens (0.7% vs. 0.4%). The prevalence of current alcohol (57.1% vs. 47.5%) and tobacco (31.3% vs. 20.2%) use was also higher in men than women. A similar epidemiological study of adolescents (ages 12–17) found smaller gender differences in general prevalence of SUDs (9.6% vs. 8.0%) [73]. In addition, for adolescents, there were no gender differences in the prevalence of current alcohol use (13.3% for both) and small differences for cigarette smoking (8.2% vs. 7.3%). However, the prevalence of current illicit drug use among adolescent males (10.8%) was greater than the prevalence in adolescent females (9.3%). Adolescent males were more likely to be current marijuana users (9.0% vs. 6.7%). However, adolescent females were more likely to report nonmedical use of prescription pain relievers (2.6% vs. 1.9%) and psychotherapeutic drugs (3.2% vs. 2.4%).

Data from large-scale epidemiological studies demonstrate a relatively high prevalence of certain co-occurring psychiatric disorders among women with SUDs as compared to men. For example, alcohol-dependent women are more

likely to suffer from mood disorders and have a higher prevalence of primary depression than alcohol-dependent men [41, 64]. Moreover, compared with treatment-seeking men, treatment-seeking women are more likely to have multiple comorbidities (i.e., three or more co-occurring diagnoses in addition to the substance use disorder) [5]. Eating disorders (EDs) are particularly common among women with SUDs [24]. A number of studies have found that over 50% of women receiving treatment for a SUD have histories of physical and/or sexual abuse and a high percentage meet criteria for posttraumatic stress disorder (PTSD) [6, 27]. Moreover, the severity of childhood trauma has been associated with an increased risk for cocaine relapse in women but not in men [37].

98.2.2 International Epidemiological Data

The United Nations Office on Drugs and Crime (UNODC) and the World Health Organization (WHO) have provided the most recent estimates of the prevalence of drug use and SUDs among men and women at a global level. Consistent with data from the United States, UNODC reported that the lifetime, 12-month, and past-month prevalence rates of cocaine, amphetamine, marijuana, and ecstasy use were greater among men than women. However, the prevalence of tranquillizer and sedative use among women exceeded that observed in men [79]. In Afghanistan, women were more than twice as likely as men to report daily use of tranquillizers [78]. In South America and Central America, the lifetime prevalence of tranquillizer and sedative use in women was nearly double the prevalence estimates for men (6.6% vs. 3.8%). In Europe, the lifetime prevalence of tranquillizer and sedative use among women was 13% compared with 7.9% for men. These findings are consistent for both adult and adolescent populations [79].

The WHO collected data from 147 countries (representing approximately 88% of the global population) [82]. Estimates were based on international disease classification systems such as the International Classification of Diseases (ICD) and the DSM-IV [65]. Among males aged 15 years and older, the prevalence of alcohol use disorders was estimated to be highest in Eastern European countries, parts of Asia, and the Americas. Among females aged 15 years and older, the highest prevalence rates of alcohol use disorders were found in Eastern European countries, regions of the Americas, and the Western Pacific. The estimated prevalence of alcohol use disorders was lowest among men and women living in African and Eastern Mediterranean countries. The highest prevalence rates of SUDs for both men and women were found in select regions of South, Central, and North America.

There are a number of limitations to the UNODC and WHO reports. Data from a number of African and Asian countries were unavailable and therefore not included. Thus, gender differences in the prevalence of illicit drug use may be not be generalizable to African and Asian countries. In addition, these findings were based solely on data from countries for which gender-disaggregated data were available and thus present an underestimation of SUDs among women globally.

An interesting study investigating birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women synthesized findings from 68 studies calculating male to female ratios for alcohol problems stratified by 5-year birth cohorts from 1891 to 2001 [69]. The male to female ratio consistently decreased over time, and the closing gap was most prominent in young adults, suggesting a problematic increase in drinking-related problems in women globally.

Socioeconomic and cultural factors continue to be major challenges to accurate and reliable international assessments of SUDs among women. For example, in the United States, childhood sexual abuse is a strong predictor of SUDs in women. Women living in socially conservative cultures may be reticent to disclose childhood sexual abuse with researchers. In addition, logistical challenges can prevent researchers from collecting data from women in rural areas. Interpersonal violence and SUD data have often

been collected in the emergency departments of urban hospitals and may not be generalizable to the entire population.

98.2.3 Substance Use in Sexual Minorities

A recent review of studies of the influence of gender and sexual orientation on alcohol use found that in general, studies have found higher rates of alcohol use and alcohol-related problems among sexual minority (SM) persons than among heterosexuals and greater differences between SM and heterosexual women than between SM and heterosexual men [36]. Data from the 2012–2013 National Household on Drug Use in the United States provides strong evidence of increased risk of substance use and psychiatric disorders among gay/lesbian and bisexual men and women relative to their heterosexual counterparts, with unprecedented heightened risk among bisexual women [40].

98.2.4 Substance Use in Sex Workers

One of the most consistent epidemiological findings is the high prevalence of substance use among female sex workers. Approximately 30% of women who use injectable drugs (IDs) work in the sex trade [15]. A high prevalence of cocaine and alcohol use was found in a study of female sex workers in South Africa [81]. In addition, a community-based survey of sex workers in India found that close to 100% exhibited symptoms of alcohol dependence [9]. Sex workers are often from impoverished backgrounds, so it is not uncommon for them to use the sex trade as a means to support not only their own drug habit but also their partner's habit [46]. Female sex workers have a high risk of exposure to interpersonal violence and are often encumbered with economic challenges and childcare issues. Thus, substance use among female sex workers may be an attempt to self-medicate and alleviate stress and anxiety. Substance use reduces the likelihood of sex workers to engage in harm reduction behaviors. In India, more than half (52%) of female sex workers reported alcohol use prior to sex, and 38% were less likely to use condoms after alcohol use [45]. In India, the prevalence of HIV infection among sex workers who use injectable drugs (IDs) was 16%, which is nearly double the HIV prevalence estimate of 8.4% for female sex workers. A meta-analysis of drug use across 14 countries found that women who use IDs have a significantly greater risk for HIV infection than males that use IDs [12]. Despite these data, few studies have employed a systematic approach to ID use among women at a global level, and countries with the highest prevalence of HIV often fail to provide gender-disaggregated data. Moreover, underestimates of the prevalence of SUDs among women in developing countries could undermine the implementation of effective prevention strategies addressing both sexual risk and drug use.

98.3 Gender Differences in Course of Illness

One of the most consistent findings in studies focused on gender differences in SUDs is the increased vulnerability of women to adverse medical and psychosocial consequences of addiction [30, 31, 51]. Women advance more rapidly than men from initial to regular use and to the first treatment episode. Despite fewer years and smaller quantities of use at treatment entry, substance use severity is generally equivalent in men and women, and women average significantly more medical, psychiatric, and adverse social consequences from substance use [31, 51]. This has been called the "telescoping" of SUDs in women, and differences in biology as well as psychosocial factors contribute to this phenomenon.

98.4 Gender Differences in Biology and Pharmacotherapy

98.4.1 Biological Influences

Important gender differences exist in the physiologic effects of alcohol. Women have higher

blood alcohol concentration after drinking equivalent amounts of alcohol as compared to men. This is primarily because women have a lower percentage of total body water [53] and a lower concentration of gastric alcohol dehydrogenase, the primary enzyme responsible for the metabolism of alcohol [22]. These gender differences contribute to higher blood alcohol concentrations in women which provide a biological basis for the heightened vulnerability to psychological and medical consequences of alcohol consumption in women. Women develop alcoholic liver disease after comparatively shorter and less intense drinking as compared to men, and neuroimaging studies suggest increased sensitivity to alcohol-induced brain atrophy in women as compared to men [32, 51].

There is less data available concerning gender differences in physiologic effects and medical consequences of other drugs of abuse. Women generally metabolize nicotine more slowly than men [3]. Some studies suggest that men are more sensitive to the rewarding effects of nicotine than women [60]. In addition, negative affect regulation may be a stronger motivation for nicotine use in women [54]. Both animal studies and human laboratory data indicate that females are more sensitive to the subjective effects of stimulants [44]. Of interest, cocaine-dependent women experience fewer cerebral perfusion defects and less frontal cortical neuronal loss [10] compared to men with comparable drug use histories, findings that could be related to gender differences in cocaine-induced cerebral vasoconstriction [39]. There have been many gender differences observed in the pharmacologic properties of opiates, including analgesic effects, but gender differences in abuse potential have not been systematically studied in humans. However, animal studies suggest that mu agonists may be reinforcing to females over a broader dose range, and females self-administer greater quantities of opiates as compared to males [11].

Accumulating evidence from preclinical and clinical studies indicate that hormonal changes associated with the menstrual cycle may impact both craving and the behavioral responses to drugs. For example, estrogen augments behavioral responses to cocaine in female rats by modulating the mesocorticolimbic dopamine system [50, 67]. In humans, this may explain reports of increased responsiveness to cocaine cues and higher quantities of use in women presenting for treatment [66]. In one study, women reported less pleasurable effects of cocaine during the luteal phase, compared to women in the follicular phase and men [70]. As such, women may be more vulnerable to relapse during the follicular phase, when progesterone levels are lower. In another study, administration of progesterone to women during the follicular phase attenuated the positive subjective effects of cocaine [19]. This is an area of active investigation which could have important treatment implications.

Neuroimaging studies have also provided important information about the neural processes underlying sex differences in SUDs. During a stress task, female cocaine users showed greater left frontolimbic brain activation than males [48].

Using positron emission tomography (PET) during cue-induced cocaine craving, Kilts and colleagues found greater activation in women in the dorsal striatum and anterior cingulate cortices and lower activity in the amygdala, which assesses the pleasure of an experience and connects it with its consequences [42]. In a recent exploration of sex differences in neurocognitive and brain responses to emotions, stress, and drug-related cues, Potenza and colleagues found that women had greater reactivity to stress-related cues and men showed higher responses to drug cues [63]. Consistent with these findings, a series of animal and human laboratory studies suggest that both the HPA axis and noradrenergic systems in cocaine and opioid dependence are more dysregulated in females as compared to males [25, 55]. This suggests that women may be more responsive to noradrenergic agents as compared to men.

Gender differences in the physiologic and subjective effects and medical consequences of opiates, marijuana, and other drugs of abuse are under-explored. Considering the important gender differences that have surfaced with careful investigation to date, this is clearly an area that warrants future studies and could have major

implications for gender-sensitive prevention and treatment efforts.

98.4.2 Pharmacotherapy

The findings concerning gender differences in the neurobiology of SUDs and the potential impact of hormones on the subjective effects of substances of abuse and relapse suggest that there may be gender differences in response to pharmacotherapeutic treatment. Animal studies also indicate important gender differences in response to the medications to treat addictions. Campbell and colleagues reported that baclofen-treated female rats were less likely to acquire cocaine self-administration as compared to baclofen-treated male rats [7]. In another study, ketoconazole was found to decrease opiate self-administration more in female as compared to male rats [8]. However, there has been little clinical research exploring gender differences in response to agents currently used in the treatment of substance use disorders. Based on animal research studies demonstrating that progesterone decreases response to stimulants, Evans and Foltin explored the impact of exogenous progesterone on smoked cocaine and found an attenuation of the positive subjective effects of cocaine in women, but not in men [19]. This is clearly an area which warrants further gender-specific investigation.

As detailed above, substance-dependent women are more likely to suffer from mood and anxiety disorders and to be victims of physical and sexual abuse as compared to men. As such, medication treatment of comorbid conditions is likely to be particularly important in the treatment of substance-dependent women. In this regard, one study comparing an SRI (sertraline) to a tricyclic antidepressant (imipramine) in the treatment of depression found that premenopausal women had a preferential response to sertraline [43]. A recent study exploring treatment with a combination of sertraline and naltrexone in individuals with alcohol dependence and major depression found significantly improved alcohol-related and depression outcomes in the combination treatment group [61].

As such, while the evidence does not support the use of antidepressant medications in the absence of depression in substance-dependent individuals, addressing depression will likely improve treatment outcomes. Other studies have provided preliminary evidence that bupropion, a pharmacologic agent with FDA approval for both the treatment of depression and smoking cessation, may be more efficacious in women as compared to men [60].

98.5 Treatment

Although women are generally underrepresented in substance abuse treatment programs, retention and relapse rates for women are comparable to men [26]. Data from several studies suggest that women exhibit more favorable treatment outcomes than men. For example, studies have demonstrated that women have shorter relapse periods and a higher incidence of abstinence at 6 months (79.3% women vs. 54% men) and 5 years (odds ratio 1.9) following treatment [30, 57]. In addition, women demonstrate greater improvement in physical health and are more likely to seek support after a relapse episode [33]. A recent Canadian study found that women are more likely to use technology as a recovery support ($p < 0.05$) and more likely to use art, poetry, writing ($p = 0.007$), and yoga ($p < 0.001$), as part of their recovery journey [56].

98.5.1 Gender-Specific Treatment Programs

Arguments in favor of gender-specific treatment include differences in interaction styles and men's traditional societal dominance, which might negatively affect women in mixed-gender programs. Moreover, women and men with SUDs differ significantly in terms of risk factors, co-occurring psychiatric conditions, motivations for treatment, and risks for relapse. Gender-sensitive treatments can address these issues directly and may improve treatment seeking, retention rates, and treatment satisfaction. However, data from

studies examining effectiveness of gender-specific treatment programs for women are mixed [2, 26, 58]. For example, residential programs that allow children to accompany their mothers have higher retention rates [35, 74]. In addition, women enrolled in women-focused outpatient or residential treatments have higher completion rates than women enrolled in standard substance abuse treatment programs [4]. Although other studies have found that women-only programs provide similar treatment outcomes as mixed-gender programs, these studies have noted that socioeconomic status, addiction severity, and comorbid psychiatric diagnoses are significant factors in determining the effectiveness of women's treatment programs [26, 58].

Prevention strategies and treatment programs for women must incorporate the culture and diversity of each region. For example, in India, the UNODC has distributed guidebooks outlining prevention strategies to women's groups, health-care providers, legislators, and the public and also sponsored nongovernment pilot programs aimed at prevention strategies particularly for women at risk for the development of SUDs [77]. In other regions of the country that have a high population of female sex workers and women who are considered "social outcasts," funding has been provided for a SUD treatment center for women that employs peer educators who are often HIV positive and have a history of a SUD [77]. A general lack of awareness of the prevalence of SUDs in women may interfere with the development of gender-sensitive prevention and treatment efforts in some countries. Thus, identifying ways to include women in epidemiological studies of SUDs may be the first step in garnering support for gender-sensitive treatment programs. In addition, education of treatment providers about gender differences in the etiology of SUDs may help overcome the attitude that women do not require specialized treatment options. It is also critical that standards and guidelines for treatment include measures that protect the confidentiality of victims of domestic violence, restore relationships with family and community members, and use a nonconfrontational approach to therapy. Treatment programs, whether mixed gender or women only, that pay special attention to psychiatric comorbidity, family and parenting issues, victimization, and gender-specific barriers to treatment are likely to be more successful for women.

98.5.2 Gender-Specific Barriers to Treatment

In the United States, women are less likely than men to enter treatment programs [26]. Consistent with this finding, studies from countries that have collected gender-specific data demonstrate that women are consistently underrepresented in SUD treatment programs. For example, in Europe, the ratio of men to women in treatment for marijuana, cocaine, and amphetamine use is 4:1, which is significantly higher than the gender ratio of use for these substances [79]. Across substance use treatment centers in India, only 3% of the 16,942 new patients were women. Men represent approximately 76–90% of patients enrolled in substance use treatment programs across South Africa [76, 81].

Globally, women with SUDs have less access to treatment programs and harm reduction services than men with SUDs. For example, although 10% of all substance users in Afghanistan have access to treatment, only 4% of female drug users have access to treatment [78]. In Eastern European countries, budgetary constraints and bureaucratic challenges have excluded incarcerated women from antiretroviral and opioid replacement treatments but have not excluded incarcerated men [21, 62].

Globally, there are a limited number of gender-based treatment programs. This is a particular challenge for women who have been exposed to domestic violence, who may be more reluctant to attend group treatment programs that include men. In addition, there are few treatment programs for individuals with comorbid substance use and psychiatric disorders.

Sociocultural factors (e.g., shame, lack of spousal/family support) can also be significant barriers to women seeking treatment for SUDs. The social stigma attached to substance use in

societies that value traditional roles for women as domestic caregivers can prevent women from seeking treatment. Women who drink alone may transition to alcohol dependence without their family's knowledge. In fact, one study found that in South Korea, women sought treatment only after the physical symptoms of drug withdrawal appeared [47]. In addition, women living in culturally conservative societies may not feel comfortable discussing sexual abuse and/or may not be knowledgeable of their own family history of SUDs. Relationship dynamics can also impact women's decision to seek treatment for SUDs. Women may be more reluctant to leave home for long-term treatment out of fear that separation from the family will lead to divorce and threaten family stability [29]. In addition, women who are exposed to domestic violence exhibit self-destructive behaviors and are more reliant on their partners and thus less likely to engage in treatment and harm reduction strategies [14, 23].

98.5.3 Special Issues: Pregnancy

Although global awareness of the adverse consequences associated with maternal substance use during pregnancy has increased, drug use during pregnancy remains a significant problem. For example, in the United States and Canada, 32% of the 863 pregnant women who were surveyed reported occasional alcohol use, 16% reported regular alcohol use, and 11% reported heavy alcohol use [13]. In utero exposure to alcohol is associated with fetal alcohol syndrome (FAS), characterized by irreversible neurological damage, developmental delay, facial malformations, and behavioral problems [52]. In another study of 1632 mothers, 25% reported using tobacco, 23% alcohol, 6% marijuana, and 1% barbiturates during pregnancy [1]. The growing opioid use epidemic in the United States has been associated with a significant increase in the prevalence of pregnant women with opioid use disorder (OUD) [16] and neonatal abstinence syndrome (NAS)/neonatal opioid withdrawal syndrome (NOW) [28]. Screening for substance use in primary health-care and obstetric clinics is problematic since pregnant women face social stigma and legal problems which may prevent them from discussing substance use habits with health-care providers. In some countries, legislation and health-care policies are significant treatment barriers for pregnant women with SUDs. In the United States, laws that criminalize drug use during pregnancy in some states can prevent pregnant women from speaking openly with clinical care providers about their substance use [59]. In Russia and Ukraine, pregnant women with SUDs risk forced abortion and termination of parental rights [17, 18]. A number of groups, including WHO, have recommended that opioid-dependent pregnant women should be maintained on either methadone or buprenorphine treatment [83, 71]. Relative to methadone, BUP offers the advantages of greater convenience for pregnant women and lower NAS/NOWS severity in their infants [38]. Some disadvantages of BUP include increased risk of diversion, poorer adherence, greater treatment dropout, and daily peak-trough effects [49, 34].

Pregnant women seeking substance abuse treatment often have additional health problems including HIV and other STDs, as well as psychiatric problems and abusive living situations. Thus, routine screening for trauma, victimization, and depression for this at-risk population is necessary [75, 80]. A multidisciplinary approach to treatment that provides state-of-the-art treatment for SUDs integrated with psychosocial support and psychiatric, medical, prenatal, and gynecological care has been implemented in a number of countries, including Austria, Canada, the Czech Republic, and India [77].

98.6 Conclusion

International research clearly indicates that gender-sensitive substance use policies and programs cannot ignore cultural influences. Large cross-national variation in gender differences in substance use disorders makes it clear that biological factors alone do not account for gender differences in substance use and addictions. Policies, education, and prevention and treatment

efforts must take into account both the biological differences and the culturally defined gender roles that specify expected and tolerated drug use behavior in men and women. Cross-national research can help to explicate the complex interactions between biology, individual-level, and societal-level variables that influence alcohol consumption and drug use and allow us to design better-targeted prevention and intervention efforts for both genders worldwide.

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Older People and Substance Misuse

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Rahul Rao

Contents

R. Rao (✉)
Institute of Psychiatry, Psychology and Neuroscience, London, UK
e-mail: tony.rao@slam.nhs.uk

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Abstract

Over the past decade, older people have shown higher rises in rates of substance misuse compared with younger age groups. This has impacted upon both public health and clinical outcomes such as hospital admissions and the presence of co-morbid disorders such as alcohol-related cognitive impairment.

The presence of accompanying physical and mental disorders and the physiological effects of ageing call for greater vigilance over the adverse effects of substances in older people. Greater complexity in clinical presentations calls for special considerations in assessment, treatment and care planning. This also applies to legal and ethical considerations and alcohol-related cognitive impairment.

Older people with substance misuse experience positive health and social outcomes that are equal if not better than younger people. To sustain and improve the mental and physical health of older people with substance misuse, an integrated approach to care is required. This will need to involve old age psychiatry, addiction psychiatry, geriatrics, primary care and their interface with housing and social care.

Keywords

Alcohol · Drugs · Addiction · Ageing
Substance use disorders

99.1 Introduction

At a global level, alcohol is responsible for 7% of deaths in people under the age of 70. In the Eastern Mediterranean region, the highest rate of alcohol-attributable deaths occurs in the 45–49 age group. In the African region, although the proportion of such deaths is highest (11.2%) in the 25–29 age group, it remains high (8.1%) even in the 60–64 age group [98].

For all age groups, using disability-adjusted life years (DALYs) to measure both years of life lost and years lived with disability from alcohol use disorders, the 70 and over age group is the only one to have increased over the past 15 years, from 125 to 150 DALYs per 100,000 population [43].

In developed countries, increasing longevity has been associated with large increases in the number of people aged over 50 years. It is also now this population of 'baby boomers' who are at highest risk of increasing rates of substance misuse. This observation is also mirrored in developing countries [56]. The number of older people with drug and alcohol use disorders receiving treatment is expected to treble in the United States and double in Europe by 2020 [99].

For the purposes of this chapter, the term 'older people' will refer to those aged 50 years and over.

99.1.1 Epidemiology

Alcohol remains the most widely used substance in older people. Using disability-adjusted life years (DALYs) as a marker of morbidity, alcohol rose from 16th to the 5th highest risk factor in people aged 50 to 69 years in England between 1990 and 2013. Smoking remains the top risk factor.

There remains a direct association between alcohol misuse and deprivation. Although higher socio-economic status is associated with higher alcohol consumption [67], co-morbidity from physical and mental disorders in areas of high deprivation may explain poorer health outcomes in areas with higher socio-economic deprivation [44].

There are considerable differences in drinking patterns among older people globally [92]. In England, 87% of older people report drinking alcohol over the previous year, compared with 18% in India. For drinking quantity and frequency, the findings are different. Thirty-two percent of older people in China report frequent heavy drinking, compared with 3% in Mexico. The prevalence of tobacco smoking in people over 60 is 13% worldwide (22% of men and 8% of women).

Lifetime use of illicit drugs in older people has increased sharply over the past 15 years, with rises most marked in the 65–74 age group. In this age group, lifetime cannabis use increased from 0.9% in 2000 to 6.8% in 2014 [75].

In the United States, past-year use of cannabis in people aged 65 and above increased from 0.15% in 2003 to a high of 2% in 2014 [79].

Older adults are the largest per capita consumers of prescription and over-the-counter drugs in most developed nations [81].

Prescription drug misuse is also a growing problem. Inappropriate prescribing of these drugs, especially for opioids and benzodiazepines, occurs in up to 20% of older people [29]. There is now also growing evidence for increasing rates of inappropriate prescribing of gabapentinoid drugs in older people [89].

99.1.2 Risk Factors

Approximately one-third of people with alcohol misuse aged 65 years and over have developed this after the age of 50 [34]. People with their first onset of alcohol misuse after the age of 45 years are less likely to have a family history of alcohol misuse, a history of alcohol-related injuries or nicotine dependence. This group also has a lower number of alcohol-related medical disorders [94].

However, older people with alcohol misuse are as likely as younger people to have a history of mental disorder [94] and more likely to have accompanying psychosocial precipitants to alcohol misuse.

Low social interaction [45], fewer responsibilities, bereavement, loneliness [17], increased financial strain [86] and social isolation [25] are all risk factors for alcohol misuse. Homelessness also has a strong association with alcohol misuse in older people [26], but retirement has shown a conflicting association [13, 91].

Risky drinking had positive associations with male sex, depression, smoking and working in an urban area [42].

Alcohol misuse in response to stress is more common in older women, who use alcohol to self-medicate [21]. Anxiety disorders carry a higher risk of alcohol misuse in older women [97].

Chronic pain has a consistent association with alcohol misuse in older people [41] and is a strong predictor of relapse [96], but is not consistently associated with the extent of the pain [15].

Insomnia is also known to be associated with alcohol misuse [88]. As many as 26% of older people use alcohol for medicinal purposes such as insomnia [3].

99.1.3 Low-Risk Drinking

Our Invisible Addicts [75] recommended that 'low-risk' drinking for people aged 65 years and over be defined as drinking no more than 12 UK units per week, or an average of 1.75 UK units per day. These are broadly in line with low-risk drinking in the United Kingdom, which state an upper limit of no more than 14 units per week for both men and women [30]. However, this guideline may still need to be applied with caution to older people, who are likely to be more sensitive to alcohol-related harm through the effects of ageing, accompanied by physical and mental health problems, a higher risk of interactions with prescribed and other medications and a higher likelihood of the cognitive impairment than younger people.

Across all age groups, comparatively higher mortality rate has been found in men drinking above 2.5 UK units per day and women drinking above 1.25 UK units per day, compared with non-drinkers [87]. This equates to 17.5 units for men and 8.75 units for women per week. There is no evidence of increased mortality for older women drinking an average of no more than 1.25 units of alcohol per day [46].

However, any perceived health 'benefits' may be attributable to inappropriate selection of a reference group and weak adjustment for confounders.

99.1.4 Economic Costs

The total cost of alcohol globally is estimated to be 2.5% of gross domestic product (GDP) [7], equivalent to £47 billion in 2016. The majority of these were indirect costs (72% of all costs), followed by healthcare costs (13%), other direct costs (12%) and law enforcement costs (3%).

The direct economic burden of alcohol dependence in Europe accounts for between 0.39% and 2.99% of annual GDP spent on healthcare per country. The main cost driver is hospitalisation for alcohol-dependent patients, which accounts for as much as 15% of this annual spending per inhabitant for a single patient [80].

For direct and indirect costs, harmful use of alcohol ranks among the five top risk factors for disease, disability and injury throughout the world [50].

99.1.5 Premature Ageing and Mortality

Substance misuse is associated with both cellular and organ damages [85]. This can lead to premature vascular damage and neuronal toxicity. Substance misuse is also associated with unprotected sex or intravenous drug use that increases exposure to blood-borne viruses [47].

Alcohol and illicit drug misuse reduce life expectancy by between 9 and 24 years [22]. For tobacco smoking, this reduction is between 8 and 10 years [23].

99.2 Assessment

Table 99.1 illustrates the considerations relevant to the assessment of older people with substance misuse. It is essential to adopt an approach that takes into the account the narrative and experience that comes with age. The interview should not be rushed. It should consider sensory impairment, embarrassment about reporting and more than one assessment may be necessary. Taking a history should include any accompanying physical disorders and mental disorders such as depression and dementia. The impact of problems with activities of daily living from or upon substance use and misuse should be considered, as should social vulnerability and life events such as loss of employment and bereavement. There is a wealth of information to inform diagnosis and further care interventions, covering health, social care and housing, as well as information from carers. Investigations should include both laboratory tests to gauge the extent of liver disease, neuropsychological evaluation and comprehensive medical and functional assessment.

99.2.1 Presentation of Substance Misuse in Older People

The clinical presentation of substance misuse is often atypical and complex. For alcohol misuse, these are outlined in Table 99.2.

Table 99.1 Assessment of substance misuse in older people

General approach	History taking	Collateral information	Investigations
Non-ageist	Co-morbidity	Family practitioner	Cognitive screening
Preserve dignity, privacy and comfort	Cognitive and mood state	Housing	In-depth cognitive assessment
Adjust tempo	Functional abilities, nutrition and self-care	Social care (including domiciliary and day care)	Laboratory blood tests
Hearing and eyesight	Social factors (e.g. abuse and isolation)	Voluntary agencies	Neuroimaging
Stigma and under-reporting	Multiple substances	Hospital summaries	Occupational therapy assessment
Multiple assessments	Loss events	Family and carers	Comprehensive geriatric assessment

Table 99.2 Atypical presentations of substance misuse in older people

Sleep complaints
Cognitive impairment, memory or concentration disturbance
Liver function abnormalities
Incontinence
Poor hygiene and self-neglect
Unusual restlessness/agitation or persistent tiredness
Unexplained nausea and vomiting
Changes in eating habits
Slurred speech, tremor, poor coordination
Frequent falls and unexplained bruising
Masking by other mental and physical disorders

99.2.2 Screening

Screening instruments for substance misuse in older people have only been validated for the identification of alcohol misuse (Table 99.3). The CAGE questionnaire detects the core features of alcohol dependence [33] but is relatively insensitive to harmful/hazardous drinking [2]. Its acronym stands for felt that you should *c*ut down; *a*nnoyed by others criticising drinking; feel *g*uilty about drinking; have an *e*ye-opener on waking to get rid to steady nerves.

The most widely used screening tool for older people is the Short Michigan Alcoholism Screening Test – Geriatric version (SMAST-G; [11]). Questions tap into problems more commonly seen in older people, such as 'drinking after a significant loss' or 'drinking to take your mind off your problems'.

Different adaptations of the Alcohol Use Disorders Identification Test (AUDIT) tool [82] have been validated in older people [73]. A cut-off score of 5 for older men and 3 for older women shows the greatest sensitivity and specificity, using the full AUDIT. The AUDIT-5 [62] is also used in the screening of older people with co-morbid mental disorders [61], as well as the AUDIT-C [20]. Suggested cut-off points for the AUDIT-5 [61] and AUDIT-C [1] are 4 for both instruments.

The total score on the full AUDIT indicates a drinking risk category – low, increasing, higher or possible dependence. The AUDIT also serves as a clinical decision tool as the score provides an indication of appropriate interventions. It can also be used as an outcome measure. A score of 0–7 refers to low risk, 8–15 to hazardous/increasing risk, 16–19 to harmful/higher risk and 20 or higher to possible dependence.

Given a lack of sensitive screening tools for alcohol problems in older people, such tools need

Table 99.3 Screening instruments for alcohol misuse in older people

Screen	Full name	Description
AUDIT [82]	Alcohol Use Disorders Identification Test	10 items, self-administered
AUDIT-C [20]	AUDIT – quantity/ frequency Items	Items 1–3 from AUDIT
AUDIT-5 [62]	Five questions from the AUDIT	Questions 1, 2, 4, 5 and 10 from AUDIT
CAGE [33]	Acronym from keywords in four questions	Four items, self-administered
MAST [83]	Michigan alcohol screening test Test	22 items, self-administered
MAST-G [11]	'Geriatric' version of MAST	24 items, self-administered
SMAST [84]	Short version of MAST	13 items, self-administered
SMAST-G [11]	The short MAST geriatric version	Ten items, self-administered, derived from MAST and MAST-G
ARPS [35]	Alcohol-related problems survey	18 questions, 60 items, self-administered, but requires computer scoring
shARPS [55]	Shortened ARPS	32 questions, self-administered; does not require computer scoring
CARPS [58]	Fully computerised ARPS	18 items, 60 questions self-administered via a computer, requires computer scoring

to be combined with a comprehensive assessment assessing use, misuse and dependence.

99.2.3 Barriers to Assessment

There are several barriers to the assessment of substance misuse in older people (Table 99.4). Assessments may need to be multiple and frequent, with engagement of patient, families and carers. There is often ambivalence about admitting to substance use and resistance to changing drinking behaviour. There may also be awkwardness in practitioners asking about it. There should always be a high degree of clinical suspicion.

A full assessment needs to be supplemented with information from collateral sources. This includes information from relatives, friends and informal carers (taking account of information sharing and confidentiality), GP consultations (including current prescribed medication), hospital discharge summaries, home carer reports, day centre reports, reports from housing officers/wardens of supported housing and criminal justice agencies and results from previous investigations such as psychometry and neuroimaging [77].

Greater prominence needs to be given to social functioning and social networks in older people than in younger adults. In older people, there is comparatively less emphasis on forensic history and occupational history than in younger people. Social pressures such as debt or even substance-using 'carers' or open drug dealing may impact on the older person's welfare. Vigilance about safeguarding is essential.

Functional ability also has greater relevance when assessing older people. This can be assessed using the Barthel Index which rates the ability to perform activities of daily living (ADLs) [93].

Table 99.4 Barriers to identification of substance misuse in older people [75]

Practitioner barriers	Individual barriers
Ageist attitudes	Attempts at self-diagnosis
Failure to recognise symptoms	Symptoms attributed to ageing or illness
Lack of knowledge about screening	Many do not self-refer or seek treatment
Discomfort with topic	Perceived stigma of 'addiction'
Lack of awareness of substance misuse in older people ('If you don't think about it, you won't see it')	Reluctance to report – shame, denial, desire to continue using, pessimism about recovery
Misuse traditionally considered to be rare in old age	Cognitive impairment
Symptoms may mimic or be hidden by symptoms of physical illness	Unwillingness to disclose
Unwillingness to ask	Collusion of informant(s)
Absence of informant(s)	Screening

99.2.4 Diagnosis

There are limitations to using standardised diagnostic criteria for substance misuse in older people [12]. Cognitive impairment may interfere with self-monitoring; there may be reduced incentive to increase harmful use, such as fewer social pressures and fewer personal and family pressures; negative effects may occur at relatively low levels of use; cravings may be attributed to depression or anxiety; roles and expectations may have changed; social or interpersonal problems may not be attributed to substance use; activities may have been given up for other physical or mental health reasons; physical harm may be denied; low levels of substance misuse may lead to tolerance and withdrawal.

99.2.5 Physical Examination

Physical manifestations of alcohol misuse can provide clues to damage from several substances. There may be weight loss and poor self-care. Gait may be impaired through intoxication, cerebellar damage or stroke. Complications from intravenous drug use can present as superficial and deep vein thrombosis, subacute bacterial endocarditis, nail fold infarcts, splinter haemorrhages, Osler's nodes and Janeway lesions. There may also be gum disease and dental caries. Chronic obstructive pulmonary disease (COPD) may arise from tobacco and/or cannabis smoking, and cocaine smoking can present with 'crack lung'. Alcohol misuse may present with acute (e.g. Mallory-Weiss tear, rup-

tured oesophageal varices, hepatic encephalopathy or arrhythmia) physical problems or else with stigmata of chronic liver disease, hypertension and oral and gastro-intestinal malignancy, as well as with stroke. Falls are also a common presentation of heavy drinking in older people.

There may be neurological manifestations such as cerebellar damage and traumatic intracerebral or extracerebral bleeding. Thiamine deficiency is associated with Wernicke's encephalopathy, Korsakoff's syndrome and peripheral neuropathy.

99.2.6 Mental State Examination

Certain aspects of the mental state examination have greater relevance for older people with substance misuse. Delirium is associated with intoxication or withdrawal. Delirium tremens has a high morbidity and mortality and is treatable. Wernicke's encephalopathy may also present with or be mistaken for delirium or intoxication, and the opportunity for treatment may be missed. The 'classic triad' of oculomotor abnormalities, cerebellar dysfunction and altered mental state only occur in 20%. However, 80% of patients present with an altered mental state of mental sluggishness, apathy, impaired awareness of an immediate situation, disorientation, poor attention, agitation and hallucinations.

Low mood and anxiety accompany misuse of a range of substances, particularly depressant drugs such as alcohol, sedatives and hypnotics. It is not uncommon to find the presentation of substance misuse compounded by mood disorder and cognitive impairment or 'somatised' by presenting as physical symptoms such as lack of energy. Suicidal ideation is highly relevant for older people with depression who are known to be at high risk of suicide when accompanied by alcohol misuse.

Psychotic symptoms are associated with a variety of substances such as cannabinoids, stimulants and hallucinogens; withdrawal states accompanying alcohol and/or sedative/hypnotics are also associated with transient psychotic symptoms. Chronic use of stimulant and depressant drugs (e.g. alcohol) can manifest as psychosis.

Cognitive impairment may arise from alcohol brain injury, alcohol-related traumatic brain injury, benzodiazepine use, stroke or chronic subdural haematoma. Cognitive impairment may be assessed using the mini-mental state examination (MMSE) [38] and Addenbrooke's Cognitive Examination (ACE) [53].

99.3 Co-occurring Mental and Physical Disorders

Co-occurring mental disorders occur in as many as 66% or people with substance misuse [6]. Depression and cognitive impairment are the most common mental disorders, with the latter mostly alcohol-related brain damage.

Depression is common in alcohol misuse [5, 16]. Older adults with depression are up to four times more likely to have alcohol-related problems than those without [32] and are also at higher risk of suicide [28]. Depression is also associated with a higher risk of past-year cannabis and cocaine use [10]. Other mental disorders such as anxiety, antisocial personality disorder and post-traumatic stress disorder are associated with alcohol misuse in over 60s [14, 63, 78].

Older heroin and methadone use is accompanied by physical co-morbidity, with prevalence rates varying from 11% for diabetes mellitus to 54% for hypertension. Other co-morbid disorders within this range include arthritis, cirrhosis, hepatitis C, lung disease and cardiac disease [74].

99.4 Interactions Between Substances and Prescribed Drugs in Older People

99.4.1 Alcohol

Alcohol has a number of potential adverse effects when taken with both prescription and non-prescription drugs. This is relevant to older people, in whom polypharmacy is common. Up to 28% of older people in the United Kingdom take medica-

tion that has not been appropriately prescribed. The most common drugs implicated are benzodiazepines and amitriptyline [8, 40]. Potential interactions between prescribed drugs, as well as with food and drink, are detailed in Table 99.5.

Table 99.5 Interactions affecting blood alcohol levels

Drug	Interaction	Risk
Over-the-counter drugs	Multiple interactions	Aspirin ↑ risk of bleeding into the gut Heavy drinking ↑ risk of liver damage from paracetamol
Antibiotics	Disulfiram-like reaction	Flushing, headache, palpitations, vomiting
Food	Multiple interactions	Food and milk ↓alcohol absorption
Nicotine patches	Pharmacodynamic	Tachycardia
Psychotropic drugs	Pharmacodynamic	Amitriptyline, clozapine, Mirtazapine, olanzapine, quetiapine, trazodone and zuclopenthixol ↑ drowsiness
Opiate analgesics	Pharmacodynamic	↑ risk falls/ respiratory depression
Sedating antihistamines	Pharmacodynamic	↑ risk drowsiness
Anti-hypertensive drugs	Pharmacodynamic	Low blood pressure and falls
Warfarin	Pharmacokinetic	Acute alcohol intake: ↑ levels Chronic alcohol intake: ↓ levels
Anti-emetics	Pharmacokinetic	Metoclopramide ↑ alcohol levels
Anti-epilepsy drugs and mood stabiliser drugs	Pharmacokinetic	Carbamazepine levels ↓ by heavy drinking; blood alcohol levels ↑ by meprobamate

99.4.2 Other Substances

Buprenorphine, methadone and loperamide are inhibited by antibiotics (ciprofloxacillin, clarithromycin, erythromycin, itraconazole, ketoconazole and ritonavir), the anti-hypertensive diltiazem, grapefruit juice and the antidepressant nefazodone. They are induced by drugs for epilepsy (carbamazepine, phenytoin, phenobarbital), the antibiotic rifampicin and the herbal remedy St John's wort.

Oxycodone, codeine, dihydrocodeine and tramadol are inhibited by the antidepressants fluoxetine and paroxetine, the anti-emetic metoclopramide and the anti-arrhythmic drug quinidine.

Pentazocine is inhibited by the anti-arrhythmic drug amiodarone, the beta-blocker propranolol, antibiotics ciprofloxacillin and rifampicin, the antidepressants duloxetine and fluvoxamine, the antipsychotics olanzapine and clozapine and caffeine.

Morphine, naloxone and naltrexone are minimally affected by pathways involving the above opioid drugs and therefore have clinically insignificant drug interactions with non-substances.

Nicotine alone has few interactions with other drugs. Its metabolism is inhibited by ketoconazole, isoniazid and grape juice. Phenobarbital and rifampicin are associated with enzyme induction. Polycyclic aromatic hydrocarbons in tobacco smoke affect the same enzyme pathway affected by metabolism of the drug pentazocine. However, in this case, smoking is associated with enzyme induction or inhibition of the drugs affecting its metabolism. The anti-epilepsy drug carbamazepine is induced by chronic smoking.

99.5 Treatment

A systematic review including people aged 50 years and over [54] concluded that older people have equally favourable or even better outcomes than younger people. An updated systematic review using a similar approach [9] found that interventions for at-risk drinking, cigarette smoking and prescription drug misuse

were associated with positive outcomes. A third review [48] with broader inclusion criteria included studies with mixed ages where non-age-specific treatments were also delivered to older people, focussing mainly on alcohol. There was a greater response to treatment (with longer duration and intensity of interventions) and greater treatment adherence in older than in younger people.

99.5.1 Alcohol

99.5.1.1 Pharmacological Approaches

Most pharmacological agents should be used with caution in older people. There is no specific guidance on the use of acamprosate, naltrexone or disulfiram in older people [52]. Addiction psychiatrists initiating treatment in older people should therefore work jointly with older people's mental health and medical services. Treatment needs to take account of co-morbid physical problems such as neuropsychiatric disorders and hepatic complications (e.g. alcoholic liver disease and hepatitis C), as well as respiratory complications such as chronic obstructive pulmonary disease (COPD). Older people are also likely to be taking multiple medications, with the potential for adverse drug reactions.

Alcohol withdrawal may be more severe and more prolonged in older patients in general hospital settings, compared with a younger age group [19]. Benzodiazepines such as chlordiazepoxide are clinically effective in managing alcohol withdrawal and detoxification [95]. For older patients, a lower starting dose of chlordiazepoxide is advised, with an increase in dose if withdrawal symptoms are not controlled. A longer-acting drug may prevent seizures and delirium but could lead to accumulation.

A lower starting dose should be used in older people, with regular monitoring using the Clinical Institute Alcohol Withdrawal Scale [90]. Shorter-acting preparations are preferable [57]. Chlormethiazole is not recommended for older patients because of its effect on respiration, cardiovascular complications and the unpredictability of the serum levels achieved [18].

Likewise, carbamazepine has not been evaluated in older populations and is therefore not recommended. Acamprosate, disulfiram and naltrexone are all licenced for the prevention of relapse in abstinent alcohol-dependent adults [52]. However, less evidence is available for their use in older adults. A trial comparing naltrexone as a relapse prevention medication with placebo found that the group aged 55 years and over had longer drinking careers and greater physical disability. However, their greater rates of treatment engagement and medication adherence were associated with a greater likelihood of abstinence [59].

99.5.1.2 Psychosocial Approaches

Several studies using age-specific treatment have evaluated the impact of psychosocial interventions. A study using the Computerised Alcohol-Related Problems Survey (CARPS) at baseline and 12 months found that adding physician input to education was more effective in reducing the quantity and frequency of alcohol consumption than education alone [36]. A telephone disease management (TDM) programme for depression and/or at-risk drinking was more effective than usual care. At 4-month follow-up, response rates were better in TDM (39%) compared with usual care (18%).

A controlled clinical trial (Project GOAL: Guiding Older Adult Lifestyles) compared the impact of enhanced brief physician advice compared with usual treatment [37]. Older people receiving the physician intervention demonstrated a significant reduction in 7-day alcohol use, episodes of binge drinking and frequency of excessive drinking.

The Primary Care Research in Substance Abuse and Mental Health for the Elderly (PRISM-E) compared integrated treatment in primary care with enhanced specialty referral for older adult at-risk drinkers [49, 60]. Both interventions produced an overall reduction in drinking or binge drinking. However, the integrated approach was associated with greater treatment engagement, especially for those with greater problem severity.

In the Healthy Living as You Age (HLAYA) study, participants were randomised to either active intervention or a booklet on healthy behaviours [51]. At 3 months, intervention group participants reported drinking fewer drinks in the past 7 days and less heavy drinking and had lower risk scores. At 12 months, only the difference in the number of drinks remained statistically significant.

A naturalistic retrospective study in London, UK, followed up 108 people aged 65 years and over with alcohol misuse who were referred to an old age liaison psychiatry service over a 5-year period [65]. Of the 50 people who were managed by community mental health teams, 19 (38%) had achieved abstinence from alcohol or controlled drinking at 6-month follow-up. Treatment comprised assessment and brief intervention, accompanied by psychosocial support.

99.5.2 Opioids

The prescription of strong opioid drugs for non-cancer pain has increased over the past 25 years. There are no controlled trials extending beyond 4 months of treatment, so the long-term effectiveness and safety of prescribed opioids are unknown. Inconsistencies in definition of aberrant analgesic use, in objective measurement of medication consumption and in description of clinical outcomes, can make identification of those overusing analgesics difficult [24].

99.5.2.1 Intravenous Opioids

Ninety percent of heroin users initiate drug use before the age of 30, with only 3% initiating after 50 years of age [100]. It was once believed that illicit drug users 'matured' out of their drug use, but there is evidence that older heroin users do not reduce their use as they age [74]. In the United States, the proportion of older adults seeking treatment for substance misuse is increasing relative to younger adults, and the pattern of drug use is changing, with increasing consumption of heroin [4]. In the United Kingdom, the initiation of drugs such as methadone, buprenorphine and adrenergic pre-synaptic agonists (clonidine and lofexidine) is not licenced for management of withdrawal states in older people. There is therefore a dearth of research into the use of these drugs in older people.

99.5.3 Tobacco

Older smokers appear to be more motivated to stop than younger people. One study showed a 4% increase in likelihood of enrolling in a smoking cessation trial for every year increase in age [27]. One review of 13 RCTs examined the effectiveness of smoking cessation interventions among people aged 50 years and over. Nine of 13 studies found a significant intervention effect at one or more follow-up assessments, suggesting successful interventions with older adults are available and feasible. The best results come from interventions of longer duration. Most studies included counselling of varying intensity, and eight provided medication for smoking cessation [101]. The impact on reducing harm from cigarettes through 'vaping' remains to be seen.

99.6 Service Provision

Older people with co-occurring mental and physical disorders have specific needs. Mental health services for older adults should provide integrated care. This should involve input from alcohol and drug services, geriatrics and primary care, so that physical, mental health and psychosocial needs are met. Ideally this should also be community based.

Older people with alcohol addiction frequently have co-morbid mental disorders, and in the absence of specialist services, they are mostly under the care of older people's community mental health teams. In the United Kingdom, the combination of alcohol addiction and other mental disorders is commonly referred to as 'dual diagnosis' [31]. However, at an international level, the most commonly used term is substance misuse and co-morbid mental disorder (SMCD) [66].

Traditional service configuration for SMCD is delivered through sequential or parallel treatment. Sequential treatment results in patients receiving treatment for one problem at a time, with treatment for the other problem being deferred until the first is resolved or improved. Parallel treatment involves different providers from different services system treating the two disorders simultaneously.

Integrated treatment models offer comprehensive services for both mental illness and substance misuse from a multidisciplinary treatment team, thereby overcoming barriers to care and debate over which disorder is primary. Both disorders are case managed to improve health and social function within a single care plan.

Targeting service delivery for SMCD in older people requires consideration given to those at highest risk. Such groups include those older people at risk because of their previous history of mental illness or else bereavement, retirement, social isolation or physical problems as well as those with depression, anxiety and cognitive impairment. However, integrated approaches cannot be effective unless older people with comorbidity receive the treatment that they need.

An 'assertive' approach involves the use of outreach models such as a home-based model, particularly for housebound older people who cannot access traditional substance misuse services. This is critical to success in engaging older people with SMCD and incorporates crisis intervention, practical support (monitoring safety, food intake, medication management, benefits, arranging transport), monitoring of mental disorders, review of treatment, social engagement and family support. The final component is the largest in terms of time and resource allocation, covering harm reduction and relapse prevention.

Approaches to harm reduction will involve substituting substance use with alternative activities, including:

- Improving social networks
- Improving physical function
- Reducing risks such as adverse drug interactions, delirium and falls
- Encouraging new hobbies
- Brief intervention and brief advice
- Supportive psychotherapy and cognitive behavioural therapy
- Social skills training around refusal of alcohol
- Psycho-education (including family education)
- Detoxification
- Consideration of alternative housing

Once harm reduction has been implemented, relapse prevention will involve a longer-term perspective and involves expanding opportunities for social integration, attending self-help groups (e.g. Alcoholics Anonymous), increasing family support, maintaining healthy lifestyles and living environments and encouraging volunteering activities.

In the United States, the Treatment Improvement Protocol Consensus Panel [11] recommends incorporating integrated assessment and treatment for SMCD, which included:

- Outreach, screening and intervention by addiction specialists, nurses, social workers and mental health counsellors
- Specific settings targeted to the elderly, including health fairs, day centres, retirement communities and housing sites
- Working with community agencies to develop referral networks such as primary care, social, ageing and other service providers
- Screening protocols for misuse of alcohol, prescription medications, over-the-counter medications and illegal drugs, as well as depression and risk of suicide

In 2009, a strategic vision for all clinical services for older people with SMCD within London, UK was developed [71]. The main aim was to improve the detection, treatment and health outcomes for older people with dual diagnosis (SMCD). The following objectives were identified:

- Building on existing good practice improving access to services
- Creating new service options where possible
- Developing clinically effective care pathways

- Promoting robust partnerships with key stakeholders (including working with service users and carers)
- Building a skilled workforce to address unmet needs
- Promoting health education/prevention/early intervention

A recent study of this service has shown that 40% of older people with SMCD referred from medical in-patient settings achieved either abstinence or controlled drinking within the Mental Health of Older Adults Clinical Academic Group.

Older people with SMCD require a considerably different approach to younger people, focussing more on chronic physical disorders, depression, organic brain disorders as well as social aspects such as social isolation, bereavement, activities of daily living, mental capacity, safeguarding and carer support. Challenges also lie within the prevention of hospital admission and institutionalisation through the delivery of home-based services.

99.7 Legal and Ethical Considerations

Older people with drug and alcohol misuse may present with difficulties around capacity, consent and principles used to determine the best interests of a patient. There should be presumption that all adults have the capacity to make decisions for them, unless proven otherwise. Capacity may also vary over time with intoxication or delirium, or according to the time of the day. Any decisions should be put off until the person regains capacity, if practically possible. If a person is deemed to be 'lacking capacity', it means that they lack capacity to make a specific decision or take a particular action for themselves at the time the decision or action was taken.

Older people from black and minority ethnic (BME) backgrounds face major challenges in accessing drug and alcohol services. These may include language barriers, social stigma as well as cultural and family values. Individuals from some BME backgrounds have higher levels of alcohol misuse and resulting health problems than the general population, such as older Irish and South Asian (Sikh) male migrants to the United Kingdom [64]. Both alcohol misuse and ethnicity can contribute to social disadvantage.

Each racial/ethnic group is not homogeneous and may include many subcultures that may be influenced by cultural values such as traditional beliefs, family structure, lifestyle preferences, gender roles, degree of assimilation and religious belief. These need to be borne in mind by various health professionals and during service developments.

99.8 Alcohol-Related Cognitive Impairment

Alcohol is known to be associated with cognitive impairment (ARCI) through a variety of mechanisms [68]. In older people with ARCI, there is also likely to be accompanying cerebrovascular disease with or without a history of stroke or cerebellar damage as well as a history of traumatic head injury with or without a history of chronic subdural haematoma or intracerebral haemorrhage [76].

Mechanisms of alcohol neurotoxicity [69] include direct toxicity (frontal and hippocampal damage), malnutrition (Wernicke's encephalopathy/Korsakoff's syndrome), metabolite toxicity, electrolyte imbalance, hepatic encephalopathy/infection, inflammatory (e.g. tumour necrosis factor alpha) and modifying factors (e.g. Apo E allele/elevated homocysteine).

ARCI shows better performance on language tasks but poorer performance on visuospatial tasks compared with Alzheimer's disease [72]. Frontal lobe damage is particularly common in ARCI, which may explain the high rate of behavioural problems seen in ARCI [70]. Unlike other forms of dementia, there is partial reversibility of some people with ARCI such as in frontal white matter integrity, particularly for late-onset alcohol misuse [39]. Alcohol use disorders also frequently complicate primary dementia, increasing cognitive decline [69].

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100 Treatment in Criminal Justice Settings; Mandatory vs Voluntary Treatment and Rehabilitation

Tim McSweeney

Contents

Abstract

The public health and community safety challenges associated with the use of illicit drugs have intensified in recent years, with the number of people using illicit drugs increasing globally and rates of fatal drug-related overdose rising considerably, particularly in North America and parts of Western Europe. Yet prevention efforts and treatment provision typically fail to meet levels of need and demand in many parts of the world. At the same time, 'drug-related' offending continues to be a significant driver of global prison populations and its associated costs. While a growing number of countries have implemented alternative policy innovations for dealing with drug-using suspects, defendants and convicted offenders using forms of depenalisation, diversion or decriminalisation, most continue to incarcerate and criminalise people for the possession or use of illicit drugs and rely on punitive sanctions, such as imprisonment, as the default response to 'drug-related' crime. This chapter draws upon international evidence for the effectiveness of 'coerced' and mandated forms of treatment (which are ordered, motivated or supervised by the CJS) as a response to 'drug-related' offending. It also highlights what this evidence base tells us about how different contexts and mechanisms

T. McSweeney (✉)
Department of Psychology,
University of Hertfordshire, Hatfield, UK
e-mail: t.mcsweeney@herts.ac.uk

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for implementation and delivery can hinder or enhance the effectiveness of these approaches.

Keywords

'Coerced' treatment · Diversion · 'Drug-related' crime · 'EMMIE' framework

100.1 Introduction

A range of diverse indicators suggest that the public health and community safety challenges and costs associated with the use of illicit drugs have increased in recent years. Official estimates suggest that in 2017 more than 270 million people worldwide (aged between 15 and 64 years) had used illicit drugs at least once in the previous 12 months. This is equivalent to around 6 per cent of the global population or 1 in every 18 people within this age range. The number of people using illicit drugs has increased by 30 per cent since 2009 when there were an estimated 210 million illicit drug users globally [74].

UNODC further estimates that there are 35 million people – around 13 per cent of all past-year users – who suffer from drug use disorders and require treatment services. While cannabis is by far the most commonly used illicit drug, opioids present the greatest harm to the health and wellbeing of users. There were over half a million global deaths attributed to drug use in 2017, with rates of fatal drug-related overdose increasing considerably in North America and parts of Western Europe.

However, prevention efforts and treatment provision typically fail to meet levels of need and demand in many parts of the world, with the UNODC reporting that only one in seven people with drug use disorders receives appropriate treatment each year. Findings from a recent systematic review [45] identified some of the most pronounced gaps between levels of need and provision existing in the Middle East and North and sub-Saharan Africa, where only around one third of the estimated regional population of people who inject drugs (PWID), for instance, have access to opioid substitution therapy (OST). Elsewhere, the proportion of opiate users in treatment varies considerably: from 28 per cent in Canada and the United States to 60 per cent in England and 76 per cent in France [59].

100.2 The Social and Economic Costs of Illicit Drug Use and 'Related' Crime

International evidence has consistently shown that rates of illicit drug use are significantly higher at all stages of the criminal justice system (CJS) – whether that be in police custody, through the courts and sentencing process, while subject to probation supervision or starting a prison sentence – relative to those found in the general population [10, 54]. Consequently, the CJS represents an important point for identifying, engaging and intervening with illicit drug users. Despite the challenges associated with generating reliable national estimates in this area of policy [53], illicit drug use is known to impose significant social and economic costs on societies, with considerable direct costs borne by the CJS [12]. These costs are incurred in response to a range of 'drug-related' crimes, such as drug:

- *Defined* (violations of legislation linked to possession or supply).
- *Induced* (committed while under the influence of drugs).
- *Inspired* (committed to generate funds to support drug use).
- *Systemic* offences (committed as part of the 'business' of drug supply, distribution and use, such as violence between rival dealers or supply networks) [26].

Globally, prison populations are estimated to have grown by 24 per cent since the turn of the century (a rate of growth broadly in line with population trends over the same period). During 2018, it is thought that there were over 10.7 million people held in various forms of detention throughout the world, either as pre-trial detainees/remand prisoners or having been convicted and sentenced [76]. These increases in the prison

population have occurred despite available police-recorded data from different countries worldwide pointing towards overall reductions in violent and property crimes between 2003 and 2013. By contrast, drug possession offences showed a marked increase, rising by 13 per cent over the same period [72]. These trends have led the United Nations to conclude that 'The global increase in drug-related crime is driven mainly by a rising number of offences related to drug possession, particularly in Europe and Africa… offences related to drug possession currently comprise 83 per cent of total global drug-related offences' [71: 6]. Consequently, one in five (20 per cent) of the global prison population in 2012 had been imprisoned for drug law offences, with the highest rates of incarceration for these offences apparent in Asia [72].

These punitive responses have been shown to disproportionately impact upon minorities and the economically marginalised in societies [2, 16, 63]. They are also associated with human rights abuses, including the extrajudicial killing of suspected drug dealers and users [3] and at least 35 countries and territories worldwide where drug offences were punishable by death in 2018 [24].

Recent estimates suggest that annual expenditure by European Union (EU) countries on drug law offenders in prisons is within the range of EUR 3.7 billion to EUR 5.9 billion [20]. The United States, by contrast, incarcerates more people per capita than any other country. Since the mid-1980s, state expenditure on corrections in the United States increased by 793 per cent: from USD 6.7 billion in 1985 to USD 59.8 billion in 2017. The United States held over two million people in its prisons and jails in 2017. At the federal level, people incarcerated following a drug conviction made up almost half (47%) the prison population during this period [69].

Despite its overuse as a response to 'drug-related' offending, prisons are acknowledged as being particularly ineffective and problematic settings, where detainees are especially vulnerable to drug use and exposed to heightened risks of HIV and hepatitis C transmission [29]. The presence of illicit drugs and associated markets within prisons can also have a destabilising effect on rehabilitative regimes, leading to increased rates of violence, self-harm and corruption [33]. In the few jurisdictions where monitoring regimes exist, these tend to show high rates of illicit drug use on both reception to and release from custody. In the United Kingdom, for example, the Scottish Prison Service identified not only high rates of illicit drug use on reception to custody in 2018/2019 (71 per cent), but as many as one in four (26 per cent) prisoners also tested positive for illicit drug use upon release [61].

100.3 A Shift in Policy Responses?

These pressures on and costs to the CJS persist despite legislation and policy existing in many jurisdictions which enables the diversion of drug-using suspects, defendants and convicted offenders, at different stages of the criminal justice process, to various forms of education and treatment [19, 35, 37]. While a small number of countries have recently implemented policy innovations for legalising and regulating production and supply of some drugs (such as cannabis in Canada and Uruguay, heroin prescribing in Switzerland, coca in Bolivia and some novel psychoactive substances in New Zealand), dozens of jurisdictions worldwide have policies in place for using alternatives to conventional criminal law responses to drug possession offences [17]. Some have adopted a de jure approach (where the changes are formally enshrined in law), while others have introduced de facto decriminalisation, by officially de-prioritising drug possession for law enforcement agencies.

A recent rapid realist review examined evidence and experiences of 9 of these countries and 158 published papers relating to 12 studies on alternatives to possession offences. While the authors identified advantages and drawbacks associated with each of the three models examined (depenalisation, diversion and decriminalisation), and did not find evidence that any of these approaches consistently increased the use of illicit drugs, they nevertheless concluded that 'research in this area is

complex, incomplete and not capable of providing definitive answers' [36: 4].

Most countries, however, continue to incarcerate and criminalise people for possession or use of drugs, and the use of punitive sanctions, such as imprisonment, prevails and typically remains the default response to 'drug-related' crime. This chapter draws upon international evidence for the effectiveness of drug treatment delivered in criminal justice settings, measured across a range of outcomes. It also highlights what this evidence base tells us about how different contexts and mechanisms for implementation and delivery can hinder or enhance the effectiveness of these approaches [55].

The discussion which follows is structured around the dimensions of the 'EMMIE' framework, developed in the crime reduction field [39], and presents existing evidence from key pieces of research in a format that helps users to access and understand it quickly. The elements of the framework are:

- *E*ffect (the impact of an intervention).
- *M*echanism (how it works).
- *M*oderator (where it works).
- *I*mplementation (how to do it).
- *E*conomic cost (how much it costs).

In keeping with much of the contemporary debate in the field, this chapter largely focuses on CJS-based treatment interventions targeting the illicit use of opiates and stimulants like cocaine. The links between alcohol use and crime, and CJS responses to it, are not explored. This terrain is avoided here simply because of constraints of space. That said, most of the themes and issues examined will have relevance to debates about treating alcohol misuse and dependence using the justice system. A prominent model of 'coerced' treatment – in the form of drug courts – is examined elsewhere (see Chap. X).

100.3.1 Effect

The evidence for the effectiveness of treatment for opioid dependence is both considerable and persuasive. In aggregate, the findings from this body of evidence point to the considerable benefits of retention in different forms of OST, and in particular methadone maintenance treatment (MMT), in contributing towards reducing (but not eliminating) the frequency and intensity of illicit heroin use. These reductions can in turn promote broader physical, social and behavioural changes and contribute towards greater social integration, with commensurate benefits for both the individual and wider community ([1]; see Bell [8] for a more recent comprehensive review of OST effectiveness and Strang, Groshkova and Metrebian [67] for evidence on the impact of supervised injectable heroin).

By contrast, our knowledge of 'what works' for treating cocaine dependence is far more limited. A meta-analysis of six reviews [21] found that antipsychotic medications appeared the most effective approach for reducing users' cravings for cocaine, while disulfiram was better (than placebo, versus anticonvulsants, and antidepressants) at retaining users in treatment. The reviewers concluded that these medications, when supplemented with other forms of effective intervention, such as psychosocial support and contingency management, may form the core components of an effective treatment intervention for cocaine users.

The case for using drug treatment as a crime prevention measure is however compelling: international research (e.g. [25, 28, 47, 68]) and meta-analytic reviews (e.g. [34, 58]) have consistently shown that exposure to different forms of drug treatment reduces the need for individuals to engage in crime by curtailing their use of illicit drugs. The impact on crime has been described as one of the 'most striking' benefits to arise from drug treatment [27: 301].

A key focus for policy makers and practitioners has been to understand the extent to which these positive outcomes might be diminished when drug treatment is 'ordered, motivated or supervised by the criminal justice system' ([49]: 471; citing [65]). Uncertainties about treatment effectiveness for criminal justice populations are further compounded by the range of ongoing conceptual [73], ethical [64] and practical [6] challenges presented by attempts to deliver drug treatment within a criminal justice context.

Conceptually, for example, there are no clear or universally agreed definitions of 'coerced' treatment. Instead, terms such as 'involuntary', 'incentive-based', 'legal referral' and 'compulsory' treatment have been employed interchangeably – often without any effort to directly assess the client's subjective perception of the referral process. And evidentially, there is little scientific research which documents improved outcomes related to compulsory diversion and treatment approaches [13], with some studies identifying potential harms [48, 75, 77].

It is 'coercive' treatment – distinct from involuntary or compulsory forms of intervention found in some jurisdictions, requiring patient consent and involving an element of constrained choice, which Stevens et al. [65] referred to as 'quasi-compulsory treatment' in the QCT Europe study. This research, involving 845 participants accessing support from 65 different services across 5 countries, found that those who enter treatment via the CJS can perceive greater external pressure to be in treatment, but that this does not adversely impact their motivation for change, relative to 'volunteers' accessing the same support via non-CJS routes. Many 'coerced' patients reportedly value the opportunity to access treatment via the CJS [66]. Results from the study showed that 'coerced' forms of treatment can be as effective as 'voluntary' interventions provided by the same services in terms of their ability to retain clients in treatment, reduce their self-reported substance use, and offending behaviours and improve health and social integration [60].

These findings are broadly consistent with those found by Jones [40] who examined outcomes for 1796 adult patients accessing 342 community and residential drug misuse treatment services in England during 2006/2007, as part of the Drug Treatment Outcome Research Study (DTORS). CJS workers were involved in referring 35 per cent of the DTORS sample to treatment [41]. The study found no negative association between referral source and levels of motivation or readiness for treatment; in fact, conditional referrals were positively associated with motivation at the point of treatment entry. Data from DTORS showed that coercion can positively affect treatment retention, and while changes in drug-taking behaviour were more strongly associated with level of intrinsic motivation, coercion was associated with cessation of offending among Class A (i.e. opiate and/or crack) users. Jones concluded that a coercive CJS referral is not detrimental to treatment success and may have particular benefits for specific populations.

However, the findings from systematic reviews and randomised control trials (RCTs) tend to be far more equivocal about the impact of treatment delivered via the CJS. A recently published review by Hayhurst et al. [32], for example, considered the results from 16 studies published between 1985 and 2016 on the effectiveness of both 'voluntary' and court-mandated community-based diversion programmes for criminally involved users of heroin and cocaine (including crack). The review identified:

- A small impact of diversion to treatment on drug use reduction.
- Problems retaining users of heroin and/or cocaine in treatment (compared to users of other illicit drugs).
- An uncertain impact on offending outcomes (due to a lack of outcome measure comparability and heterogeneity within the studies identified).

The authors noted that the poor methodological quality of the studies considered, and the focus of much of the existing evidence on US methamphetamine users, limited their ability to generalise the results from this body of work to other contexts and settings (see reviews by [9], and [43], who reach similar conclusions and also raise concerns about the range and quality of the existing evidence base).

Perry et al. [56] reviewed evidence from 14 RCTs which considered the impact of pharmacological interventions[1] for adult drug-using offend-

[1]The interventions considered as part of the review included (1) naltrexone in comparison with routine parole, social psychological treatment or both; (2) methadone maintenance in comparison with different counselling options; and (3) naltrexone, diamorphine and buprenorphine in comparison with a non-pharmacological alternative and in combination with another pharmacological treatment.

ers. The studies were published over a 45-year period (1969 and 2014) relating to outcomes for 2647 participants. Nine of the RCTs were US-based studies. While noting that their review was limited by the lack of information reported by the studies and that the quality of the evidence considered was deemed to be low, the authors found 'that pharmacological interventions do reduce subsequent drug use and criminal activity (to a lesser extent)…[but that there were] individual differences and variation between the degree to which successful interventions were implemented and were able to sustain reduction of drug use and criminal activity'. The review further found that agonist treatments were not effective in reducing drug use or criminal activity (when compared to non-pharmacological interventions) and there were no significant differences between the pharmacological interventions examined (i.e. methadone versus buprenorphine, diamorphine and naltrexone) on any of the outcome measures considered. The authors urged caution when interpreting the results of the review given the small number of trials which were limited mainly to male adult offenders.

A separate systematic review by Perry and others [57] considered the results from 9 RCTs (8 originating from the United States and 1 from Spain) relating to outcomes for 1792 female participants. The authors concluded there were too few published studies to evaluate whether the treatment setting (court or community) had an impact on the success of interventions for female drug-using offenders. It did however identify how psychosocial treatment (in comparison to treatment as usual) had an impact on reducing subsequent re-incarceration, but not re-arrest or drug misuse outcomes.

100.3.2 Mechanism

The justification for using 'coercive' forms of treatment is often premised on the utilitarian notion that diverting and engaging illicit drug users into a therapeutic intervention as they come into contact with the CJS will contribute towards addressing a key amplifier of their offending behaviour. Exploiting the coercive potential of the justice system in this way can provide a powerful mechanism for encouraging or incentivising illicit drug users to engage in a therapeutic intervention (including diversion to forms of education, advice and/or assessment) – using a range of both positive and negative forms of reinforcement [46]. Models in some jurisdictions draw explicitly upon constraint-based strategies which seek to remove or restrict opportunities for non-compliance by elevating the risk and severity of punishment. These constraint-based approaches can involve the use of formal controls such as drug testing, physical restraints like curfews and electronic tagging, or restrictions on associates and places to promote engagement and compliance. Sanctions such as fines and short spells of incarceration can also feature as constraint-based elements of 'coerced' treatment approaches. Hawaii's Opportunity with Probation Enforcement (HOPE) programme [31] and South Dakota's 24/7 Sobriety Project [42] are high-profile examples of such an approach.

Engagement and retention in forms of evidence-based psychosocial and/or pharmacological treatment, of sufficient duration and intensity, seeks to significantly reduce or eliminate the number and intensity of substance misuse-related problems. Within this theory of change, skilled workers can use techniques such as motivational interviewing to accelerate dependent users through the 'cycle of change' to a point where they find internal motivation to change their behaviour [30]. In tackling drug use, misuse and dependency, the treatment and support facilitated by forms of CJS-mandated intervention also aims to deliver commensurate reductions in any 'related' offending behaviours. This in turn generates wider benefits for communities and society (e.g. in terms of reduced rates of victimisation and antisocial behaviour).

To sustain any benefits and changes facilitated by the treatment process, 'coercive' approaches should ensure sufficient throughcare and aftercare arrangements are in place post-intervention, to encourage integration back into the community and allow for continuity of care. This can include onward referral to drug treatment ser-

vices and any ancillary support, or social care needs linked to issues like housing, or education, training and employment.

Some of these assumptions are illustrated in a theory of change for addressing drug dependence using 'coerced' forms of treatment, as set out in Fig. 100.1. Given the range and diversity of approaches available globally, it is intended to be illustrative rather than precise.

100.3.3 Moderator

Early evidence for the effectiveness and operation of mandated treatment was largely derived from the North American literature which emerge from the experiences of the California Civil Addict Programme (CAP) [4] and initiatives like the Treatment Alternatives to Street Crime (TASC) [38], and following the expansion of drug courts from the late 1980s [7].

Increasingly, studies outside the United States provide important insights to inform our understanding of the different contexts under which these interventions can operate more effectively. The findings from a recent large-scale review of interventions across Europe [44], funded by the European Commission, found that all 28 Member States (MS) reported operating at least one form of what the authors described as 'alternatives to coercive sanctions', or ACS. The study, which drew on insights from national experts, data from 178 interviews with stakeholders and extensive desk-based research, defined ACS as 'rehabilitative measures of treating, educating or reintegrating drug users as alternatives or additions to conviction or punishment…' [19: 1], which included '…measures that had some rehabilitative element or that constituted a non-intervention (for example, deciding not to charge or prosecute), as well as those used instead of prison or other punishment (for example, a suspended sentence with drug treatment)' [44: iii].

The review found that the most commonly occurring form of ACS in operation across Europe was a drug treatment order (offered by 17 jurisdictions). While there was considerable variation between different MS in their use of ACS, it was acknowledged that most forms were underutilised across the CJS. ACS appeared to be mainly offered at the latter (court and sentencing) stages of the CJS process, and there was considerable scope to expand its availability through diversion from arrest, prosecution or investigation. Though limited in scale and quality, the reviewers noted that there is a developing body of evidence about features that might make forms of ACS more effective (though again this was typically limited to drug courts and evidence originating from the United States).

The research identified several common factors which appeared to influence use and uptake of ACS options. These were strongly influenced by the individual beliefs of those stakeholders responsible for imposing ACS, such as prosecutors and judges. These beliefs tended to centre on issues linked to:

- The perceived benefits of treatment over incarceration (e.g. in relation to public protection concerns).
- A perceived lack of clarity around intervention objectives (e.g. what does success look like?)
- The relapsing nature of drug dependence and motivations of drug users (and the flexibility of the justice system to respond constructively to this).
- Levels of awareness about what ACS options are available (and their relative effectiveness).

Importantly, Kruithof and colleagues identified how the use of ACS is shaped by factors that can be influenced by policy makers. They highlighted how legislative changes can both increase the use of these measures (in the case of laws mandating their use in certain circumstances) and unintentionally curtail them (for instance, where legislation imposes restrictive conditions or narrow eligibility criteria).

There were a range of practical and administrative barriers identified too. These included the availability of financial resources to fund treatment; instances where the use of ACS was associated with lengthy and/or bureaucratic procedures; varying levels of partnership working within and

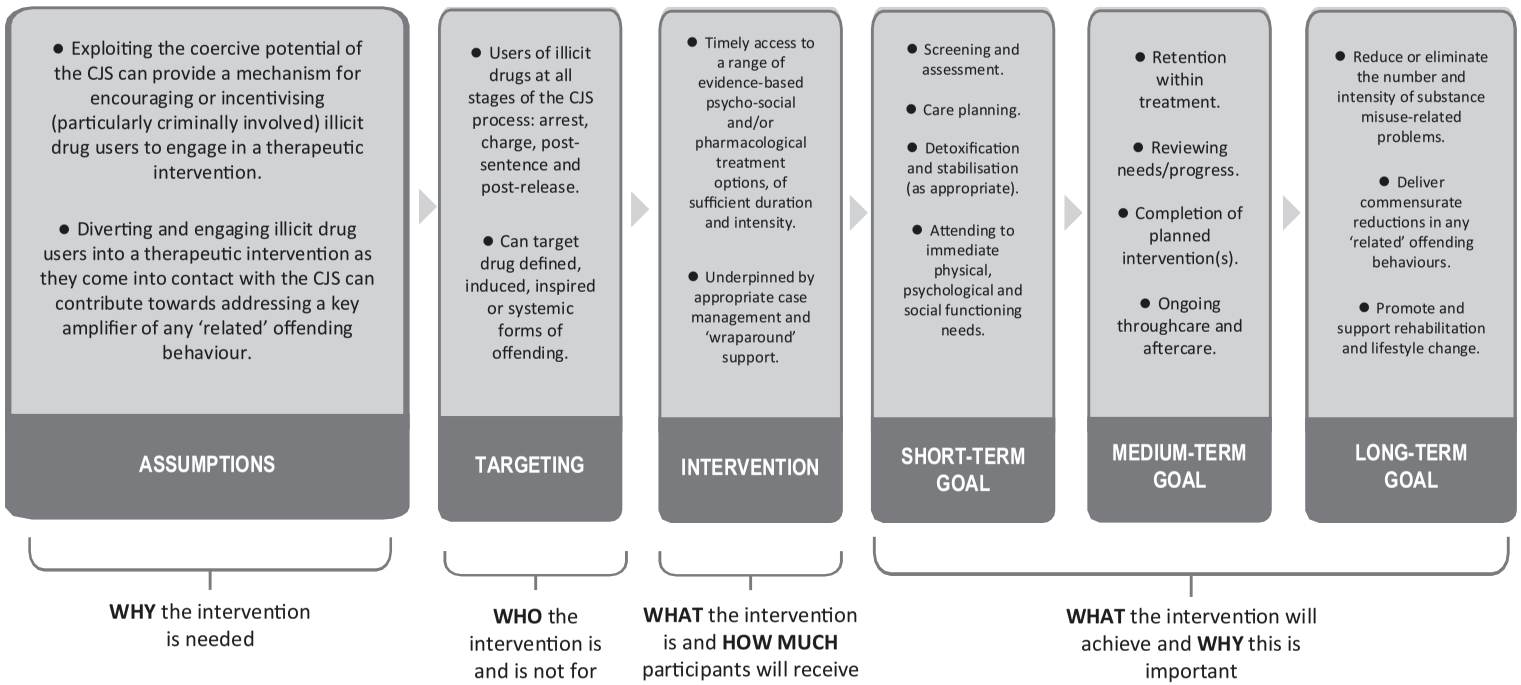

Fig. 100.1 A theory of change for 'coerced' treatment. (Adapted from Asmussen et al. [5]: 129)

between health, social care and justice systems; and problems ensuring effective forms of communication between those delivering treatment (e.g. health professionals) and those monitoring compliance (such as judges). In the absence of these elements, those imposing ACS may lack confidence in the quality, content and effectiveness of support, which may in turn serve as a significant barrier to their use.

A similar set of barriers and facilitators have been identified more recently concerning CJS responses to the personal possession and use of illicit drugs in Australia [36]. Key barriers to the uptake and expansion of diversionary approaches, identified using a mixed method approach which integrated insights from 24 professional stakeholders, included:

- The absence of a full range of programmes (e.g. with some jurisdictions only offering diversion for cannabis-related offences, but not other illicit drugs).
- Changes in drug trends (increasing use of methamphetamine and cocaine) and policing capacity.
- Narrow eligibility criteria employed by programmes.
- Lack of treatment access (linked to limited capacity and accessibility).
- Cultural resistance to diversion among (some) police sources.

By contrast, a range of key facilitators were identified. These included the establishment of diversionary options for all illicit drugs, in all states and territories, and for this to be underpinned by a supportive national policy framework which promoted the use of these measures. These efforts could be reinforced, the authors argued, in different ways: by introducing a legislative – or hybrid legislative – requirement to divert eligible offenders and integrating drug diversion into police performance monitoring systems. This would require greater streamlining of referral systems for police and improving feedback mechanisms to them about the operation and impact of drug diversion. There was considerable scope too for developing and testing innovative models of diversion delivery (such as online or using smartphones). Finally, investment in developing and improving the evidence base on 'what works' – including identifying the most effective or promising approaches and establishing their cost-effectiveness – could contribute towards building support for and increase the use of these measures.

100.3.4 Implementation

Despite some enduring reservations about the quality and range of evaluative evidence on 'coerced' or court-mandated interventions, the theories and principles underpinning effective drug treatment for criminal justice populations are, by contrast, well established [14, 23, 51]. These tend to highlight the importance of attending to a range of process and implementation issues, a focus which resonates with research findings pointing to service-level characteristics being better predictors of treatment outcomes than client-level variables [22, 50].

The results of a qualitative comparative analysis of best practice guidelines[2] for various diversionary programmes delivered in different parts of the world identified a number of distinct themes considered germane to effective implementation [11]. Achieving a consensus on *programmes objectives* was a key prerequisite identified. This included establishing and agreeing the overall aim(s) of the intervention – such as crime reduction or preventing future drug use. Clarifying the overall *treatment philosophy* for the intervention also emerged as an important best practice principle. This is concerned with whether the drug treatment component should be abstinence-based or harm reduction in focus and whether residential or community-based modalities would predominate, though the weight of

[2]Guidelines are usually systematically developed statements to assist and inform stakeholders in their decision-making about appropriate interventions for specific situations and circumstances. Typically, guidelines include a set of recommendations or steps that can be followed when implementing an intervention. Guidelines are commonly based on the available research evidence [18].

evidence suggests that, where possible, the full range of options should be available. There are inherent risks in adopting a 'one-size-fits-all' approach which privileges one treatment philosophy over another [70].

Establishing appropriate *eligibility criteria* for the targeting and identification of suspects, defendants and/or convicted offenders and observing *client rights* – gaining informed consent from participants and implementing ethical processes for securing this – were key areas highlighted by Bull's [11] review. Integrating a system for *compliance monitoring and judicial review*, which could include the use of sanctions and rewards, was another aspect of best practice identified. A focus on *reintegration* is an important consideration too, ensuring appropriate follow-up services and aftercare support – such as housing, education, training and employment – are in place to promote social integration.

Given the multidisciplinary nature of efforts which bring together public health and criminal justice practitioners, the review underlined the need for effective *partnership working* where the different stakeholders involved had clearly defined and demarcated *roles and responsibilities*. Regular *training* for different stakeholders such as the police, magistrates or judges, court workers and drug treatment providers should feature prominently, and approaches should be underpinned by appropriate *management and communication structures*, and informed using tailored and relevant *documentation* relating to all aspects of a programme or intervention (from referral, assessment, review, discharge, to monitoring and evaluation).

Bull's comparative analysis underlined the importance of *monitoring and evaluation*, establishing and imbedding at the outset requirements to routinely monitor throughputs, outputs and outcomes and independently evaluating (and re-evaluating) programme effectiveness. Finally, establishing and securing sustainable sources of *funding* for delivering all aspects of provision was an important best practice principle identified.

These best practice considerations linked to effective implementation are illustrated in Fig. 100.2.

100.3.5 Economic Cost

Research suggests that investment in drug treatment is likely to substantially reduce the economic and social costs associated with drug misuse and dependence. Official estimates from England, for example, suggest that in one 12-month period (2010–2011), drug treatment services may have prevented 4.9 million offences, leading to wider societal savings of £960 million during this period [52]. These estimates were derived from the multi-site, longitudinal DTORS study which reported a net benefit-cost ratio of investment in drug treatment in England of approximately 2.5 to 1 [15]. As noted above, more than one in three respondents to DTORS had been referred to treatment via the CJS [41].

Bright and Martire's [9] review of 'coerced' treatment approaches identified three studies which included an economic component: one produced mixed results, and another found that prison-based substance abuse programmes generated savings of between 1.8 and 5.7 times the cost of implementation, while a third study identified cost savings associated with drug courts.

While there is evidence from some jurisdictions which demonstrate the cost-effectiveness of diverting drug possession offenders [62], findings from systematic reviews of diversion and mandated forms of treatment have typically been unable to produce any economic or cost-benefit analyses based on the evidence assembled given the absence of data in this area [32, 43, 56, 57]. Therefore, the cost-effectiveness and value for money offered by 'coerced' forms of treatment still need to be quantified and measured.

100.4 Conclusion

While dozens of jurisdictions worldwide now have policies in place for using alternatives to conventional criminal law responses to drug possession offences, most countries continue to incarcerate and criminalise people for possession or use of drugs. The use of punitive sanctions prevails and typically remains the default response to 'drug-related' crime. Diverting and engaging

Fig. 100.2 Best practice principles for CJS-based treatment of criminally involved drug users [11]

illicit drug users into a therapeutic intervention as they encounter the CJS can contribute towards addressing a key amplifier of their offending behaviour. Engagement and retention in forms of evidence-based psychosocial and/or pharmacological treatment, of sufficient duration and intensity, can significantly reduce the number and intensity of substance misuse-related problems.

International research evidence from observational studies indicates that 'coerced' forms of treatment can be as effective as interventions accessed 'voluntarily'. These studies suggest no negative association between referral source and levels of motivation or readiness for treatment; that coercion can positively affect treatment retention; and that coercion at referral can be associated with a reduction in offending behaviour. This evidence points towards coercive CJS referrals as not being detrimental to treatment success and that this particular route may have particular benefits for specific populations. The findings from systematic reviews and RCTs, however, tend to be far more equivocal about the impact of treatment delivered via the CJS. These

studies consistently raise concerns about the range and quality of the existing evidence base.

This existing evidence provides some important insights to inform our understanding of the different contexts under which these interventions can operate more effectively. Comparative analysis of best practice guidelines points to the importance of achieving a consensus on programmes objectives; clarifying treatment philosophies; establishing appropriate eligibility criteria; observing client rights; integrating a system for compliance monitoring and judicial review; ensuring a focus on reintegration; the need for effective partnership working; clearly defining and demarcating roles and responsibilities of different stakeholders; the provision of regular training; appropriate management and communication structures; the importance of monitoring and evaluation; and establishing and securing sustainable sources of funding for 'coerced' treatment options.

The weight of evidence suggests that investment in drug treatment is likely to substantially reduce the economic and social costs associated with drug misuse, dependence and 'related' crime. That said, the cost-effectiveness and value for money offered by 'coerced' forms of treatment still need to be quantified and measured.

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Drug Courts

101

Douglas B. Marlowe

Contents

Abstract

Drug courts provide judicially supervised substance use treatment and other indicated services in lieu of criminal prosecution or incarceration. Substantial research demonstrates that drug courts significantly reduce criminal recidivism, incarceration rates, and illicit substance use, improve the psychosocial functioning of persons involved in the justice system, and produce positive cost-benefits for taxpayers. Evidence has identified the optimal target population for drug courts and a range of best practices that are associated with improved outcomes in these programs. Although most studies have been conducted on adult criminal drug courts, emerging evidence reveals comparable benefits and best practices for other types of treatment courts, including mental health courts, driving under the influence (DUI) courts, and family drug courts. Emerging evidence is beginning to reveal positive benefits in European, Australasian, South American, and Caribbean nations as well. The challenge now is to extend the reach of drug courts and other treatment courts without sacrificing efficacy or safety.

D. B. Marlowe (✉)
National Association of Drug Court Professionals, Chadds Ford, PA, USA
e-mail: dmarlowe@nadcp.org

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Keywords

Drug courts · Treatment courts · Problem-solving courts · Specialty courts · Criminal justice · Corrections · Correctional rehabilitation

101.1 Introduction

Approximately 60% of state prison and jail inmates in the United States and 40% of probationers and parolees have a moderate to severe substance use disorder [4, 58]. Approximately one-quarter to one-half of individuals in European, Australasian, South American, and Caribbean criminal justice systems misuse illicit drugs or alcohol [10]. Relapse to drug use is among the greatest predictors of criminal recidivism, increasing the odds of re-arrest by two- to threefold and the risk of multiple re-arrests by more than sixfold [14]. Completing substance use treatment reduces recidivism significantly [7]; however, the more a person needs substance use treatment and the higher the risk of recidivism, the less likely he or she will complete treatment [60].

Drug courts were created to reduce recidivism by improving compliance with substance use treatment. The drug court judge leads a multidisciplinary team of professionals that commonly includes representatives from the prosecution, defense bar, treatment agencies, probation department, and law enforcement. Team members meet frequently in staff meetings to review participants' progress in treatment and offer recommendations to the judge about suitable consequences to impose [45]. These consequences may include rewards such as verbal praise, reduced supervision requirements, or small gifts; punitive sanctions such as verbal reprimands, community service, or brief intervals of jail detention; or adjustments to the participant's treatment regimen. The consequences are administered in court during regularly scheduled status hearings, in which the judge discusses the matter with the participant or participant's legal representative. In pre-adjudication drug courts, the ultimate legal incentive is to have the criminal charge(s) dropped or withdrawn, and in post-adjudication drug courts, participants can avoid incarceration or reduce the length or conditions of probation.

The earliest drug courts were developed to serve adults charged with drug-related crimes. Eligible participants for these programs, referred to as adult drug courts, have a moderate to severe substance use disorder and are charged with a drug-related offense, such as possession or sale of a controlled substance, or another offense caused or influenced by drug use, such as theft or forgery to support a drug addiction. The success of adult drug courts spawned a variety of other types of drug courts, such as juvenile drug courts serving adolescents charged with drug-related offenses, family drug courts serving parents or guardians with substance use disorders accused of child abuse or neglect, and DUI courts serving persons charged with repeated instances of driving under the influence of drugs or alcohol. In addition, a broader range of treatment courts has been developed to address other social service needs commonly encountered in the court system, such as mental health disorders, homelessness, domestic violence, gambling, and prostitution.

The first adult drug court was founded in Miami/Dade County, Florida, in the United States in 1989. Currently, there are more than 3000 drug courts in the United States and more than 1300 other types of treatment courts [40]. Nearly 30 countries other than the United States have also established or are planning to establish drug courts, including Argentina, Australia, the Bahamas, Barbados, Belgium, Bermuda, Brazil, Canada, Cayman Islands, Chile, Columbia, Costa Rica, the Dominican Republic, El Salvador, England, Grenada, Ireland, Jamaica, Mexico, Norway, Panama, Peru, Scotland, Suriname, Trinidad and Tobago, and Vietnam [10].

In 1997, the National Association of Drug Court Professionals in the United States promulgated what are commonly referred to as the 10 Key Components of drug courts [45]. A few years later, the International Association of Drug Treatment Courts (IADTC) adopted the 10 Key Components and added three components focus-

ing on social reintegration of participants, ensuring flexible treatment for indigenous populations and ethnic minorities, and planning for aftercare recovery services. The IADTC principles are embodied in a document entitled the *13 Key Principles for Court-Directed Treatment and Rehabilitation Programs* ("13 Key Principles") (see below Box).

International Association of Drug Treatment Courts (IADTC)

13 Key Principles for Court-Directed Treatment and Rehabilitation Programs

1. The programs integrate substance dependency treatment services with justice system case processing.
2. Using a non-adversarial approach, prosecution and defense lawyers promote public safety while protecting offenders' due process rights.
3. Eligible offenders are identified early and promptly integrated into the program.
4. The programs ensure access to a continuum of substance dependency treatment and other rehabilitation services.
5. Compliance is objectively monitored by frequent substance abuse testing.
6. A coordinated strategy governs responses of the court to program noncompliance (and compliance) by offenders.
7. Ongoing judicial interaction with each offender in a program is essential.
8. Monitoring and evaluation measure the achievement of program goals and gauge effectiveness.
9. Continuing interdisciplinary education promotes effective planning, implementation, and operations of these court-directed programs.
10. Forging partnerships among courts directing treatment programs, public agencies, and community-based organizations generates local support and enhances program effectiveness.
11. Ongoing case management includes the social support necessary to achieve social reintegration.
12. There is appropriate flexibility in adjusting program content, including incentives and sanctions, to better achieve program results with particular groups, such as women, indigenous people, and minority ethnic groups.
13. Posttreatment and aftercare services should be established in order to enhance long-term program effects.

101.2 Effectiveness of Adult Drug Courts

101.2.1 Criminal Recidivism

Meta-analyses are advanced statistical procedures that calculate the average effects of an intervention across numerous research studies. Several meta-analyses conducted in the United States and Canada [2, 30, 34, 44, 55, 61] and national multisite studies in the United States [5, 52] concluded that adult drug courts significantly reduce criminal recidivism—typically measured by re-arrest rates within 2 years of entry—by an average of 8–14%, with the best programs reducing recidivism by 30–80%. Reductions in recidivism were determined to last for at least 3 years after entry [44], and in two studies, the effects lasted 15 years [15, 27].

Comparable effects have been reported in meta-analyses of DUI courts [44], family drug courts [62], and mental health courts [33]. Juvenile drug courts, in contrast, have shown small to statistically insignificant effects on recidivism [44, 61]. As will be discussed, this disappointing finding appears to stem from the fact that many juvenile drug courts are not following best practices or serving the appropriate target population of high-risk and high-need teens.

A meta-analysis in the United States concluded that adult drug courts also significantly reduce incarceration rates by an average of 8–12% [53]. Notably, however, this impact did not translate into less use of jail or prison beds. Although drug court participants were less likely to be incarcerated than comparable persons charged with the same crimes, participants who were unsuccessfully terminated from drug court ultimately served more jail or prison time. In other words, drug courts reduced the number of individuals who were sent to jail or prison but increased the length of jail or prison sentences for unsuccessfully terminated cases.

This finding could be interpreted as an indictment of drug courts because they may not reduce jail or prison overcrowding or overreliance on the most expensive correctional resources. An alternative interpretation, however, is that drug courts achieve larger crime reductions than other correctional programs without increasing jail or prison censuses. It is unknown whether crime rates would increase if drug courts reduced the consequences for unsuccessful termination. Some participants might be less likely to apply themselves in treatment if the consequences for program failure were less severe. Further research is needed to address this important question.

101.2.2 Cost-Effectiveness

In line with their positive effects on crime reduction, adult drug courts have also proven to be cost-effective. Meta-analyses of cost-effectiveness studies concluded that adult drug courts produced an average return on investment of approximately $2–$2.25 for every $1 invested [3, 12, 52]. These savings reflect direct cost offsets to the criminal justice system stemming from reduced re-arrests, law enforcement contacts, court hearings, use of jail or prison beds, and tangible impacts of crime victimization. When more distal cost offsets were also examined, such as savings from reduced child foster care placements and healthcare service utilization, studies have reported net economic benefits ranging from approximately $4 to $27 for every $1 invested, resulting in savings to local communities of roughly $3000 to $22,000 per participant [2, 15, 43].

101.2.3 Psychosocial Outcomes

The US National Institute of Justice (NIJ) funded a national study to examine the effects of adult drug courts on outcomes other than criminal recidivism, such as substance use, employment, family functioning, and mental health [52]. This study, the Multisite Adult Drug Court Evaluation (MADCE), compared outcomes between more than 1100 participants in 23 adult drug courts to those of a carefully matched sample of over 600 persons arrested for comparable offenses who underwent adjudication as usual. In addition to less involvement in crime, drug court participants reported significantly less use of illicit drugs and heavy use of alcohol at 6- and 18-month follow-ups, had significantly fewer positive saliva tests after 18 months, reported significantly greater improvements in their family relationships, and exhibited non-significant trends favoring higher employment rates and school enrollment. These findings confirm that adult drug courts produce substantial psychosocial benefits in addition to crime reduction. Comparable studies have not been conducted in other types of drug courts or treatment courts.

101.3 Effective vs. Ineffective Drug Courts

Meta-analyses indicate the average effects of an intervention; however, the results can mask substantial variability in the performance of individual programs. On the positive side, over three-quarters of drug courts included in the meta-analyses reduced criminal recidivism significantly; however, a substantial minority (roughly 20%) had no impact on recidivism, and about 5% were associated with increased recidivism [5, 34, 54]. A critical task is to identify prac-

tices that distinguish effective from ineffective drug courts and ensure programs apply those practices accordingly.

101.3.1 Target Population

A substantial body of research indicates which individuals are most in need of the full range of services embodied in adult drug courts. These are the individuals who (1) are addicted to or dependent on illicit drugs or alcohol and (2) are at substantial risk for criminal recidivism or failure in less intensive rehabilitative dispositions. Drug courts that focus their efforts on these individuals—referred to as *high-risk and high-need* individuals—reduce crime approximately twice as much as those serving less impaired individuals and return approximately 50% greater net cost savings [3, 5, 12, 34]. The same finding has been reported in DUI courts [49], juvenile drug courts [28], and family drug courts [37]. Unfortunately, evidence suggests that many juvenile drug courts are not serving the appropriate population of high-risk and high-need teens, leading to unimpressive outcomes and even increases in re-arrest rates [59].

These findings are consistent with a well-validated criminological paradigm referred to as risk-need-responsivity, or RNR [1]. According to RNR theory, intensive programs such as drug courts are hypothesized to offer the greatest benefits for high-risk individuals who have more severe antisocial propensities or treatment-refractory histories; however, such programs are often unnecessary or counterproductive for low-risk individuals. High-risk individuals have a relatively poorer prognosis for success in standard treatment programs and will often require intensive and sustained interventions to dislodge their entrenched negative behavioral patterns. Low-risk persons, in contrast, are less likely to be on a fixed antisocial trajectory and are apt to improve their conduct following a run-in with the law. Therefore, intensive interventions may offer small benefits for these individuals at a substantial cost. Worse, low-risk individuals often learn antisocial attitudes and behaviors from associating with high-risk peers, which can make their outcomes worse [35]. Providing intensive supervision or substance use treatment for low-risk or non-addicted individuals has been shown to increase rates of reoffending and substance use [32].

101.3.2 Best Practices

The key components of drug courts are hypothesized to include an ongoing schedule of judicial status hearings, a multidisciplinary team approach to managing cases, evidence-based substance use treatment services, frequent drug and alcohol testing, and contingent sanctions for infractions and incentives for achievements [45]. Each of these key components has been examined carefully by researchers to determine whether it is required for effective results.

Judicial Status Hearings Judicial status hearings are the defining ingredient of drug courts. Many correctional programs offer substance use treatment, drug testing, and sanctions and rewards for drug-involved individuals; however, only drug courts are led by a judge and require participants to appear frequently in court for status hearings. Evidence is exceptionally strong that judicial status hearings are a critical ingredient of drug courts, assuming the programs are treating the appropriate population of high-risk and high-need individuals.

A substantial body of research establishes the importance of scheduling status hearings no less frequently than every 2 weeks (biweekly) during the first phase of drug court. In a series of experiments, researchers randomly assigned drug court participants to appear before the judge every 2 weeks for status hearings or to be supervised by clinical case managers and brought to court only in response to repetitive rule violations. Results revealed that high-risk participants had significantly better counseling attendance, drug abstinence, and graduation rates when they were required to appear before the judge every 2 weeks

[13]. This finding was replicated in Australia [25] and confirmed in a prospective matching study, in which participants were randomly assigned to biweekly hearings if they were assessed as being high risk [39]. Similarly, a meta-analysis of studies of 92 adult drug courts [44] and a multisite study of nearly 70 drug courts [5] reported significantly better outcomes for drug courts that scheduled status hearings every 2 weeks during the first phase of the program. Scheduling status hearings at least monthly during subsequent phases of the program was also associated with significantly better outcomes and nearly three times greater cost savings [5].

Outcomes are also influenced by the length and quality of the judge's interactions with participants. Effects on recidivism are significantly greater when judges spend an average of at least 3 min, and as much as 7 min, interacting with participants in court [5]. Studies further find that drug court participants perceive the quality of their interactions with the judge to be among the most influential factors for success [19, 26, 48]. The MADCE reported significantly greater reductions in crime and substance use for judges who were rated by independent observers as being respectful, fair, attentive, enthusiastic, consistent, and caring in their interactions with participants [52]. A statewide study in New York similarly reported significantly better outcomes for judges who were rated by participants as being fair, sympathetic, caring, concerned, understanding, and open to learning about the disease of addiction [8].

A study of approximately 70 drug courts reported nearly three times greater cost savings and significantly lower recidivism when judges presided over the drug court for at least 2 consecutive years and thus had greater seniority and experience [5]. Significantly larger reductions in crime were also found when the judges were assigned to drug court on a voluntary basis and their terms were indefinite in duration. Evidence suggests most judges are less effective at reducing crime during their first year on the drug court bench [15]. Presumably, this is because judges, like most professionals, require time and experience to learn their jobs. For this reason, drug courts that annually rotated their judicial assignments or had participants appear before alternating judges had the poorest outcomes in several research studies ([15]; [48]). Participants in drug courts often lead chaotic lives and require structure and consistency to alter their maladaptive behaviors. Unstable staffing patterns, particularly when they involve the central figure of the judge, are apt to exacerbate the disorganization in participants' lives.

Multidisciplinary Team A controversial feature of drug courts is having professionals from different disciplines meet regularly to coordinate their functions as a team. Traditionally, judges, prosecutors, defense attorneys, and treatment providers did not sit down together to decide how to respond to defendants' behaviors. This practice has raised concerns among some commentators that drug court professionals might be sacrificing their ethical obligations of neutrality, objectivity, confidentiality, or zealous representation of their clients. Although anecdotal arguments abound, no empirical evidence indicates whether these ethical concerns are justified. Evidence does, however, confirm that a multidisciplinary team approach is necessary to improve outcomes. Studies reveal that the most effective drug courts require ongoing attendance at pre-court staff meetings and status hearings by the judge, defense counsel, prosecutor, treatment providers, program administrator, and law enforcement [5]. When any one of these professionals was regularly absent from team interactions, programs were approximately 50% less effective at reducing recidivism. Observational studies further revealed that when drug court judges did not attend pre-court staff meetings, they were often inadequately informed or prepared to deal effectively with participants in court [50].

Substance Use Treatment Substance use treatment lies at the heart of the drug court model. The core assumption of drug courts is that addiction fuels or exacerbates participants' criminal activity; therefore, treating substance use disorders is believed to be essential to reduce crime

and improve the psychosocial functioning of participants [45].

Studies confirm that the success of drug courts is attributable, in part, to the fact that they increase participant engagement in substance use treatment. The longer participants remain in treatment and the more sessions they attend, the better their outcomes [20, 55]. Outcomes are also significantly better in drug courts that offer a continuum of care for substance use treatment, which includes residential treatment and recovery housing where indicated [5]. The best results are achieved when participants meet individually with a treatment provider or clinical case manager at least once per week during the first phase of the program [5, 52]. Because many participants are unstable clinically and in a state of crisis when they first enter drug court, group sessions alone may not provide adequate time or opportunity to address their pressing clinical and social service needs. Individual sessions reduce the likelihood that participants will fall through the cracks in the early stages of drug court when they are most vulnerable to cravings, withdrawal symptoms, and relapse.

Better results have also been reported in drug courts that developed culturally proficient and gender-specific services for participants with specific clinical or social service needs, such as women with trauma histories or young African American or Hispanic males [41]. Finally, outcomes are better when programs deliver manualized cognitive-behavioral counseling that addresses participants' irrational criminal thinking patterns, improves their interpersonal problem-solving skills, and teaches them to consider the consequences of their actions before behaving impulsively [21].

Medication-Assisted Treatment Medication-assisted treatment (MAT) can significantly improve outcomes for persons with severe substance use disorders involved in the criminal justice system. Buprenorphine or methadone maintenance administered prior to and immediately after release from jail or prison has been shown to increase opioid-dependent inmates' engagement in treatment; reduce illicit opiate use; reduce re-arrests, technical parole violations, and reincarceration rates; and reduce mortality and hepatitis C infections [7]. These medications are referred to as agonists or partial agonists because they stimulate the central nervous system (CNS) via a comparable neural mechanism as illicit drugs. Because they can be addictive and may produce euphoria in non-tolerant individuals, they are sometimes resisted by criminal justice and treatment professionals. Positive outcomes have also been reported for antagonist medications such as naltrexone, which are non-addictive and non-intoxicating. Naltrexone blocks the effects of opiates and partially blocks the effects of alcohol without producing psychoactive effects of its own. Although research on MAT in drug courts is sparse, two small-scale, open-label studies reported better outcomes in drug courts for alcohol-dependent participants receiving an injectable form of naltrexone called Vivitrol [16].

A 2012 survey found that nearly one-half of drug courts in the United States did not use MAT [42]. One of the primary barriers was a lack of familiarity with the medications. For this reason, best practice standards published by NADCP require drug courts in the United States to learn the scientific facts about MAT, obtain expert consultation where available, and allow the use of evidence-based medications when prescribed by an addiction psychiatrist, addiction physician, or comparable medical professional who has personally examined the participant and will manage the case moving forward [47].

Drug and Alcohol Testing The success of any drug court depends on reliable monitoring of participant behavior. If a drug court does not have accurate information as to whether participants are abstaining from substance use and are compliant with other requirements in the program, there is no way to apply incentives or sanctions correctly or adjust treatment and supervision services accordingly.

The most effective drug courts perform urine drug testing at least twice per week during the first several months of the program [5]. Because the metabolites of the most commonly used sub-

stances are detectable in human bodily fluids for only about 2–4 days, testing less frequently leaves an unacceptable time gap during which participants can use substances and evade detection. In addition, drug testing is most effective when it is performed on a random basis. If participants know in advance when they will be drug tested, they can adjust the timing of their usage or take other countermeasures, such as frontloading on water, to elude the tests.

Although urine testing is the most common methodology in drug courts, other technologies that extend the time window for detection are becoming commonplace. Continuous alcohol monitors (CAM) are anklet devices that detect alcohol vapor in sweat and transmit a wireless signal to a remote monitoring station. Research suggests CAM can be effective at deterring alcohol consumption among recidivist participants in drug courts when worn for at least 90 consecutive days [17]. Similarly, ethyl glucuronide (EtG) and ethyl sulfate (EtS) testing extend the time window for detection of alcohol metabolites from a few hours to several days. At least one randomized controlled trial reported improved outcomes when a drug court employed EtG/EtS testing [18].

Graduated Sanctions and Rewards Drug courts administer gradually escalating sanctions for infractions and rewards for accomplishments. The nearly unanimous perception of staff members and participants is that sanctions and rewards are strong motivators for behavioral change [19, 31]. A randomized experiment confirmed that administering gradually escalating sanctions for positive drug tests and other infractions significantly reduced substance use and crime among drug court participants [22].

The use of jail sanctions in drug courts is controversial. Although some commentators have theorized that a realistic threat of a jail sanction provides the necessary leverage for drug courts to retain recalcitrant offenders in treatment, research on this issue is understandably sparse. It is difficult, if not impossible, to study the question in a controlled experiment. Few participants, staff members, or research ethics boards would permit jail to be imposed in a non-individualized and randomized manner. The most practical way to study this issue is to compare outcomes between similarly matched drug court participants who did or did not face the realistic possibility of receiving a jail sanction. Thus far, such studies have yielded mixed findings. One study reported better outcomes when participants faced a realistic prospect of jail [6], whereas another found no differences in outcomes [24]. Another method for addressing this question is to interview drug court participants. A consistent finding from focus groups is that participants viewed the threat of jail sanctions as a highly motivating factor to keep them engaged in treatment and committed to their sobriety [9, 19].

At least two randomized experiments investigated the effects of enhancing positive rewards for achievements in drug courts [38, 51]. The rewards were delivered in the form of payment vouchers or gift certificates for negative urine tests and other accomplishments. Neither study found improved outcomes, apparently due to a statistical ceiling effect. Outcomes were so favorable in both drug courts that it was difficult to improve upon them any further. In one of the studies, however, a pre-planned interaction analysis revealed a non-significant trend ($p = 0.08$) in which high-risk participants with more serious criminal histories may have performed better in the enhanced reward condition [38]. This preliminary finding suggests tangible rewards may improve outcomes for the most incorrigible participants in drug courts. Further research is needed to confirm this hypothesis.

101.4 Best Practice Standards

Armed with knowledge of what works and what does not, the drug court professional has an obligation to spread the word, raise the bar for all programs, and provide needed training and technical assistance to help programs comply with best practices. Until drug courts define appropriate standards of care, they will be held accountable, fairly or unfairly, for the worst practices in the field. Scientists will continue to analyze the

effects of weak drug courts alongside those of exceptional drug courts, thus diluting the average benefits of drug courts. Critics will attempt to tarnish the reputation of drug courts by attributing to them the most noxious practices of the feeblest programs. Only by defining the bounds of acceptable and exceptional practices will drug courts be in the position to disown poor-quality or harmful programs and set effective benchmarks for new and existing programs to achieve.

In 2013, NADCP released volume I of the *Adult Drug Court Best Practice Standards* [47]. Volume II followed 2 years later [46]. These landmark documents were the product of more than 6 years of exhaustive work by dozens of experts who painstakingly reviewed scientific research on best practices and distilled that vast literature into measurable and enforceable practice recommendations. Within 2 years of publication, more than 20 US states had already adopted the standards for purposes of credentialing, funding, or training new and existing drug courts in their jurisdictions. Comparable efforts are now underway in the United States to develop and test best practice standards for juvenile drug courts and family drug courts. Disseminating the standards widely and ensuring that all drug courts in the United States heed their provisions are the next great challenges facing the drug court field. It is too early to know whether other countries may adopt all or part of the standards to guide operations in their programs.

101.5 International Drug Treatment Courts

Rigorous experimental and quasi-experimental studies in Australia [25, 29] and Canada [30, 56] reported that adult drug courts—referred to as drug treatment courts in most other countries—significantly reduced criminal recidivism compared to traditional criminal justice programs and were cost-effective or cost-neutral. Similarly, a quasi-experimental study in London found that participants in a family drug treatment court engaged in significantly less substance use, were significantly more likely to be reunited with their children, and had significantly fewer recurrences of child abuse or neglect than matched parents in traditional dependency proceedings [23]. Finally, a quasi-experimental study in Vancouver, Canada, reported significantly lower recidivism for participants in a community court serving persons with co-occurring disorders compared to matched individuals undergoing traditional adjudication for low-level public order or summary offenses, such as public intoxication or disorderly conduct [57].

In other countries, most drug treatment courts are in the formative stages, and efforts to evaluate their outcomes have only recently been initiated. A survey conducted by American University on behalf of the Organization of American States (OAS) analyzed responses from criminal justice officials in Belgium, Bermuda, Brazil, Canada, Chile, Ireland, Jamaica, Mexico, Norway, and Suriname [11]. Most respondents reported that drug treatment courts in their country appeared to be reducing crime better than traditional criminal justice approaches, and approximately one-half reported achieving substantial cost savings. In 2010, the OAS Inter-American Drug Abuse Control Commission (CICAD) adopted the *Hemispheric Drug Strategy*, which, among other provisions, encourages member states to develop drug treatment courts and other court-supervised treatment alternatives to incarceration for individuals suffering from addiction who are charged with drug-related crimes. In 2012, representatives from Argentina, the Bahamas, Barbados, Canada, Chile, Costa Rica, the Dominican Republic, Jamaica, Mexico, Trinidad and Tobago, and the United States convened to develop an evaluation manual to guide evaluation activities for drug treatment courts in the Americas. The product of that work [36] includes a core dataset of performance indicators to be reported on a voluntary basis by member states and will hopefully guide drug treatment court evaluations in South American, Caribbean, and North American nations.

No studies have addressed the appropriate target populations or best practices for drug treatment courts in other countries. It is possible that the average risk and need level for drug court par-

ticipants may be substantially higher in some other countries than in the United States. Much of the increase in the US arrestee population has been fueled by drug possession cases, and in some US jurisdictions, individuals can be sentenced to jail or prison for simple drug possession. Because drug possession is less likely to receive a sentence of incarceration in many European and South American nations, drug treatment courts in those countries may serve persons facing more serious criminal charges. Future studies should address whether risk and need levels of participants differ significantly in other countries and, if so, whether this influences drug treatment court outcomes.

Virtually all countries surveyed by American University reported that they were providing services in their drug treatment courts consistent with the 10 Key Components or 13 Key Principles. It appears that many international drug treatment courts are exporting the model from the United States largely as designed and with modest adaptations. Future research will hopefully reveal what changes, if any, may be required to adapt the drug court model to the needs and traditions of other countries and peoples.

101.6 Conclusion: Going to Scale

Despite their proven efficacy, drug courts in the United States serve only a fraction (about 5–10%) of adults arrested each year who meet criteria for a moderate to severe substance use disorder [40]. The primary obstacle to expanding the reach of drug courts in the United States is a lack of resources and not an absence of judicial interest or public support [40]. Convincing lawmakers that they will recoup their investment and reap substantial economic gains by investing in drug courts is a primary goal of rational drug policy in the United States.

Other countries seeking to extend the reach of drug treatment courts face comparable challenges. The American University survey identified several barriers reported by other countries to implementing drug treatment courts. The most frequently reported barriers were a lack of funding (especially for treatment services), high rates of staff turnover, under-appreciation by policymakers of the serious problems faced by participants, inadequate services for teens and young adults, and insufficient availability of adjunctive services, such as child care and vocational training [11]. These barriers are virtually identical to those reported in the United States and do not appear to reflect unique problems encountered by Latin-American or Caribbean nations.

The major challenge for all nations is to extend the reach of drug treatment courts without diluting the intervention below effective levels. Any program can be made cheaper by reducing the dosage and providing fewer services to more participants. The difficult task is to maintain effectiveness in the process. Many interventions show efficacy on a small scale only to have the quality of implementation drift unacceptably downward as they are applied in day-to-day practice. The big question is whether the criminal justice systems in various countries will move in the indicated direction. Facing huge budget deficits, some governments are imposing across-the-board funding cuts to correctional and treatment programs. There is no need to speculate about the likely effects of such actions. If history is a guide, any cost savings that may be realized in the short term will shift the financial burden to a later date as the result of increased crime, drug use, and related impairments.

The appropriate course of action is to shift funds from costly and ineffective programs to those that are proven to reduce crime and conserve scarce resources. Rather than taking an axe to cost-effective programs, policymakers should reallocate funds away from inefficient programs, redouble their efforts to invest in evidence-based programs, and return net cost savings to taxpayers. Much is possible if lawmakers apply what works rather than what is expedient, familiar, or popular. If lawmakers do not rise to this challenge, all the research in the world will have little impact on public health or public safety.

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Addictions in Physicians: An Overview

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María Dolores Braquehais, Eugeni Bruguera, and Miquel Casas

Contents

Abstract

An estimated 10–14% of physicians are said to be at risk of becoming chemically dependent at some point in their careers. Defense mechanisms (as denial, minimization or intellectualization), greater stigma associated with mental disorders amongst doctors and easy access to self-treatment with licit drugs, added to specific individual risk factors, may account for this increased vulnerability. Substance use can appear as a an unhealthy strategy to cope with unpleasant emotional states, or it can be for recreational purposes. When it becomes an addiction, it poses risk both on the individual wellbeing and to their clinical practice safety. Among physicians, alcohol, sedatives and opioid misuse are the most prevalent substance use disorders (SUDs). In the last decades, Physician Health Programmes (PHPs) have been developed in several countries to address this problem. Although sharing some similari-

M. D. Braquehais (✉)
Integral Care Program for Sick Health Professionals, Galatea Clinic, Galatea Foundation, Catalan Medical Association, Barcelona, Spain

Group of Psychiatry, Mental Health and Addictions, Vall Hebron Research Institute, Barcelona, Spain
e-mail: mdbraquehais.paimm@comb.cat

E. Bruguera
Integral Care Program for Sick Health Professionals, Galatea Clinic, Galatea Foundation, Catalan Medical Association, Barcelona, Spain

Group of Psychiatry, Mental Health and Addictions, Vall Hebron Research Institute, Barcelona, Spain

Department of Psychiatry and Legal Medicine, Hospital Universitari Vall d'Hebron, CIBERSAM, Universitat Autònoma de Barcelona, Barcelona, Spain

M. Casas
Department of Psychiatry and Legal Medicine, Hospital Universitari Vall d'Hebron, CIBERSAM, Universitat Autònoma de Barcelona, Barcelona, Spain

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ties, they differ in organizational and clinical aspects. Addicted physicians in treatment prove significantly higher abstinence rates (70–80%) compared to other patients. However, concerns about ethical issues related to the treatment of sick doctors at PHPs, mainly in the USA, have recently arisen in public discussion and need to be carefully considered.

Keywords

Physicians · Addictions · Physician Health Programmes · Drugs · Impairment

102.1 Introduction

Physicians are not free from the risk of developing substance use disorders (SUDs). Easy access to self-medication and delay in help seeking when they have developed an addiction are common features in this patient subgroup. Addictions in physicians are a cause a serious concern due to their potential impact on their patients' safety, the lives and careers of the affected physicians, and the socio-economic burden to the healthcare system as a whole.

The main aims of this chapter are to: (a) provide a brief epidemiological review of addictions in physicians; (b) analyze the psycho-social barriers that prevent doctors with SUDs from asking for help; c) outline some signs which can facilitate early recognition of affected individuals and some tips to promote help seeking; and, (d) to describe the main Physician Health Programmes (PHP)'s models of intervention with a discussion of their benefits and limitations from clinical and ethical points of view.

102.2 Epidemiology

Physician impairment refers to those situations where physicians are rendered unable to carry out their professional responsibilities adequately due to a variety of health issues, including a medical disease, psychiatric problems, SUDs or dual diagnosis [1]. Physician impairment due to addictive behaviours may be episodic or chronic, leading to psychosocial deterioration and, finally, becoming dangerous both to the physician well-being and to their patients' safety [2–4].

The prevalence of addictions among doctors is said to be similar to that of the general population. Therefore, an estimated 10–14% of physicians may become chemically dependent at some point in their careers [5]. Physicians are less likely to experiment with illicit substances (such as marijuana, cocaine and heroin) but more prone to using alcohol and self-prescription of controlled medications such as benzodiazepine tranquilizers, opioids and/or stimulants [5–10]. However, trends in drug addictions are changing among new physicians and should be adequately evaluated in the future.

Boisaubin and Levine [11] point out that medical students, like their peers outside Medicine, may be fascinated by drugs, during their early medical training, but tend to overestimate their understanding of pharmacology and underestimate, or fail to comprehend, what addictions really entail. They may even continue to use drugs throughout medical school and into residency.

Some physicians start using drugs during their residency training, when they first receive prescribing privileges. They may use them to relieve stresses generated during that time period (e.g. fatigue, early responsibilities, professional disillusionment, lack of emotional support, less time to spend with friends and family, etc.), for recreational purposes or as "performance enhancers" [12]. Hughes et al. [6] found that more residents reported lifetime usage of benzodiazepines (22.7% versus 19.6%) as well as barbiturates (8.5% versus 7.3%) but fewer of them reported cocaine use (29.2% versus 32.5%) compared to other college students. With regard to alcohol use, Flaherty and Richman [5] found that 20.3% of medical students met criteria for alcohol abuse or dependence in the 12 months prior to the interview.

Hughes et al. [6], in a mailed survey to 9600 physicians affiliated to the American Medical Association, reported that practising physicians were as likely to have experimented with illicit substances in their lifetime as their age and gender

peers in society, but less likely to be current users of illicit drugs. Physicians' use of prescribed drugs (e.g. benzodiazepines, barbiturates, minor opiates or amphetamines) was primarily related to self-treatment, while the higher prevalence of alcohol use could be related to other socio-economic determinants. Schneider et al. [13] also reported that Swiss primary care physicians tended to self-medicate with analgesics and tranquilizers.

In a nationwide, prospective and longitudinal study following young Norwegian physicians from internship through the subsequent 9 years, Hem et al. [14] found that physicians self-prescribed not only antibiotics (71–81%) or contraceptives (24–25%) but also analgesics (18–21%) and hypnotics (9–12%). Those suffering from mental disorders used sedatives or hypnotics as a form of self-treatment. In other studies, such as those conducted by the Galatea Foundation in Catalonia (Spain), both medical students and resident physicians were found to have higher problematic alcohol and sedative use compared to the general population [15, 16].

With reference to medical speciality, the reported prevalence of addictions among physicians is higher for anaesthesiologists, psychiatrists and emergency medicine/intensive care physicians compared to other specialities [6].

Particularly, anaesthesiologists and intensive care and emergency physicians are considered high-risk specialties because of their increased knowledge of and availability of highly addictive drugs [17–20]. As recently as 2005, the drugs of choice for anaesthesiologists entering addiction treatment were fentanyl and sulfentanyl. They also have an increased potential risk of misusing agents such as propofol, ketamine, sodium thiopental or inhalation agents. Prevalence rates of other SUDs, such as alcoholism, among them are not different from other physicians. Among anaesthesiology trainees, the main drugs abused are: intravenous opioids (fentanyl, in 64%), alcohol (35%), cannabis (14%), cocaine (12%), hypnotics (such as midazolam, 12%), oral opioids (10–14%) and anaesthetic agents (propofol 5–8% or inhalation agents, i.e. nitrous oxide, 2–3%) [19].

Hughes et al. [6] also found that general practitioners and obstetric/gynaecology physicians were more prone to using minor opiates, while anaesthesiologists, emergency doctors and chronic pain physicians tend towards self-prescribing major opiates. The trend was found to be similar among residents.

Psychiatrists were more likely to use benzodiazepines [6].

In a recent study [21], surgeons were found to be more likely than non-surgeons to enrol in PHPs because of alcohol-related problems but less likely to be admitted because of opioid use. However, they had positive treatment outcomes similar to those of non-surgeons.

In relation to mandatory treatment, McLellan et al. [8] reviewed the laboratory and medical records of 904 physicians admitted to 16 PHPs in the USA. Five specialities represented more than 50% of physicians: family medicine (20.0%), internal medicine (13.1%), anaesthesiology (10.9%), emergency medicine (7.1%) and psychiatry (6.9%). Alcohol use disorders and opioid abuse and dependence were found to be the most frequent conditions among physicians compulsory referred to PHPs [22].

The combination of affective and alcohol disorders is the most common form of psychiatric comorbidity among physicians [3, 23]. Some type II personality disorders, such as the narcissistic and/or the antisocial types, are often comorbid in physicians treated within specific programs for doctors under compulsory treatment [1]. In non-punitive programs [3], as well as antisocial traits avoidant and obsessive-compulsive ones are also present in doctors suffering from addictive disorders.

Increased suicidal risk has also been associated with the presence of addictions and dual diagnosis in doctors [3, 24, 25].

Smith DR [26] underlined that most developed countries had shown a steady decline in physicians' smoking rates in the last decades. The lowest smoking prevalence rates (less than 10%) have been consistently documented in the United States, Australia and United Kingdom [26, 27]. However, physicians in some developed

countries and newly-developing regions still appear to be smoking at high rates [28].

In summary, alcohol, sedatives and opioids are the drugs most commonly used by physicians with addictions, followed by cocaine, stimulants and cannabis (the latter, higher among younger doctors). Little evidence is yet available with regards to the use of new drugs and to behavioural addictions. However, they should also be considered whenever they may negatively affect both the individual wellbeing and pose risk to the safety of their practice.

102.3 Identifying and Helping the Sick Doctor

Doctors experience significant work-related mental health distress, as working long hours caring for others may be physically, emotionally and psychologically demanding. Other specific occupational factors may increase distress: high stressful situations, work-home time unbalance, conflicts with patients, injury or accidents at work, life-and-death decisions, etc. [29, 30]. Although some of the defense mechanisms for working as a doctor are initially adaptive, they become unhealthy coping mechanisms when physicians are in trouble [31]. In this situation, physicians may tend to self-medicate and will be at a higher risk of burnout or at an increased risk of self-harm behaviours, including suicide [32].

A high proportion of doctors show inadequate attitudes towards their general healthcare [14, 33], a phenomenon that has been popularly reflected in the old saying "the shoemaker always wears the worst shoes".

When it comes to SUDs, delaying help seeking will worsen their evolution [6], increasing the risk of developing comorbid conditions [14], their morbid-mortality [3], and the likelihood of having malpractice behaviours [8, 10, 34, 35].

Other reasons have been related associated with the tendency to delay help seeking: (1) the fear of licensure problems [36]; (2) the physician's identity construction, with an exaggerated sense of responsibility together with an increased sense of invulnerability; (3) their proneness to coping alone; (4) their survival mentality; and (5) their high level of self-doubt and insecurity [37].

In some individuals, barriers may be related to [38, 39]: high self-criticism; low self-esteem; poor bonding with relatives; competitive, humiliating and status-conscious work environment; and burnout symptoms related to high job demands.

In such situations, physicians may tend to self-medicate and will be at a higher risk of burnout and of self-harm behaviours, including suicide [32]. Alcohol use may become a "socially accepted" strategy to deal with stressful conditions [40]. The confluence of these factors with an increased vulnerability, due to factors unrelated to the profession, may lead to an addiction. Once the addiction pattern is established, it becomes even more difficult for the sick doctor to ask for help.

As some doctors with addictions do not ask for help, some direct or indirect signs may help their colleagues identify their problem [4, 11]. Some specific signs and symptoms appear when there is an intravenous drug addiction [17, 19] (see Table 102.1).

Besides professional impairment, some other personal and environmental problems can arise: (1) sexual, marital and/or financial difficulties; (2) driving convictions; (3) decreased involvement in family activities and commitments; (4) dependent children behavioural problems; (5) frequent arguments or unexpected mood shifts; (6) social isolation and/or loss of friends; and (7) cessation of hobbies and other interests (Bryson and Silverstein; [19]).

In fact, relatives or close friends may be the first to identify addiction problems and may encourage the doctor to seek help, although it is not uncommon to find the physician not accepting such recommendations.

Nevertheless, it is the peer-physician responsibility to identify alcohol-impaired or drug-impaired physicians in order to help them return to optimal functioning and to safeguard patients from the care of impaired physicians [4, 11].

Voluntary help seeking should be tried first. Some tips may be of help in this scenario: (a)

Table 102.1 Identifying physicians with drug addictions

	General signs and symptoms	Parenteral drug use
Indirect signs	Abnormal behaviour Loss of reliability Unjustified absences from work Frequent medical complaints Abnormal prescription (tendency to self-prescription) Mood changes Isolation from colleagues Staff concerns	Decreased performance Requesting extra shifts Preference to working alone Extra offering to colleagues for breaks, extra calls or wards Poor anaesthetic record keeping Offering to handle or manage drugs in exceptional environments Difficulty finding the person when on-call Suspicious or protective behaviour around locker or briefcase Using anaesthetic techniques without narcotics, falsifying charts, diverting drugs for own use
Direct signs	Smell of alcohol Somnolence Hyperactivity Disinhibition Ataxic gait Slurred speech Tremor Dishevelled appearance Depressed mood	Nasal rubbing/itching of drowsiness after drug "top-ups" Recurrent minor physical or facial injuries Favouring covered arms and feet to conceal injection sites Nasal discharge, yawning, tears, pallor, sweating, pilo-erection, feeling cold when abstinent from drugs Weight loss, pallor Gastrointestinal or pain complaints Frequent vague, unexplained complex illnesses

avoid "corridor" consultations; (b) find a quiet, private place to talk without interruptions, (c) try to be empathic and non-judgemental; (d) provide a comprehensive non-stigmatized model for addictions as mental disorders that can be successfully treated in specialized treatment settings; (e) underline the benefits of early help seeking; (f) focus on the physician-as-patient own strengths and competencies; and (g) offer support and advice of how and where adequate treatment or help can be provided. Refraining from working should be encouraged in this situation until the physician has demonstrated maintained abstinence and that s/he is not impaired from practising safely.

If the impaired physician does not accept to be treated, the senior doctor/manager or the regulator needs to be informed in order to avoid any danger to the public as well as to the physician. When found unfit for practice because of an addiction, the physician-as-patient may feel ashamed and/or fearful of the negative consequences of their misconduct. In some cases, this overwhelming distress may lead him/her to desperate solutions, including suicide [41, 42]. Providing easy and quick referral to adequate highly confidential treatment may help prevent this risk.

Some strategies specifically designed to prevent drug use among physicians should also be encouraged. Educational programs that identify and address the risk and protective factors related to addictive disorders in physicians help destigmatize and may change some unhelpful coping strategies among doctors. Safety measures inside and outside the workplace are also recommended. Careful record keeping, evaluation of use patterns and computerized record keeping and dispensing system in hospitals may decrease the misuse of highly addictive drugs such as opioids or other sedatives [17]. Systems that adequately and effectively monitor medical prescriptions may also be useful.

102.4 Treatment

Specialized programs to help doctors who are dependent on substances seem to provide the best available measures for protecting patients and for recovering physicians' careers and wellbeing [29, 43].

In the late 1970s, Physician Health Programs (PHPs) started to be developed in the USA in order to identify and treat impaired physicians involved in misconduct allegations as a conse-

quence of their mental disorders, mainly SUDs [35, 44]. PHPs were initially established with the primary focus on early detection and treatment of physicians with substance misuse but gradually expanded to address other mental disorders and even physical problems or disruptive behaviours. Similar programs were developed later in other countries such as Canada, Australia Spain and the UK [43]. In recent years, Ireland has launched a program similar to the UK´s.

In the US, physicians identified as having SUDs are referred to their state PHP to facilitate formal evaluation and assessment of treatment needs. US PHPs mainly follow a model which provides an active care management, monitoring and supervision (typically for 5 years) of physicians who have previously signed mandatory contracts with them. US PHPs refer addicted physicians to non-funded treatment resources where they start their rehabilitation process.

There is a close relationship between the treatment provider and the medical licensing boards, who may accept the PHP intervention plan instead of directly imposing disciplinary actions. Lapses during their treatment process lead to intensified treatment strategies. That also means bringing the physician back to the medical licensing board's disposal if necessary. In addition, those who refuse to sign the contract or continue to use drugs may end by losing the licence to practice. Nowadays, PHPs exist in 47 US states and in the District of Columbia ("Federation of State Physician Health Programs", 2018).

PHPs' clinically recommended interventions often include an intensive inpatient residential program lasting around 3 months followed by a less intensive outpatient substance addiction treatment, up to 1 year, which includes several group meetings per week [45]. After this intensive treatment phase, on-going care agreements are enacted with clients including meetings with counsellors and case managers, 12-step group attendance, support meetings for health professionals and 5-year random drug and alcohol screening (Brown and Bohler 2019; [46]). Follow-up interventions in US PHPs mainly adhere to the principles of Alcoholics Anonymous (AA), Narcotics Anonymous (NA) or other 12-step approaches [32].

The first national study of the state PHPs tracked 904 physicians from 16 PHPs over a period of 5 or more years, 78% of those who completed the stipulated contract were licenced and working, 11% had their licence revoked, 4% had retired and 3% had an unknown status [8, 46]. Although there were differences between each state PHP, the study described the core pattern of care management of all programs running at that time.

Similar results to the US PHP's model were reported by the Ontario Physician Health Program in Canada, where 71% physicians in treatment had no relapse during a 5-year follow-up and a total of 85% successfully completed the program. Most of them (66%) had been compulsorily referred to the program by their College of Physicians, and 16% had been sued for malpractice behaviours [22].

The Practitioner Health Programme in the UK, delivered by the National Health Service (NHS-PHP), is offered as a free, confidential, self-referral treatment service for physicians and dentists with mental and addictive disorders [47]. The national program is delivered through a central hub and has been led since the outset by a general practitioner with training in psychiatry. As such, the service acts as a hybrid between a mental health service and a primary care service. It provides what any standard mental health services do and also has access to residential rehabilitation services for patients with addiction problems [47]. The key difference from US PHPs is that the NHS-PHP deliberately does not have any formal links with the regulators (though it will meet and review treatment with them if the patient consents).

In 2018, the NHS-PHP reported that around 10.1% (n = 381) of all physicians attending the program suffered from addictive disorders. In 2017, they found a complete abstinence rate of 77.8% at 12 months or at discharge (usually >5 years) for 255 addicted doctors in treatment. Overall, 100 out of the 381 addicted doctors had been temporarily admitted to a specific inpatient unit for detoxification at the beginning of their

treatment process. Patients at the NHS-PHP receive a combination of psychological and pharmaceutical interventions (alcohol- or drug-assisted detoxification, antidepressants if necessary) and a case management approach. All addicted doctors are followed up, drug-monitored if necessary and encouraged to attend long-term mutual self-help meetings such as Narcotics/Alcoholics/Cocaine Anonymous or a specific group for addicted physicians ("Garden Group").

The Integral Care Program for Sick Doctors (PAIMM, in Catalan; PAIME, in Spanish) was created in 1998 in Barcelona and later extended to other Spanish Autonomous Regions [48, 49]. The PAIMM can be defined as a free, highly confidential, mental health treatment service whose main aim is to promote voluntary help seeking of physicians with mental disorders, including addictions, while safeguarding safe practice. In Barcelona, the programme is funded by both all Catalan Medical Council-Associations and the Catalan Department of Health. Patients in Catalonia are offered outpatient, day hospital or inpatient interventions in the Galatea Clinic depending on their clinical severity.

The Medical Council-Association mandates specific treatment measures as a condition for keeping the licence to practice only when there is evidence or risk of practice problems [40, 43]. In those cases, physician-as-patients voluntarily sign a specific contract where they commit to remain abstinent and to refrain from working if impaired by their mental disorder. Safety when returning to practice is adequately supervised by a tutor in the workplace. Physicians mandated to follow this type of therapeutic agreement are given all ethical and legal warranties to protect their rights both as individuals and as professionals. In Catalonia, the PAIMM mental health service model has been progressively extended to other health professionals whose practice needs to be regulated by a professional council-association (i.e. nurses, pharmacists, veterinarians, dentists, psychologists, social workers and physiotherapists).

At the beginning of the PAIMM, physicians with addictions followed long-term individual psychiatric and psychological treatment, regular drug screening and a case management approach. Since 2008, the PAIMM launched the Integral Treatment Program for Physicians with Addictions; the long term follow-up, drug screening and assessment were enhanced with an initial intensive psychotherapeutic phase followed by 2- to 5-year weekly group psychotherapy. All admitted physicians working in Catalonia completed the intensive intervention, and 87.3% kept being monitored afterwards. Mean length of treatment was 48 months. A total of 72.2% sick physicians remained abstinent at last contact. Good adherence to follow-up psychotherapy groups predicted both lower risk of lapse during treatment process and higher rates of abstinence at follow-up [50].

New PHPs are being estabilished place in other countries such as Argentina, Costa Rica, Uruguay and Chile following the Spanish PHP model. Since December 2017, a European Practitioner Health Provider Network (PHPN) has been formed in order to provide the opportunity to share practice, understand variance between different services and define a common Europe-wide service specification for practitioner health services. France, Ireland, Germany, the Netherlands, Belgium, England, Spain, Malta and Scotland have already joined the institution [47], although not all of them have set intervention programs yet.

In recent years, some concerns have been raised with regard to certain managerial and ethical questions related to US PHPs' procedures. In cases where physicians with addictions are mandated to treatment, two ethical principles are in conflict: a) the imperative to protect their practice safety ("social contract") and b) respecting of the impaired physicians' rights and autonomy [51–53]. Accepting treatment can be seen as an opportunity for impaired physicians to regain their professional standing [52]. Removing the financial barriers to being treated will help in this sense. Moreover, following unified national standards with periodical oversight of PHPs' activities will benefit the soundness and fairness of their practice [54].

Some programs, such as the Barcelona PHP, have addressed these ethical requirements by: (1)

offering free and easy access to all physicians working in Barcelona; (2) balancing the regulator's duty of preserving safe practice but also respecting the physician rights; (3) obtaining approval for big data analysis and reporting from a recognized Ethics Research Committee; (4) providing a highly confidential treatment; and (5) giving public visibility to the program.

Regardless of the country, physicians have a good response to addiction treatments when compared to the general population. Reports of several programmes reveal long follow-up abstinence rates for physicians with addictions to be around 70–80% [8, 11, 22, 43, 46, 50]. Results of follow-up studies support the need for and the efficacy of highly specialized programs for physicians with addiction problems [2, 11, 29].

Some keys to success of this "New Paradigm for Long-Term Recovery" of drug addicted patients are [2, 46, 55]:

1. Offering immediate and highly confidential intervention. Providing an appropriate, easy-access and confidential treatment as soon as the sick doctor seeks help is critical.
2. Addictions can be conceptualized as mental disorders with complex bio-psychosocial underpinnings. Careful and empathic presentation of the nature of the disorder may help avoid self-stigmatizing attitudes or responses.
3. Evaluation and triage at the appropriate facility where a comprehensive case management is offered. Treatment at outpatient or inpatient facilities will depend on the severity of their addictive disorder. However, an initial intensive treatment approach is recommended.
4. The treatment staff should be trained to deal with the particular occupational components and with the most common defence mechanisms of the impaired physician.
5. Peer-group therapies, formal group psychotherapy and/or mirror image techniques are useful in breaking through denial and overcoming the physicians' barriers to ask for help.
6. A non-interrupted, long follow-up program with extensively monitored and structured aftercare is a key factor to foster physician recovery.
7. Drug testing is a key component of adequate monitoring. Failure to attend screening is a prognostic indicator of imminent relapse.
8. Family involvement. Psycho-education with families and significant others as well as family therapy when needed should be part of the patient-tailored treatment.
9. Appropriate re-entry into practice when the impaired physician remains abstinent should be warranted. Supervision at work may become necessary in some cases.
10. Advocacy and a relapse contingency plan must be implemented when needed.

When back at work, some precautions are recommended. For example, resident anaesthetists who abuse parenteral drugs are usually encouraged to find another specialty. Practising anaesthesiologists allowed to re-enter medical practice must agree to certain conditions such as temporary avoiding access to the operation room, to calls or to handling opioids. For physicians with self-prescribed oral medications, adequate monitoring of prescription is desirable. Although careful long-term monitoring in the workplace is very important, it should never lead to discriminatory attitudes (Table 102.2).

Table 102.2 Treating physicians with addictions successfully

Key ingredients to treat physicians with addictions
SUD as a mental disorder with complex bio-psychosocial determinants
Immediate response, easy access and highly confidential treatment
Ethical guarantees during referral and assessment and along all treatment process
Case management approach
Specialized treatment setting run by expert care professionals
Initial intensive treatment
Uninterrupted long follow-up assessment and support
Long-term drug screening
Follow-up support through peer or psychotherapy groups
Family involvement
Supervised re-entry into practice when not impaired
Advocacy and relapse contingency plan

102.5 Conclusions

Addictions are said to affect 10–14% of physicians during their careers. This phenomenon is a matter of public health interest because of their negative impact on the physician's wellbeing and the potential risk of malpractice behaviours. Physician Health Programmes (PHPs) have been developed in several countries to address this issue. Abstinence rates of physicians in treatment in those programs are significantly higher than in the general population. Initial intensive treatment, long-term follow-up and drug screening, group therapy attendance and a case management approach are common factors that may explain the positive clinical outcomes of this new paradigm for long-term recovery.

Useful Websites

- Physician Health Programs (EEUU)
  https://www.fsphp.org/
  https://www.physicianhealthprogram.com/physician-health-programs/
- Practitioner Health Programme (Reino Unido)
  https://php.nhs.uk/
- Canadian Physician Health Programs (Canada)
  https://www.cma.ca/En/Pages/provincial-physician-health-programs.aspx
- Australian Physician Health Programs (Australia)
  https://www.racp.edu.au/fellows/physician-health-and-wellbeing
  http://www.vdhp.org.au/website/home.html
- PAIMM – Galatea Foundation and Clinic (Catalonia, Spain)
  https://paimm.fgalatea.org/es/index.php
  https://www.fgalatea.org/es/
  http://www.clinica-galatea.com/es/home-2/
- PAIME – Organización Médica Colegial (Spain)
  https://www.fpsomc.es/paime_fott
- Bien pro (Uruguay)
  https://www.colegiomedico.org.uy/bienpro-bienestar-profesional/
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Substance Use Disorders in Conflict-Displaced Populations

103

Nadine Ezard, Hussein Manji, and Anja Busse

Contents

Abstract

Forced displacement is at an unprecedented high. Globally, by the end of 2018, more than 70 million people had been displaced by conflict, the vast majority in low- and middle-income countries. Substance use is increasingly recognised as a major cause of morbidity and mortality in populations displaced by conflict. Alcohol use is the best studied; male gender, older age, multiple traumatic episodes and co-existing depression, along with environmental changes such as increased alcohol availability, have been associated with increased alcohol use disorder in displacement. Transitions in substance use appear to reflect a combination of pre-displacement and host population patterns of use and are influenced by exposure to trauma and adaptation to a new post-conflict environment. Theoretical models suggest that psycho-

N. Ezard (✉)
St Vincent's Hospital Sydney / UNSW, Sydney, Australia
e-mail: nadine.ezard@svha.org.au

H. Manji · A. Busse
United Nations Office on Drugs and Crime, Vienna, Austria
e-mail: hussein.manji@un.org; anja.busse@un.org

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logical distress, social stressors, changes in social norms and networks and growing poverty and inequality may underlie these transitions. Documented harm specific to conflict-displaced populations includes injection-related infection risks, HIV transmission, mental health problems, suicide and intimate partner violence directed towards women. Sudden interruption of substance consumption may precipitate acute withdrawal and necessitates rapid establishment of withdrawal treatment. Precipitation of withdrawal can also be experienced when treatment programmes are interrupted, such as with opioid agonist therapy. Resumption of substance use after prolonged interruption may result in decreased tolerance and increased overdose risk. The treatment literature is mainly limited to feasibility of screening and brief interventions in conflict-affected settings. Evidence-based and evidence-informed interventions should be adapted to local contexts and inclusive of displaced populations; more study of intervention effectiveness in displaced settings is needed.

Keywords

Refugee · Substance use · Conflict · Displacement · Addiction · Intervention

103.1 Introduction

Forced displacement is at an unprecedented high. By the end of 2018, there were around 70.8 million people displaced by conflict [53]. The majority are fleeing conflicts in Africa, Asia, Latin America and the Middle East and remain within those regions. Almost 60% are internally displaced within their own countries and not entitled to international legal protection afforded to refugees [26]. Although many displaced people live in camps or collective settings, most are hosted among non-displaced populations, and more than half live in urban settings. New crises cause acute onset displacement, yet the majority of displaced people have been so for decades. Close to three-quarters of refugees are in so-called protracted situations of more than 5 years' duration [53].

Conflict-displaced populations are at risk of substance use disorders and related harms [24, 35]. Economic, psychosocial and cultural aspects of displaced contexts can promote vulnerability to newer and more hazardous patterns of substance use. Limited and disrupted access to health and social services can contribute to an increased burden of illness due to substance use disorder.

This chapter provides an overview of substance use among populations displaced by conflict and highlights key clinical practice points, with an emphasis on low- and middle-income countries. The majority of conflict-displaced people reside in low- and middle-income countries, where patterns, determinants and interventions will differ from high-income countries. Starting with an outline of the literature on substance use and changing patterns in displacement, it will then explore the literature on substance use disorder and substance-related harm among populations displaced by conflict. The chapter will conclude with a survey of the evidence for clinical interventions to respond to substance use disorder and highlight future directions to treat and care for substance use disorder among displaced populations.

This chapter is concerned with substance use among populations displaced by armed conflict. A widely used definition of armed conflict is that of the Uppsala Conflict Data Program, which defines an armed conflict as "a contested incompatibility that concerns government and/or territory over which the use of armed force between the military forces of two parties, of which at least one is the government of a state, has resulted in at least 25 battle-related deaths each year" ([40], p. 536). This chapter outlines a number of themes that may be common to other "Big Events" that can cause mass displacement such as natural disasters. For example, disruption to treatment services, alcohol and drug supply lines, community and social organisation, and changes in HIV risk behaviours have been associated with floods and hurricanes [36]. Furthermore, natural disasters can occur in situations affected by conflict (such as volcano eruption in eastern Democratic Republic of the Congo in 2002 or

tsunami in Aceh in 2004). Nevertheless, armed conflict brings with it a number of features that are distinct from natural disasters. These features include duration of displacement, often repeated displacement, ongoing internecine violence, experience of war-related trauma, war-associated social disruption and livelihood imperatives. The active involvement of at least one government of a state in the armed conflict introduces additional complexity. Taken together these elements may influence substance use and subsequent disorder in ways that are distinct from natural disasters.

103.2 Substance Use in Displacement

Use of a number of different substances has been reported from conflict-displaced populations. Globally, alcohol use is the most prominent, its use documented from a range of settings, including camps in Uganda and the Thai-Burma border [14] and among urban displaced in Colombia [44]. Khat use is prevalent among the most conflict-affected areas of Somalia among combatants and civilians [21, 39]. Opiate and cannabis use is common among displaced populations in Pakistan and Iran [13]. Documented use of other classes includes amphetamine-type stimulants, cannabis, glue and other inhalants.

Patterns of use also vary widely. These patterns can be characterised as an extension of pre-displacement patterns, a transition to host patterns or a mix of the two [13]. For example, frequent high-volume use of home-brewed alcohol has been documented among some men living in long-term conflict-displaced settings in northern Kenya, Uganda and Thailand [13]. Refugees from Somalia in Ethiopia describe a transition in patterns of khat use from celebratory and weekend use to daily use [21]. These patterns of use are considered an exaggeration and modification of pre-displacement use patterns. On the other hand, new-onset use, mirroring that of the host population, can occur. This is the pattern observed among some Afghan refugees in Iran, who have adopted the use of Iranian *kerack* (a concentrated form of heroin) and *crystal* (a predominantly methamphetamine preparation). Transition to injection use of opiates among Afghan refugees in Iran, Pakistan and Turkmenistan has been well documented; this practice was diffused on return

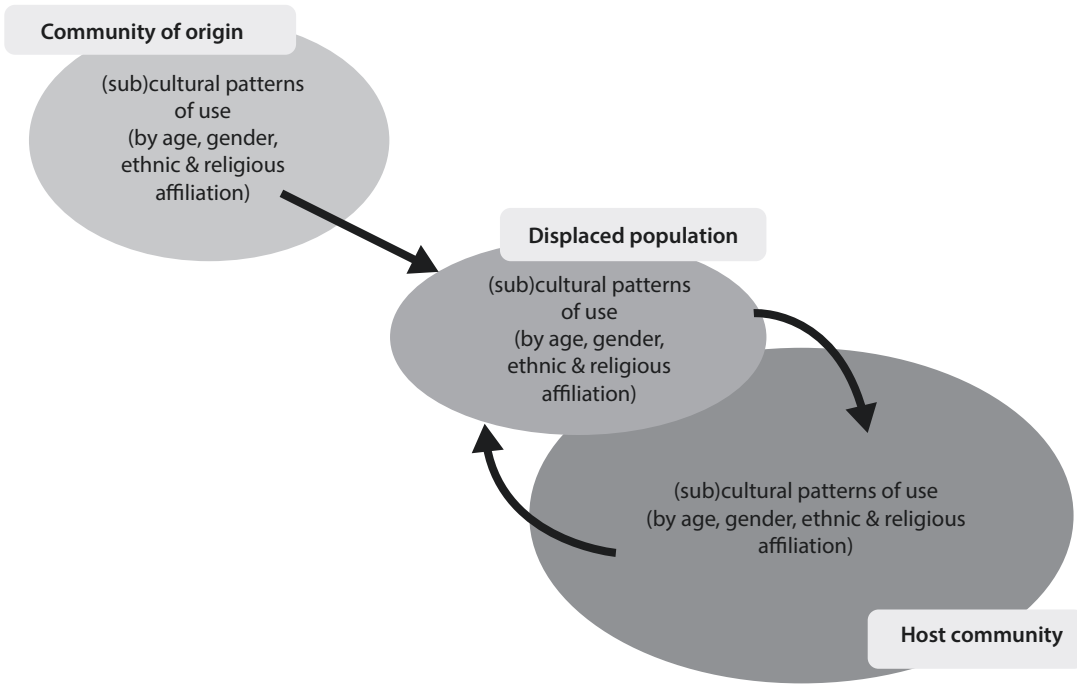

Fig. 103.1 Changing patterns of substance use in displacement [13]

and is now normalised in Afghanistan [51]. Figure 103.1 shows a diagrammatic schema for understanding changing patterns of use in displacement.

Supply factors will also influence observed patterns of substance use. Opiates, for example, are widely available and used among Afghani refugees, although believed to be less than among the host populations [13]. Grains supplied in food rations have been used to manufacture alcohol in long-standing displaced settings, such as refugee camps in Kenya and Thailand. Similarly transition to urban patterns of frequent heavy drinking – such as seen among some displaced populations – is believed to be stimulated by the more ready availability of alcohol [46].

Economic drivers underlie these observed transitions. Alcohol brewing and sale is an important source of income in settings where other livelihood options are constrained – such as in among camp-based internally displaced people in northern Uganda and refugees in north-western Kenya [13]. Arguably this may contribute to the availability – and use – of alcohol.

103.3 Substance Use Disorders in Displacement

Increased substance use in the face of trauma and social stressors may lead to the development of substance use disorder. Yet epidemiological data on the prevalence of substance use disorder are scant and subject to methodological limitations. A systematic review by Horyniak and colleagues showed that the prevalence of hazardous or harmful alcohol use ranged from 17% to 36% in camp settings in low- and middle-income countries [24]. Meaningful data on the prevalence of other drug use disorders are scant. The prevalence of drug use disorder among adult refugees from Liberia, Sierra Leone and Togo in a long-standing refugee camp in north-western Nigeria was around 20% [1]. Among camp-based Syrian refugees in Lebanon, the prevalence of drug use disorders was extremely low (less than 0.1%) [29].

There are a number of factors, which act at both individual and social levels, which may promote or protect from the development of substance use disorder. Individual trauma experiences, for example, have been hypothesised to promote substance use and the development of disorders. Among combatants, conflict exposure has been shown to result in increased substance use. Among conflict-displaced civilian populations, there is some (weak) evidence that male gender, older age, cumulative trauma event exposure and co-existing depression are associated with alcohol use disorder [35].

Gender emerges as an important determinant among alcohol use disorder populations studied in northern Uganda [44]. One study from the Thai-Burma border suggested that women in a long-term refugee camp drank very little alcohol, whereas around a quarter of men drank at risky levels [14]. This observation reflected social norms limiting women's alcohol use and promoting men's alcohol use. Nevertheless, women are not excluded from participating in substance use. Afghan women in Pakistan reported commonly using opiates in one study [13]. Refugee women in Kenya reported using alcohol to facilitate sex work [13].

Substance use disorders often co-exist with mental illness. Although post-traumatic stress disorder has been widely studied among conflict-displaced populations, its relationship with substance use disorder is inconsistent [28, 33]. (This is not to be confused with trauma exposure which has a more robust relationship with substance use disorder.) Mood disorders which are highly prevalent among conflict-displaced populations, such as depression and anxiety, may be associated with substance use as seen in non-displaced populations. Systematic review data suggests that depression is associated with alcohol use disorder in conflict-displaced populations [35].

There are a number of other factors associated with substance use disorder in displacement. Perhaps most importantly, a history of substance use disorder pre-displacement is likely to predispose an individual to substance use disorder following displacement. Individual socio-economic determinants are also important. For example, homelessness, unemployment and a lack of education are prevalent among opiate-dependent

Afghan refugees in Pakistan (and more prevalent than among the non-displaced hosts) [64]. Some population groups may be particularly vulnerable, such as sex and gender minorities (including lesbian, gay, bisexual, transgender and intersex people) [23].

Sudden interruption of substance consumption, including due to external circumstances, may precipitate an acute withdrawal syndrome in people with substance use disorders. In the case of people with alcohol use disorder who are not in treatment, this can be life-threatening. Reduced availability of substances consumed may also trigger transition from one route of administration to another, for example, from non-injecting to injection routes of administration of opioids such as observed among Afghan refugees in exile [50]. Abrupt and non-managed disruption of pharmacological treatments for opioid use disorders can lead to acute withdrawal in a similar way, such as discontinuation of methadone and buprenorphine supplies for the treatment of opioid use disorder during conflict [20]. Resumption of substance use after interruption (especially prolonged interruption) may result in overdose and related consequence due to decreased tolerance.

Various theoretical models can be applied to explain why substance use disorders may be prevalent among populations displaced by conflict. The self-medication hypothesis [31] proposes that psychoactive substances are used to relieve individual suffering, particularly among groups of people who are powerless and poor [49]. This hypothesis is shared by a number of displaced persons and observers. For example, research conducted among refugees from Sudan in Kenya explores the use of alcohol by refugees to manage thoughts of past trauma and the stress of confinement, hopelessness and powerlessness [13]. Similarly research from refugees from Somaliland in Ethiopia describes increased khat use to moderate guilt and emotional trauma [21].

Alternatively, the social stress model suggests that disruption of relationships between people and social networks may induce fear and anxiety and promote substance use [42]. It is likely that these social changes represent more than just psychological stress. Displacement can disrupt tight family and community networks and social hierarchies and replace them with new, expanded and unstable networks, removing pre-existing social controls on substance use.

Community-level changes in the physical environment may also increase the availability and accessibility of substances. This can in turn influence the prevalence of substance use disorder. One study of the "alcogenic" environment among internally displaced populations in Georgia showed an association between alcohol availability, advertising and pricing with alcohol use disorder [43].

Qualitative research conducted with refugees from Burma living in a long-standing refugee camp in Thailand explores how changing social structures influence changes in substance use [10]. Altered norms emerge, along with increased availability of alcohol, accompanied by transition to potentially more harmful patterns of substance use [16]. Social norms are likely to be at least as important as social stressors in mediating substance use [17].

Explanatory models have also been used to explain protective features of displacement. These include tight social networks developed and maintained in the face of conflict, such as theorised by McElrath in Northern Ireland [37]. Religious networks may also be protective, as suggested by Lopes Cardozo in Afghanistan [7]. Strong social norms proscribing excessive alcohol use, particularly for women, may persist in displacement such as seen in Thailand among Burmese refugees. Security, access to services and food rations, as well as hope for resettlement, as described in some camp settings may also protect against substance use disorder [10].

103.4 Other Harms Related to Substance Use in Displacement

Harms from non-displaced populations are well documented [9]. A number of health and social problems associated with substance use have been documented to be of particular concern

among conflict-displaced populations. These include communicable and non-communicable diseases, violence and economic impacts. For example, higher HIV seropositivity and lower tuberculosis treatment success have been documented among people who inject drugs compared with people who do not inject drugs in a conflict-displaced population in India [45]. HIV risk behaviours – unsafe sexual and injecting practice – were more common among refugees than host populations in Pakistan [64]. A similar pattern was observed among displaced refugees returning to Afghanistan [50]. Transition to injection may introduce HIV into communities. Molecular evidence from Afghanistan suggests a nascent epidemic of IDU-associated HIV infection in Hirat, with a similar strain of HIV observed in Iran, where the majority of people who inject opiates began injecting while refugees [48]. Indeed substance use is an important moderator of the relationship between HIV and conflict [30].

Compounding the health risks of alcohol consumption, the livelihood imperative to generate income from alcohol production by displaced persons may promote the addition of harmful chemicals. Qualitative research from Mae La refugee camp in Thailand explored community perceptions that consumption of artisanal alcohol may be dangerous as a result of poisonous additives [10]. Similar observations have been made in long-standing camps in African contexts. Nevertheless, although deaths have been reported from contaminants such as methanol or herbicides in poorly produced alcohol, it is the amount of ethanol and pattern of consumption of alcohol that pose the greatest threat to public health [34].

Other health problems include mental illness, which can be a cause or a consequence of substance use. Among some displaced populations, substance use is an important contributing factor to completed suicides. For example, alcohol has been implicated in the majority of suicides among war displaced in northern Uganda [32].

Substance use has been implicated in other forms of violence. Intimate partner violence against women is common and has been linked with men's substance use in camps in Iraq, Kenya and South Sudan [59]. In one long-standing refugee camp in Ethiopia, women whose male partners drank alcohol had twice the odds of experiencing intimate partner violence within the previous 12 months than those who did not [15]. Similarly in long-standing internally displaced camps in northern Uganda, women whose husbands use alcohol were 50% more likely to report intimate partner violence [3]. This connection has been made for other substances too – for example, violence against women was linked with their male partners seeking money for cannabis in a qualitative study in Pakistan [13].

Substance use has been observed to have important economic impacts at the individual, household and community level. These aspects have not been explored in depth. Household expenditure can be considerable – in refugee camps along the Thai-Burma border, 80% of households spent money on substances [6]. Theft, family conflict, poverty and child neglect among families with opium-dependent household members increased when the population was displaced away from traditional opium-growing areas in Laos [60]. Returning refugees to Somalia from Ethiopia promoted an increasingly thriving khat market, supported by third-country remittances [21].

103.5 Comparison with Non-displaced Populations

Although populations displaced by conflict are vulnerable to a range of factors promoting both substance use and substance use disorders, there are few studies comparing displaced to non-displaced populations. In community settings, no differences were reported in injecting drug use between Afghan refugees and Pakistani hosts [64] or in excessive alcohol consumption between urban displaced and hosts in Colombia [41]. In north-western Nigeria, the prevalence of alcohol use disorder was 13.5% among camp-based refugees ($n = 444$) and 19.0% among the host population (527, $p < 0.05$, not age or sex adjusted), and drug use disorder was 19.6% among refugees and

15.6% among hosts (no significant difference) [1]. Conclusions on whether displaced populations are more, or less, affected by substance use disorders post-displacement than pre-displacement are not possible; nor are comparisons with the host population. Indeed, mass trauma events in non-displaced settings in North America reveal contradictory findings regarding post-traumatic changes in the prevalence of new-onset substance use problems [38, 58], whereas resettled refugees have lower prevalence of substance use disorder when compared with the host population [47]. The lack of longitudinal data precludes further understanding of the relative contributions of *new-onset substance* use disorder following trauma or adaptation to the post-emergency environment and *exacerbation* of pre-existing substance use disorder. Such findings lend weight to the conclusion that any observation will be situation specific, and interventions must be guided by an assessment of the local context.

103.6 Treatment and Care of Substance Use Disorders

Experience of interventions to treat substance use disorders and reduce harm related to substance use among populations displaced by conflict is limited. The literature is limited largely to the assessment of feasibility of screening and brief intervention [18],

103.6.1 Community-Based Outreach

In non-conflict settings, community based outreach includes linkages to basic needs and primary care supports, needle-syringe programs, condom distribution, HIV and hepatitis C counselling and testing, hepatitis B vaccination, substance use education, overdose prevention (such as naloxone), and initial assessment, brief intervention and referral to specialist treatments [57]. Needle-syringe programs, counselling, psychoeducation, and naloxone distribution have been successfully implemented in Afghanistan among returned refugees with opioid use disorder from Pakistan and Iran [52].

103.6.2 Screening

For alcohol use disorders, the 10-item "gold standard" screening test, the Alcohol Use Disorders Identification Test (AUDIT, [5]), has been tested in a range of non-conflict settings and has been used in a number of conflict-affected settings including Thailand [12, 22] and Uganda [44]. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) has been used to detect khat use disorder among Somali refugees in Kenya [63].

In low-resource settings, single-item screening tests may be useful to identify individuals who may benefit from further assessment and treatment. For example, the third question of the AUDIT *"How often do you have six or more drinks [equivalent to 10 g ethanol] on one occasion?" with at least once a month or more often over the last year as a positive* has been used for a rapid survey [13]. The short version of the ASSIST, the ASSIST-Lite [2] has been collapsed into a single question for each drug of concern*: "do you use [substance of interest] once a week or has anyone expressed concern about your use of [substance of interest]", with the answer yes considered positive.* Further assessment of sensitivity and specificity of these tests in displaced settings is required.

103.6.3 Brief Intervention

Stand-alone brief interventions for alcohol use disorder [5] by health workers have been shown to be feasible among Burmese refugees in Thailand [12] although impact on outcomes needs further testing. Among the same population, Haroz, Bolton and colleagues delivered a brief intervention for alcohol use disorder as part of a randomised controlled trial of a trans-diagnostic psychosocial intervention delivered by lay counsellors to a sub-sample of those screening positive for hazardous alcohol use ($n = 33$) and was underpowered to detect change [22]. A randomised controlled trial of a stand-

alone single-session brief intervention (n = 330) resulted in greater decrease in khat use and increase social functioning in the intervention group compared with the control group among Somali refugees in Kenya [63].

103.6.4 Specialist Treatment

Multi-component interventions including withdrawal and continuing care have been feasibly delivered on the Thai-Burma border [8]. The United Nations Office on Drugs and Crime implemented a combined community-based treatment and prevention programme among Afghan refugee women in Pakistan. This programme included home-based withdrawal, community-based continuing care and income generation [55]. Medication-assisted treatment with sublingual buprenorphine for opioid use disorder has been delivered in conflict-affected northeast India with 73% retention at 3 months (n = 713) [4].

103.6.5 Guidance Materials

In the absence of a strong evidence base, efforts have been made to develop consensus-based guidelines drawing on evidence from non-conflict settings. These guidelines usually address the initial response in resource-poor settings and are built on human rights and community development principles. Recognising that no universal response can take into account a broad range of historical, social, cultural and political contexts, these guidance materials attempt to identify core activities that are common to many situations. For example, the Interagency Standing Committee (IASC) Guidelines on Mental Health and Psychosocial Care in Emergency Settings [25] outlines minimum health services response to minimise harms related to alcohol and other substance use [25] (Box 103.1).

A number of rapid assessment guides exist for a range of settings. These guides have an intervention focus, use multiple data sources and emphasise community participation and understanding the social context. For example, the WHO/UNHCR *Rapid Assessment of Alcohol and*

Box 103.1 Minimum Health Services Response to Minimise Harms Related to Alcohol and Other Substance Use in Emergency Settings. (Adapted from [25])

1. Conduct a rapid assessment (guidance can be found at [54])
2. Engage men and women from the community in designing and delivering a multisectoral response
3. Train and support health workers and front-line staff in screening and brief intervention
4. Train and supervise community workers to target at-risk groups for additional supports
5. Provide information, education and materials to prevent harm related to substance use (condoms, needle-syringes, naloxone, thiamine for people who consume alcohol heavily)
6. Train and supervise heath workers to treat withdrawal (especially emergency management of life-threatening alcohol withdrawal; guidance can be found at [62].
7. Establish or re-establish opioid agonist treatment.

Box 103.2 Case Study: Rapid Assessment of Substance Use and Associated Health and Social Services in Refugee Settings, Uganda, 2018 [11]

Uganda has provided asylum to people fleeing conflict for more than five decades. The Government extends an inclusive

approach to refugee hosting to an estimated more than one million refugees from neighbouring countries, with a mix of protracted displacement and new arrivals. With growing recognition of the vulnerability to substance use disorders among conflict-displaced populations, context-specific information is required to design effective interventions.

UNODC commissioned a rapid assessment of substance use and associated health and social services in one rural refugee settlement and among urban refugees in Kampala, consisting of a literature review and rapid qualitative data collection (direct observation, focus groups and key informant interviews) conducted by a team of international and national researchers in April 2018.

Epidemiological data on substance use disorder among refugees were unavailable. This observation highlights the importance of and improved routine treatment data collection, survey data on problematic drug use and inclusion of refugees in data collection activities.

Qualitative data suggested that substance use was considered a growing concern in displacement. As for the Ugandan population, alcohol was the primary drug of concern among refugees. It is ubiquitous, cheap and readily available. Cannabis and khat were considered widely used in urban and rural settings. In the urban setting, in particular, heroin, cocaine and methamphetamine were also used, although less prominently, including injecting routes of administration. Substance use and related problems were gendered, perceived as more prominent among men than women. Urban life offered a greater range of opportunities and challenges, including exposure to an increasing range of substances and problems associated with them.

Some substance use behaviours were believed to have predated displacement, while others were related to integration with host communities. Consistent with the international literature [10], youth substance use patterns in particular were believed to be adapting to host community norms, in the context of weakening parental and community controls in displacement. As one respondent explained, "youth are lost, don't take advice from elders…. divert to other cultures".

Dominant rationalisations for substance use disorders were trauma, stress, idleness, limited educational opportunities, future uncertainty, discrimination and livelihood constraints. As one man explained, "I have no house, no job, sleep outside so I need drugs to cover inside". Another woman expanded, "I lost my husband, have three children, and need to support them so I am a sex worker. I use cocaine, marijuana, and alcohol with clients, sometimes inject". Groups perceived to be most at risk of substance use disorders were considered mobile young men and women without family financial support, particularly women sex workers and men *boda boda* (motorcycle taxi) drivers. Opportunities were seen by some as increasingly constrained with the duration of displacement, particularly in the rural settlement. These understandings are consistent with the international literature [10, 24].

Health concerns related to substance use included alcohol-related liver disease, dependence, accidents and injuries. One participant explained that substance dependence can be both caused by and enhance discrimination and social exclusion. In speaking of his own khat use: "I cannot enter the mosque, [I get] stress relief while chewing but lazy and irritated the next day, get annoyed easily … more discrimination, but the body needs to have it". Another man described an unpleasant experience of being acutely unwell with opioid withdrawal syndrome while incarcerated. One

woman explained: "Me I can't stop drinking even though I burnt my house and business. Why leave drugs when it helps you forget your pain? I have children, where can I get help? Nowhere to go".

There was a dominant perception among refugees that substance use and dependence may promote risky behaviours for HIV transmission while limiting testing and treating behaviours. As one man explained: "When you are intoxicated you don't use a condom". Similarly, this risk discounting was reported in the context of heroin dependence in the urban setting "when you are using [heroin dependently] you don't care [about HIV]" explained another man. These transmission risks are important in the context of a generalised HIV epidemic, economic constraints and cross-border and rural-urban population mobility and mixing.

Socio-economic concerns included alcohol-related domestic and family violence and disruption to child-rearing, household economy, livelihoods and education. Criminal justice consequences were of particular concerns to refugees – especially parents – as they had additional implications for refugee status determination.

Despite the limited scope of the assessment, there was no evidence to suggest that refugees in Uganda experience greater problems due to substance use than host Ugandan populations. Socio-economic and psychosocial vulnerability resulting from the displacement experience, particularly in protracted displacement, warrants additional resource investment. Given the context of free access to the public health-care system, the assessment findings suggest excellent opportunities to strengthen national primary and referral level treatment for substance use disorder as part of a broader prevention and treatment strategy, including for refugees. International response capacity could be strengthened by embedding substance use disorder in minimum standards for emergency responders.

Despite growing awareness of the importance of substance use disorders, consultations for alcohol and drug use disorders in refugee settings are low [27], suggesting the need to strengthen accessible, effective and affordable interventions. More implementation research is required, adapting interventions with evidence from non-conflict settings informed by contextual assessment [19].Yet it remains unclear whether displaced contexts are so vastly different in salient ways as to limit effectiveness. The gold standard of evidence-based interventions may not be realistic in settings of high population mobility, competing health and other priorities and resource constraints and with complex ethical dimensions. At a minimum, interventions should be theory based and show positive outcomes on monitoring or evaluation. More translational research is required.

Other Substance Use in Conflict-Affected and Displaced Populations field guide has been implemented in several situations of protracted displacement in Africa and Asia [13]. An example of how a rapid assessment may be used to guide interventions for treatment and care is given in Box 103.2.

Guidance for non-specialist clinicians in low- and middle-income settings is provided in the joint WHO/UNHCR *mhGAP Humanitarian Intervention Guide (mhGAP-HIG): Clinical Management of Mental, Neurological and Substance Use Conditions in Humanitarian Emergencies* (WHO 2015). These settings are typically challenged by competing priorities; limited time and resources; lack of access to specialists for training, referral, consultation and supervision; and disruption to supply of medications. More comprehensive guidance for non-specialist clinicians is provided in the WHO

mhGAP Intervention Guide [61]. In more stable settings, comprehensive interventions can be developed (see, for example, UNODC's Treatnet [56]); these have not been tested in conflict-affected populations. The addiction medicine specialist may have an important role in training and capacity building in these settings.

103.7 Conclusion

Substance use disorders among populations displaced by conflict are important but undertreated. This chapter has described how conflict can shape transitions in substance use and development of substance use disorders and outlines current approaches to clinical interventions. Although the evidence base is at yet underdeveloped, current approaches suggest adapting evidence-based interventions from other settings. Interventions should be based on an assessment of the biopsychosocial needs of men, women and children and their context and include at a minimum community outreach, screening, brief intervention and treatment of common co-existing disorders. Addiction medicine specialists will have an important role in training, supervision, referral and capacity building. Further context-specific implementation science-based research is required.

Key Points

- More than 70 million people are displaced by conflict at the end of 2018, most of whom are in low- and middle-income countries.
- Substance use is a major cause of morbidity and mortality among conflict-displaced populations.
- Transitions in substance use may be related to exposure to trauma, adaptation to a new post-conflict environment, pre-displacement and host patterns of substance use.
- Intervention design and delivery should be based on context-specific information and involve affected community members, including minority populations.
- Guidance materials for minimum responses exist, outlining community outreach (e.g. condoms, needle-syringes, naloxone, thiamine), primary care (e.g. screening, brief intervention) and specialist treatment (e.g. alcohol withdrawal, opioid agonist therapy).
- Efforts should be made to include displaced persons in health and social services delivered to host populations.

Disclaimer The views expressed here are those of the authors and not of their employers or the United Nations.

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Part X

Children, Adolescents and Young Adults

Robert Milin and Kevin Gray

Children, Adolescents, and Young Adults: An Introduction

104

Kevin M. Gray

Contents

Abstract

Substance use disorders must be understood in a developmental framework. Substance use initiation typically occurs in adolescence or young adulthood, and earlier initiation poses a number of risks for adverse outcomes. Additionally, maternal substance use during pregnancy poses risks for the developmental course of the child. This section is intended to provide a comprehensive and timely update across a number of key areas. Epidemiology and characteristic features of adolescent substance use are reviewed, demonstrating both long-standing associations and dynamic trends. In light of the heterogeneous and often complex nature of adolescent substance use, tailored strategies for screening, assessment, and management are highlighted. Suicide, ranking among the leading causes of death in adolescents, is often associated with substance use. This relationship is examined in detail, with implications for integrated clinical strategies to prevent mortality. Risk and protective factors for adolescent substance use represent a critical area for research, given the clear implications for provision of prevention efforts. The latest advances in identifying psychosocial, genetic, and neurobiological risk factors, and their potential clinical applicability, are discussed. Finally, the array of developmental implications of maternal perinatal substance use for the mother, child, and mother/child dyad are highlighted, with a focus on practical clinical strategies to optimize outcomes. Overall, this section is crafted to synthesize the latest advances in understanding and addressing substance use in the developmental context of childhood and adolescence.

K. M. Gray (✉)
Department of Psychiatry and Behavioral Sciences,
Medical University of South Carolina,
Charleston, SC, USA
e-mail: graykm@musc.edu

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104.1 Section Introduction Text

Given its serious implications for the individual, family, community, and society, substance use has deservedly garnered increasing international attention and concern. Once highly stigmatized and derided as reflections of individual moral failings, substance use disorders are increasingly understood as both neurobiological and psychosocial in nature, and amid this awareness, a number of research advances have provided hope for improved clinical interventions and outcomes. However, while it is generally acknowledged that substance use initiation typically occurs during adolescence or young adulthood, relatively little work has focused on addressing substance use in its developmental context. Fortunately, emerging advances in this area provide a framework for clinicians working with children, adolescents, and families. This section is intended to leverage these advances and shed light on the developmental context of substance use disorders, spanning intrauterine substance exposure to childhood risk and protective factors to adolescent substance use epidemiology, potential consequences, and clinical strategies.

Olagunju, Milin, and Gray begin the section with a chapter focused on the characteristic features of adolescent substance use. Particular attention is paid to epidemiology, risk-vulnerability, developmental course, and comorbidity, all in the context of a biopsychosocial framework. Adolescent substance use is heterogeneous, with some individuals remaining abstinent throughout this developmental phase and others engaging in patterns of use that range from brief experimentation to continued intermittent use to escalating and eventually habitual use. Risks, such as motor vehicle accidents due to intoxication-impaired driving, span all facets of adolescent substance use and escalate with the degree of substance involvement. Adolescent substance use disorders pose both acute and chronic risks with potential lifelong implications.

Gray and Milin follow with a chapter that examines evidence-based strategies for adolescent substance use screening, assessment, and clinical management. Relying solely on previously established adult-targeted strategies may be insufficient and may in some cases be counterproductive. Instead, tailored strategies that acknowledge the developmental context of adolescence as well as the heterogeneity of substance use during this developmental phase are warranted. Guidance is provided on the current array of adolescent-specific evidence-based strategies, with an emphasis on practical implementation in clinical practice. Future directions for advances in care, particularly those that leverage advances in mobile technology and other platforms, are highlighted.

Shlosberg and Shoval provide a critical chapter on the associations between adolescent substance use and suicidal behavior. Tragically, suicide is among the most common causes of death among adolescents in the industrialized world, and its association with substance use necessitates clinical understanding of suicidal behavior as an inherent risk among substance-using youth. The chapter discusses important factors moderating this relationship, such as co-occurring mental disorders and demographic characteristics, to guide strategies for targeted and tailored interventions that address the potential for suicidal behavior among adolescents presenting with substance use.

Spechler, Ivanciu, and Garavan contribute an important chapter focused on risk and protective factors for substance use and addiction, a critical area of research that directly informs targeted prevention efforts. With advances in genetic and neuroimaging tools, as well as the advent of robust longitudinal studies of child and adolescent development, researchers are increasingly able to parse important psychosocial, genetic, and neurobiological factors that influence adolescent substance use and its subsequent life course. These efforts are focused on elucidating potential biomarkers to inform mechanistic models, with implications for precision in delivery of prevention and intervention services.

Velez, Jordan, and Jansson provide a comprehensive chapter on the relationship between prenatal substance exposure and neurodevelopmental outcomes. Importantly, perinatal substance use

has serious implications for all involved: mother, child, mother/child dyad, and family/community. Neurodevelopmental alterations that arise from intrauterine substance exposure may affect developmental, behavioral, cognitive, and adaptive functioning at a variety of life stages, and adverse effects may be compounded by unstable environments that often accompany chronic substance use. The authors parse a complex interplay among these factors, introducing important clinical strategies for screening and interventions for families affected by perinatal substance use.

Together, these chapters frame substance use in a developmental context, with implications spanning the full life course and across generations. The predictors, outcomes, and heterogeneous nature of adolescent substance use are elucidated, and this information is translated into practical strategies, based on an advancing evidence base, for clinical and population health approaches to enhance outcomes. Additionally, strategies for further research leveraging novel technologies and analytic techniques are highlighted, indicating that this important area will see ongoing advances to reduce associated morbidity and mortality.

Adolescent Substance Misuse/Use Disorders: Characteristic Features

105

Andrew T. Olagunju, Robert Milin, and Kevin M. Gray

Contents

Abstract

Substance use disorder (SUD) in adolescence is a serious mental health and social problem with its significant association with morbidity, disability, and mortality. Substance misuse has progressed from the more antisocial, risk-taking, and marginal groups of the population to the mainstream of society and dramatically to younger populations, reinforcing and expanding the boundaries of at-risk populations for SUD. Research in the area of adolescent substance use has expanded significantly over time, and while many studies have contributed to the growth of knowledge in this area, ongoing study remains important. Substance use may be seen through a developmental perspective progressing across adolescence into young adulthood. We have included the most recent studies and research findings on adolescent substance misuse and use disorders in this chapter. The chapter will focus on enhancing knowledge and comprehension of adolescent substance misuse in addressing the following areas: epidemiology, risk-vulnerability, developmental course, and comorbidity. The transitional period of ado-

A. T. Olagunju (✉)
Department of Psychiatry and Behavioral Neurosciences McMaster University & St Joseph Healthcare Hamilton, Hamilton, ON, Canada

Department of Psychiatry, College of Medicine, University of Lagos, Lagos, Nigeria
e-mail: olagunja@mcmaster.ca

R. Milin
Adolescent Day Treatment Unit, Royal Ottawa Mental Health Centre, Ottawa, ON, Canada

Department of Psychiatry University of Ottawa, Ottawa, ON, Canada
e-mail: Robert.Milin@theroyal.ca

K. M. Gray
Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA
e-mail: graykm@musc.edu

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lescence presents itself as an especially critical and vulnerable time for the onset of substance use with its impact on normal development, future SUD, and society as a whole. Adolescence is a period of major risk for the onset of SUD. The complexity of the risk-vulnerability for substance misuse and use disorders among adolescence is derived from the "addictive shared" effects of multi-domain factors including biological, environmental, interpersonal, socio-cultural, and psycho-behavioral factors. The changing pattern of use through adolescence and high rates of comorbid mental disorders among adolescents with SUD further emphasize the need for better understanding of the epidemiological trend, risk, and comorbidity to inform evidence-based interventions.

Keywords

Adolescent · Comorbidity · Epidemiology
Risk-vulnerability · Substance use disorders
Youth

105.1 Introduction

The goal of this overview chapter is to present the current knowledge on the epidemiological burden, risk-vulnerability, and comorbidity for substance misuse and use disorders among adolescents. Research in the area of adolescent substance use has expanded significantly over time. While many studies have contributed to the growth of knowledge in this area, further research and study remain important. As such, we have included the most recent research and findings on adolescent substance misuse and use disorders in this chapter. As preadolescent substance use is uncommon, the focus of this chapter is on the adolescent population, an age group that faces major developmental, psychosocial, and cultural challenges including substance use. Substance use may result in serious mental health and social impairments with a significant association with morbidity, disability, and mortality. The onset of substance use disorder is particularly high during adolescence. Substance use has essentially become part of mainstream adolescent development and, over time, has become increasingly common among younger populations. Adolescence may be appropriately defined as a time of major risk in the development and onset of SUD.

105.2 Youth Substance Misuse

105.2.1 Epidemiology of Youth Substance Misuse

105.2.1.1 Epidemiology of Substance Use

Substance use among adolescents remains a public health issue of global significance in spite of some shifts in the pattern of use resulting from increasing use of cannabis and other substances relative to alcohol, albeit alcohol remains the most frequently used substance. The recent World Health Organization (WHO) estimates of current alcohol drinkers show high rates of use among adolescents aged 15–19 years across many countries including Luxembourg (86.4%), Australia (69.3%), the United States (59.9%), Canada (51.7%), Brazil (26.8%), and South Africa (19.5%). Notwithstanding the differences in the rates of use across the countries, there is consistency regarding male current drinkers being several folds higher than females [1]. Similar to alcohol use, experts have underscored a worrying level of substance use among adolescents globally regardless of the disparity in the rates of use across countries, arguably informed by differences in data quality, legislations, access, and economic and other psycho-socio-cultural variables.

Adolescence is a sensitive transition period characterized by major changes in physiological, psychosocial, maturational, and cultural expressions. It is therefore conceivable that age-related trends in substance use are critical to better understand epidemiological transitions in substance use among adolescents and the underlining factors. In this regard, the Monitoring the Future survey [2] provides a unique perspective as it has been mea-

suring the annual prevalence rates and trends in substance use in adolescents attending school across the United States in a nationally representative sample for more than four decades. Substance use (alcohol and illicit drugs) in general across the grades has shown a steady and measurable decline for some time led by a decline in alcohol use, though with some exceptions. The rate of binge drinking has remained a concern at 14% in 2018 for grade 12 students, and vaping is substantially becoming common.

Marijuana, in contrast, has shown a steady increase in use over the last several years affecting the rate of illicit drug use, whereas illicit drug use other than marijuana has more or less held steady or declined. The rise in marijuana use appears to mirror the lessening attitudes toward the perceived risk of harm associated with its use. The annual prevalence rates for 2018 for any illicit drug use in grades 8, 10, and 12 stand at 13.4%, 29.9%, and 38.8%, respectively, which remain relatively high. Substance use overall shows a marked increase in prevalence from grade 8 to grade 12. By far, the two most common substances used by adolescents are alcohol and marijuana, with current rates for senior high school (grade 12) students of 30.2% and 22.2%, respectively, in 2018. Marijuana has been the most common substance of daily use among adolescents by far for more than a decade, currently standing at 5.8%. Prescription drug misuse among high school seniors remains a concern at approximately 9.9% per annum, although higher proportion of use has been recorded for specific drug classes, particularly for pain relievers with as much as 19% [2]. Included in the prescription drug group class are narcotic analgesics (Vicodin and OxyContin), stimulants (Adderall and Ritalin) used for treatment of attention-deficit/hyperactivity disorder (ADHD), and sedatives/tranquilizers [3].

105.2.1.2 Epidemiology and Burden of Substance Use Disorders (SUD)

Prevalence rates of substance use do not provide one with comparable rates of SUD in general and especially in adolescents [4]. Substance experimentation among adolescents is highly prevalent, though the vast majority of these adolescents do not develop an SUD, even with some of these adolescents engaging in more regular use for a period of time, though the latter does increase the likelihood of developing an SUD [4]. These patterns of substance use, as it would relate to alcohol and marijuana use seen in adolescents, appear for some to be within normative behavior and part of the maturation process of adolescence but for others may lead to significant SUD [4, 5].

Substance use disorders are attributed with significant contributions to the global burden of diseases among adolescents, even though a lesser proportion of adolescent substance users progresses to meet the diagnostic criteria of SUD. Importantly, the 2017 Global Burden of Diseases estimates show an annual incidence of 907 per 100, 000 for SUD worldwide and a substantial contribution from SUD to disability-adjusted life years (DALYs) and years lived with disability (YLD) among adolescents aged 15–19 years [6, 7]. See Box 105.1 for some indices of global burden of SUD in 2017 [7].

Box 105.1 Annual Indices of Global Burden of SUD in Adolescents Aged 15–19 Years

Measures	Values	Rates/100, 000
Incidence (global)	5,595,270	907
Incidence (Africa)	1,051,388	800
Incidence (Asia)	2,601,609	725
Incidence (America)	1,340,886	1713
Incidence (Europe)	703,898	1264
Disability-adjusted life years (global)	2,157,907	350
Years lived with disability (global)	1,838,773	298

The US National Comorbidity Survey-Adolescent Supplement [8] has provided us with one of the most comprehensive general estimates of lifetime prevalence rates of SUD in this population. SUD at 11.4% and mood disorders at 11.2% represent the two most common categories of mental disorders with severe impairment in adolescents. It is important to recognize that

the prevalence rate of drug use disorders at 8.9% exceeds that of alcohol use disorders at 6.4% contrary to adult prevalence rates for SUD. Notably, SUD was found to be somewhat more common in boys at 12.5% than girls at 10.2%. The median age of onset for SUD was 15 years, with a steep increase in incidence thereafter. Notwithstanding the average rates just cited, higher SUD prevalence rates have been reported in a US community sample examining higher-risk groups of adolescents receiving public sector services including those receiving mental health services. The overall past-year prevalence rate for SUD was found to be 24% across all five public sectors [9]. This rate is being more than two times greater than the reported prevalence of SUD in the general adolescent population.

Emerging areas of concern include a defined minority of adolescents who engage in polysubstance use which may carry a greater burden of related problems and the rising misuse of prescription pain relievers by adolescents with evidence of significant use disorder liability [10]. One can also surmise that cannabis is the most telling and common substance of misuse in adolescents with alcohol being the predominant misused substance [5]. Overall, the prevalence of substance use and SUD in adolescents remains a major public health issue with drug use disorders being more prevalent than alcohol use.

105.2.2 Risks and Developmental Course

Levels of substance use have been found to increase from early adolescence to early adulthood (mid-20s) and decline thereafter. Despite the overall relative decline of substance use in adolescents, the prevalence remains high and is the greatest with older adolescents. Girls may exhibit higher levels of substance use than boys during early adolescence, whereas over time boys exhibit greater rates of change, resulting in high levels of substance use from mid-adolescence through young adulthood [11]. Adolescence is a time of major risk for the onset of SUD that shows a developmental trajectory [12]. The peak age of onset for SUD, both alcohol and drug use disorders, is in late adolescence/early adulthood, between the ages of 18 and 20 [3, 4, 12].

Adolescence, as seen from a developmental perspective, represents a time of convergence of significant neurobiological, cognitive, behavioral, emotional, and social changes with continuity of risk from earlier developmental stages, providing a unique period of heightened vulnerability and susceptibility for SUD [4, 13]. Brown et al. [4] reflect on these interrelated developmental factors, the changes that occur during adolescence, and its influence on individual alcohol use trajectories and risk for problem drinking. The authors' narrative highlights the growing evidence that adolescents are particularly vulnerable to the adverse effects of heavy alcohol use both in the biological and social domains and that the consequences of drinking appear to differ between adolescents and adults. They also identify that problem drinking has the potential to redirect the normative course of adolescent development in a manner that increases the risk not only of alcohol use disorders but also of mental health and social problems. This is particularly important as adolescents tend to binge drink consuming high quantity of alcohol per occasion. Notably binge drinking has a dose-response relationship with a range of acute alcohol-related harms, which may persist into adult mental health issues or chronic mental disorders [14]. In a broader sense, prospective studies suggest that early and more frequent substance use through adolescence is associated with, and may predict, later mental disorders in young adulthood [15, 16].

Schepis and coauthors [13] in their review of the neurobiological processes involved in the etiology of adolescent SUD emphasize the significance of maturational changes of the central nervous system that occur in adolescence, the foremost of these being synaptic pruning, myelination, and neurotransmitter system modification. In general, adolescents appear to have greater neurobiological bases for risk-taking behavior with attenuated suppressive and regulatory con-

trols on behavior. The authors surmise that the abnormal neurological markers of those at risk for the development of SUD may best correspond to disinhibition and/or negative affect. Adolescents appear more vulnerable to the effects of many substances that are most likely mediated by increased neuroplasticity, neurotoxic effects on cognition, and effects of stress. It is likely that substance-induced neurobiological changes enhance drug use behaviors. These attributes reinforce the progression to SUD in adolescents [16].

A range of risk factors have been identified in the prediction of SUD in adolescence/young adulthood. These risk factors may be conceptualized into four domains: (a) culture and society (e.g., laws and availability of substances), (b) interpersonal (e.g., peers and family including attitudes), (c) psycho-behavioral (e.g., early/persistent behavioral problems, poor school performance, rebelliousness, early onset of substance use, personality characteristics such as temperament and affect), and (d) biogenetic (e.g., familial or inherited susceptibility and psychophysiological vulnerability to the effects of substances) [16–18].

It appears that social factors, especially peer influence, are the strongest determinants of initiation of substance use, whereas psychological factors, biological vulnerability, and self-reinforcing effects of a substance are more closely associated with the progression to SUD [16].

There is not much evidence to assist in distinguishing the relative importance of risk factors and their specificity in the development of adolescent SUD. It is the number of risk factors, rather than any one factor, that is predictive of SUD. Many of these risk factors are shared with those related to the onset of other mental disorders in adolescents [17]. More recently, several converging lines of evidence favor the addictive rather than sole individual effects of risk factors to better explain the complex etiology of SUD in adolescents. For instance, the combined effects of several risk factors (such as family history of alcoholism, male sex, and impulsivity, among others) via mediating the pattern of alcohol exposure have been implicated to underlie the vulnerability associated with binge drinking and progression to alcohol use disorder [19, 20].

Protective factors are those that reduce the likelihood and level of substance use. Multiple protective factors have been identified including a positive temperament (absence of depression)/self-acceptance, intellectual ability/academic performance, supportive family/home environment, caring relationship with at least one adult, external support system (e.g., religion/church) that encourages prosocial values, and law abidance/avoidance of delinquent peer friendships [16, 18]. Again, it is not one particular protective factor but, rather, the number of protective factors that has the greatest influence on reducing the likelihood of developing SUD in adolescence. As such it has been shown that those adolescents with five or more protective factors are over 20 times less likely to develop cannabis misuse than the general sample. Protective factors also appear to have a moderating influence on the risk for drug use involvement with high protective indices being found to have the strongest effect on those at high risk for greater drug involvement [20, 21]. One factor that has been identified above others as protective of substance use is having early academic success [22].

The early initiation of substance use in adolescence predicts a considerably greater likelihood of developing later SUD with a more rapid progression to SUD, being of particular relevance for cannabis and alcohol. These findings are most robust for initiation of substance use by age 15 or younger; thereafter, other variables may come into play [23]. Adolescent SUD has been found to be a strong homotypic predictor (a disorder predicting itself over time) of young adult SUD [23]. A pattern of regular weekly use of cannabis in adolescence appears to be a threshold marker for the risk of cannabis use disorder in young adulthood [24].

A widely held concept reasons that there are developmental stages in the progression of substance use through adolescence into young adulthood. The sequence of stages defines a temporal relationship progressing from legal to illegal and softer to harder drug use, with each stage acting as a potential "gateway" to the initiation of the

next stage [25]. The use of one substance increases the likelihood of initiation of the second substance. For example, very few individuals who have tried cocaine and heroin have not already tried marijuana, the majority having previously used alcohol or cigarettes. However, the use of one substance does not invariably lead to the use of other substances. Many youth will stop at a specific stage and do not progress further or may return to an earlier stage of substance use [25]. It is relatively common to carry over substance use from one stage to the next. Adolescents who engage in the use of multiple substances increase their risk of developing an SUD into young adulthood [20, 23].

The causal application of the gateway hypothesis is more open to debate and specifically as it relates to cannabis use and other drugs [26]. However, a strong association has been established for cannabis use and the use of other illicit drugs. Further to this, regular or heavy cannabis use has been significantly associated with other illicit drug use and SUD. The relationship is especially strong during adolescence and declines with age. These findings add support to the potential causal role of cannabis use on the development of other illicit drug use disorders, though the actual causal mechanisms, whether direct or indirect, remain unclear [27]. Adolescents may show a greater likelihood of developing drug use disorder (cannabis) than adults across levels of use. Importantly, positive first reaction to cannabis in adolescence predicts later misuse, and regular weekly use of cannabis in adolescence appears to be a threshold marker for later SUD as well as the absence of a definition of what constitutes "recreational" use of cannabis [27].

Substance misuse, expressly cannabis, in adolescence is clearly associated with significant developmental impairment and negative consequences in multiple life domains including behavioral, psychosocial, and academic/vocational [4, 28].

In summary, the onset of SUD in adolescence with its biopsychosocial determinants is a serious mental health problem, with a serious impact on developmental tasks and a strong link to future SUD. Box 105.2 highlights few clinically meaningful points on risk factors and vulnerability to substance use among adolescents.

Box 105.2 Vulnerability and Risk Factors of Substance Misuse/Use Disorders

Risk factors spanning the course of substance misuse/use disorders are multidimensional and can be categorized into biological, environmental, interpersonal, socio-cultural, and psycho-behavioral factors
The "addictive effect model" is plausible to explain risk factors for the development, course, and prognosis of substance misuse/use disorders
Genetically mediated individual differences in response to early use of substance and the dose-response effects of substances are prognostic indices for SUD and acute and chronic harms of substances

105.2.3 Comorbid Disorders

The association of SUD with other mental disorders is well established. In clinical and treatment studies of adolescent SUD, elevated rates of comorbid mental health disorders have been found across clinical settings with prevalence rates ranging from 55% to 80% [29, 30]. Prevalence rates of comorbid disorders are significantly greater than community control samples of non-SUD adolescents. Adolescent SUD patients often present with more than one comorbid disorder. Clinical studies, however, may suffer from Berkson's bias where it is probable that an adolescent with a particular disorder such as SUD who is seeking treatment will have a greater likelihood of a second disorder, thus confounding the ability to generalize results. Only a handful of studies have examined the comorbidity of adolescent SUD in general community samples. Two such studies have found similar elevated rates of comorbidity as seen in clinical studies. Comorbidity rates were two to three times greater in adolescents with SUD than those without SUD for anxiety, mood, or disruptive behavior disorders (DBD). In comparison to adult studies, comorbidity rates of mental disorders are similar for lifetime SUD and may be higher for current

SUD in adolescents. These higher rates of psychiatric comorbidity in adolescents with SUD are most likely reflective of the number of DBD diagnoses made in adolescents that are either not applicable to or not routinely assessed for in adults. There is some evidence to support that comorbidity of mental disorders increases with progression of SUD and severity of substance use [8, 23]. The genders share far greater similarities than any meaningful differences with respect to comorbidity characteristics, especially when gender differences seen in the general population of such disorders as conduct disorder (CD) and major depressive disorder (MDD) are considered [29, 30].

Analysis of retrospective epidemiologic data has found the age of onset of DBD and anxiety disorders to precede the onset of SUD. The most common comorbid mental disorders seen in community studies of adolescent SUD are that of DBD, in particular CD, with these disorders showing a prevalence range of 25–50% and a median of four times greater likelihood of co-occurrence with SUD than without. The next most common comorbid disorder is that of depressive disorders with a prevalence range of 20–30% and a median of over twice the likelihood of co-occurrence [29]. These findings are relatively consistent with clinical studies, though there is a fair degree of variability in prevalence rates between studies of clinical population samples. On the other hand, SUD is a common comorbid disorder in clinical studies of youth that present with serious emotional problems or mental disorders. In this section of comorbidity, we will take a closer look at selected aspects of the relationship of the more prominent comorbid mental disorders and SUD.

105.2.3.1 Conduct Disorder

CD and SUD are strongly associated, with CD typically preceding the onset of SUD. CD imparts an increased risk for the initiation of substance use by age 15 and is a powerful prediction of SUD by age 18 [31]. As well, the severity of CD has been found to predict the severity of SUD. This relationship, however, appears to be reciprocal with each condition heightening the expression of the other. In such a manner, early-onset substance use has been associated with later criminality, and if substance use or drug dealing is reduced, there is a subsequent decrease in criminality [32].

Adolescents who present with CD may rapidly progress from substance use initiation through to substance use disorder, moving from one stage to the next in a matter of months, whereas early conduct problems have not been directly linked to the onset of SUD in adulthood [33]. Also, juvenile offenders with comorbid SUD have shown greater additional psychopathology than those without SUD [33].

105.2.3.2 Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD has been found to be a common comorbid disorder in clinical studies of adolescents with SUD, with large outpatient clinical studies reporting a prevalence range of 17–38%; however, similar findings have not been found in community samples [29, 30].

There has been considerable debate in the extant literature as to whether ADHD is an independent risk factor for the development of SUD in youth or whether the association is indirect and mediated by the presence of co-occurring CD or oppositional defiant disorder (ODD) [34]. What is now clearer on the balance of evidence is that childhood ADHD is a risk factor for the development of SUD in young adulthood, independent of co-occurring ODD/CD with the dimension of hyperactivity/impulsivity being of particular significance. However, the addition of ODD/CD and severity of ADHD further increases the risk for SUD in youth [31, 35]. Adolescents with ADHD have shown an earlier age of onset of SUD, a severalfold increase in the likelihood of SUD compared to matched controls, a more rapid progression of SUD, and a greater severity of SUD [36].

Considerable evidence exists as supported by a recent meta-analysis that treatment of childhood ADHD with stimulant medication does not increase the risk of SUD in adolescence or young adulthood [12, 21]. There has also been a certain

degree of evidence to suggest that stimulant treatment of ADHD may even reduce the risk of developing SUD in adolescence, though the effect appears to wane into young adulthood [16]. However, more recent research findings have not been supportive of a protective stimulant treatment effect for the risk of adolescent or later SUD [37, 38].

The relationship between ADHD and SUD remains complex in adolescence, and with the addition of CD, this grouping of disorders may represent a worse prognosis for the persistence of antisocial behaviors and substance use disorders. In spite of the consensus about the benefits of treating ADHD, clinicians need to be cognizant about the potential risk of misuse and diversion of treatment medications associated with these patients [35].

105.2.3.3 Depressive Disorders

Depressive disorders frequently co-occur with adolescent SUD and are the second most common comorbid disorder. The association of depressive and substance use disorder in adolescents is more frequent than one would expect and has been more widely studied than other comorbidities. It is also noteworthy that adolescents with a history of MDD show an elevated rate of SUD than those without a history of depression. Rao and Chen [39] in a comprehensive review of this topic proposed that common genetic, environmental, and neurobiological factors may possibly mediate the relationship between depressive and substance use disorder in adolescents, constituting a basis for their linkage. The authors recognized the limitations of the neurobiological findings and, by design, the selectivity of various risk mechanisms examined.

In clinical studies of adolescents with SUD, the onset of MDD most often follows the onset of SUD (secondary MDD). Secondary MDD is considerably more common than MDD preceding the onset of SUD (primary MDD) [39]. In the majority of cases, irrespective of whether it is primary or secondary, comorbid MDD in adolescents has not been found to spontaneously remit with abstinence and/or early treatment (excluding pharmacotherapy) by the third week. As would be expected, comorbid MDD has been found to be more prevalent in girls with adolescent SUD than in boys, with the girls showing an earlier age of onset of depression [40].

Adolescents with SUD and comorbid depressive symptoms on admission to residential treatment have shown poor substance use outcome [41]. Adolescents with depression are more likely to develop an SUD, showing an earlier onset and a greater severity of substance misuse. Comorbid SUD in adolescents with depression appears to have a negative impact on the phenomenology and course of illness with greater behavioral and CD problems, longer duration of depressive episodes, and increased psychosocial (school, family, and legal) impairment [39, 41]. A greater severity of substance use in adolescents with treatment-resistant MDD (without comorbid SUD) has been associated with increased severity of depression and comorbid ODD and CD. Adolescents with low substance-related impairment at the end of treatment for depression showed the best response [42]. Alternatively, achieving a positive response in the treatment of adolescents with MDD has been shown to reduce the risk of subsequent drug use disorders but not alcohol use disorders [43].

SUD in adolescents has been linked to an increase in suicidal behaviors including ideation, attempts (frequency, recurrence, and seriousness), and completed suicide. The prevalence rates of suicidal events or behaviors are clinically significant, and suicide is among the leading causes of deaths in youths-adolescents. Existing literature shows that as much as 50% of adolescents who died by suicide meet the criteria for a substance use disorder. However, the risk for suicide is most significant when comorbid with MDD [2, 44]. The comorbidity of substance use and depressive disorders appears to be interactive and has at least an additive if not a synergistic effect on the burden of illness of these disorders, with significant morbidity and mortality.

105.2.3.4 Psychotic/Bipolar and Related Disorders

Few studies report an incidence of comorbid psychotic and bipolar disorders in the adolescent

SUD population. This absence of reporting is quite likely a reflection of the severity of the illnesses, with those adolescents who experience the onset of these disorders being more likely to present to psychiatric services for assessment irrespective of whether they have an SUD or not. In that comorbid psychotic and bipolar disorders are not commonly or reliably reported in the adolescent SUD population, only a few selected comments will be made in this chapter. A strong association has been found for comorbid SUD with first-episode psychosis (FEP) and bipolar disorder (BD) in adolescents/young adults. The presence of comorbid SUD has been associated with exacerbation of psychotic or manic symptoms, a more debilitating course of illness, negative events including suicide, poorer clinical and treatment outcomes, as well as greater functional impairment in patients with FEP and BD (including evidence in first-episode mania and adolescents) than without comorbid SUD. SUD has been linked to an earlier age of onset of schizophrenia and BD with its significant negative clinical implication on prognosis. In the majority of cases, SUD typically precedes the onset of psychosis/schizophrenia, whereas the onset of BD may often precede that of SUD [42, 45]. The most common SUD is that of cannabis in FEP and first-episode/early-onset BD [46, 47]. Importantly, an effective evaluation of adolescents needs to recognize the bidirectional relationship of SUD with BD which can attribute as much as threefold risk increase in either direction and the likelihood of developing SUD in proximal to the onset or early phase of BD. Notably, history of recreational alcohol or marijuana use, immediate family history of SUD, poor treatment of BD, and the presence of oppositional defiant disorder tend to correlate with higher risk particularly.

Cannabis use has been found to be an independent risk factor for the development of psychosis/schizophrenia in young adulthood with a two- to threefold increase in risk. The risk for this outcome increases in a dose-dependent manner and is greater with the onset of use in adolescence and especially in vulnerable individuals. Cannabis-induced psychotic disorder has been found to be a cogent marker in the vulnerability for developing a primary psychotic disorder. In essence, adolescents and young adults should be counseled that cannabis use may increase their likelihood of developing a clinically relevant maniac symptoms or psychotic disorder or schizophrenia-related disorder [46, 47]. Box 105.3 summarizes some important points on comorbidity of SUB with BD/psychosis.

Box 105.3 Comorbidity of SUD in Adolescents

SUD is highly prevalent in comorbidity with BD
SUD share bidirectional relationship with BD with up to threefold increase in risk on either direction
Putative predictors of SUD include mood symptoms, inadequate treatment, recreational alcohol use, and familial factors
Comorbidity of SUD especially involving cannabis may act as a causal or exacerbating factor for BD and worsens overall prognosis
Clinical evaluation of adolescents with BD or psychosis should pay attention to SUD

105.2.3.5 Other Comorbid Disorders

There is considerably less extant literature on the relationship of other comorbid disorders in adolescents with SUD. Elevated rates of anxiety disorders, including social and generalized anxiety disorders and posttraumatic stress disorder (PTSD), have been noted in clinical studies [48]. From these studies, social anxiety disorders (SAD) and PTSD have been identified as the most clinically relevant of the anxiety disorders. SAD precede the onset of SUD and inherently may have an impact in SUD treatment that is oriented toward group therapy. Those with SAD may best be served initially through individual cognitive behavior-oriented SUD treatment. The relevance of PTSD in this population is significant, given the high rate of physical and sexual abuse (57% of girls and 31% of boys) identified in a clinical sample across treatment settings (residential, inpatient, and out-/day patient programs) [49]. In a cross-sectional community

sample of adolescents, a strong association was found for the comorbidity of SUD and PTSD with a significant impact on psychosocial impairment. The findings suggested multiple pathways leading to comorbid SUD and PTSD [50]. No consistent association has been found in adolescents for comorbid SUD and eating disorders (ED). There is some clinical evidence to suggest a possible relationship of SUD with bulimia.

105.2.3.6 Co-occurrence of Physical and Other Psychosocial Complications of SUD

Substance use and related disorders among adolescents are linked with a range of physical health morbidities and public safety, psycho-legal, and socioeconomic issues. In the setting of SUD, adolescents have perpetrated serious violence and criminal offences leading to significant public safety issues. Although not a major focus of this chapter, there is a body of literature evidence showing that SUD contribute or share important risk factors with violence-prone behaviors and chronic physical health morbidities (including chronic kidney diseases, hepatitis, human immunodeficiency syndrome, and cancer, among others) in adolescents contributing negatively to the psychosocial burden and prognosis of SUD [2, 5, 32]. The co-occurrence of physical health morbidities with SUD can impact clinical presentation including proneness to delirium and the choice and the outcome of treatment in this special "high-risk" population of adolescents.

105.3 Conclusion

In sum, substance misuse among adolescents has multiple implications on normal development, future SUD, and the society in general. Adolescence is a period of significant vulnerability and risk for the development of SUD; as such, substance misuse must be viewed from a developmental perspective. High rates of comorbid mental disorders, co-occurrence of physical health morbidities, public safety issues, and psychosocial problems among adolescents with SUD further emphasize the need for clinician to pay attention to substance use when dealing with youth and adolescent populations. The need for ongoing data collection to understand trends and shifts in initiation, pattern and course, and psychosocial sequelae of substance use cannot be overemphasized.

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Adolescent Substance Misuse/Use Disorders: Management

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Kevin M. Gray and Robert Milin

Contents

Abstract

While many aspects of strategies to address substance use in adolescents bear similarities to those employed with adult patients, developmental considerations merit modification to appropriately engage youth in effective care. This chapter seeks to provide an efficient summary of evidence-based approaches to screening, assessment, and treatment, with specific consideration of the heterogeneous nature of adolescent substance use. Suggestions are made for approaches to treatment matching based on clinical presentation and context of substance use. The chapter additionally indicates areas for further research and exploration as the field progresses to advancing clinical outcomes and life trajectories for this particularly vulnerable age group.

Keywords

Adolescent · Youth · Substance · Screening Assessment · Treatment

K. M. Gray (✉)
Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA
e-mail: graykm@musc.edu

R. Milin
Adolescent Day Treatment Unit, Royal Ottawa Mental Health Centre, Ottawa, ON, Canada

106.1 Introduction

Adolescent substance use is heterogeneous, spanning a variety of substances, constituencies, quantities, frequencies, contexts, and motives. General screening is necessary to identify poten-

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tially high-risk cases, and after positive screening, careful assessment is necessary to match the adolescent with the appropriate clinical care modality and setting.

This chapter is structured to provide an efficient overview of strategies for screening, assessment, and treatment for adolescent substance use disorders. Priority is given to approaches with established evidence, though novel approaches are also highlighted.

It should be noted that adolescents are seen across a variety of settings (e.g., school, community, online/remote, general, and/or specialty clinics), and approaches discussed in the chapter can in many cases be delivered by an array of professionals. Most findings highlighted in the chapter are focused on clinic- and school-based strategies. Clinic-based strategies are the most common and therefore the default category. Other settings/contexts will be specifically mentioned if the evidence base includes them.

There is significant potential promise in incorporating mobile health technology to improve accessibility of assessment and treatment and to complement in-person services to improve outcomes [1]. This is a rapidly developing clinical research area worthy of ongoing attention by clinicians interested in adopting novel strategies.

106.2 Screening/Assessment

Substance use initiation typically occurs in adolescence. Effective tools may be used in primary care and other settings to screen for substance use-associated risks that would merit more thorough assessment and potential treatment matching.

Screening tools developed for adult substance use may not be developmentally matched for use with adolescents. For example, the CAGE (Cut down, Annoyed, Guilty, Eye-opener) screener has been shown to be ineffective in screening for problematic adolescent substance use [2]. The recommended approach is instead initiated with a general line of inquiry regarding frequency of use (e.g., never, once or twice, monthly, weekly, almost daily, daily) over the past year [3]. This process can be completed during a patient interview or submitted electronically for review by the clinician. For those adolescents indicating use in the past year, further inquiry can assess level of risk and impairment. The CRAFFT, also available as an online electronic tool, efficiently screens for problem use requiring more formal assessment and intervention [4]. Out of six items, a score of two or higher indicates the need for additional inquiry.

When the initial screening suggests problematic substance use and/or when a patient presents with substance use as the chief concern, careful assessment is necessary, given that substance use in adolescents is heterogeneous. A face-to-face discussion with the adolescent, without parent/guardian present, is critical in developing rapport and gathering details about use and associated behaviors. With agreed-upon terms of confidentiality, follow-up interview with the parent/guardian can yield necessary collateral information.

Based on information gained during patient and family interviews, an International Statistical Classification of Diseases and Related Health Problems tenth Revision second Edition (ICD-10) and/or Diagnostic and Statistical Manual of Mental Disorders fifth Edition (DSM 5) diagnosis (e.g., cannabis use disorder, mild) can be determined [5, 6]. The diagnosis reflects an array of symptoms indicating a pattern of use that persists despite associated impairments and consequences, and the severity is based on the symptom count.

The diagnostic assessment should be complemented by a functional behavior analysis, which frames substance use with associated antecedents and consequences, some of which can be modified to reduce the likelihood of continued substance use [7]. This is a critical component of assessment to identify the potentially highest-yield areas to target with psychosocial and behavioral treatments.

It is not generally recommended to serially conduct urine drug testing as a stand-alone screening approach – it should instead be strategically used as a complement to self-report [8]. Urine testing is imperfect, and in particular, in-office dipstick assays generally only provide a

qualitative (positive vs. negative) window into substance use with inconsistent ranges of detection, while self-report allows for more nuanced assessment of patterns and frequency of use. In addition, soliciting and clarifying self-report allow for rapport building and opportunities to understand patterns and aspects of use that can be approached in treatment. Regardless, urine drug testing does have a role in monitoring, particularly when trust has been eroded between patient and family and when negative results can be used as opportunities for contingent rewards during treatment.

106.3 Treatment

Considerable research efforts have been undertaken to yield efficacious interventions that are developmentally tailored for adolescents with substance use disorders. Across settings, the mainstay of care is psychosocial treatment, and a variety of modalities of both individual- and family-based interventions have been developed and tested. These vary from single-session brief feedback to intensive multimodal strategies; the treatment setting and modality/modalities are often chosen based on the clinical presentation (e.g., acuity, chronicity, risk).

Brief stand-alone treatments offer significant appeal, as they can be delivered in non-specialty medical settings as well as via mobile technology. These are generally employed in cases with relatively low clinical severity, as trials have indicated that when a substance use disorder is present, results are limited with Screening, Brief Intervention, and Referral to Treatment (SBIRT) [9], school-based [10], and motivational interviewing [11] brief treatment models. However, recent findings indicate that youth with *more* rather than *less* alcohol- or cannabis-related problems yielded benefit from a primary care brief motivational intervention [12], and in general, this approach yields reduced alcohol- and cannabis-related negative consequences 1 year later [13]. Delivery of brief interventions via mobile technology has yielded mixed findings; one meta-analysis indicated that text messaging interventions yielded a small positive effect size [14], while a recent feasibility study provided encouraging findings about computer-based delivery of SBIRT [15]. Recent research has demonstrated the feasibility of complementing school clinic-delivered SBIRT with a peer-delivered intervention [16].

Outpatient treatment for adolescent substance use has been the topic of a series of systematic reviews, most recently updated in 2018 [17]. In general, a number of interventions have evidence of efficacy at varying levels. The most established include ecological family-based treatment (including Multisystemic Therapy, Multidimensional Family Therapy, and Functional Family Therapy), individual cognitive-behavioral therapy (CBT), and group-based CBT. Motivational interviewing (MI) and behavioral family-based treatments are deemed probably efficacious. MI and CBT are commonly combined sequentially, both in five-session and twelve-session formats, to address adolescent substance use [18, 19]. The behavioral intervention contingency management (CM), in which desired behaviors are reinforced or rewarded (e.g., voucher for negative urine drug test), has been shown to enhance outcomes when added to psychosocial treatments [20, 21]. Positive findings for CM augmentation of MI have also been demonstrated in school-based treatment delivery [22]. In practice, elements of MI, CBT, family therapy, and CM are often incorporated into eclectic treatment, with variations based on adolescent and family clinical presentation, provider orientation and experience, and logistical considerations.

While Twelve-Step facilitation is commonly employed in adult substance use disorder treatment and relapse prevention, it has been less studied among adolescents. A recent trial tested an integrated Twelve-Step facilitation (iTSF) model, which includes both Twelve-Step facilitation and motivational and cognitive-behavioral strategies, versus established MET/CBT for adolescent substance use disorders [23]. While the treatment groups did not differ in rates of substance abstinence, the iTSF group had better

attendance and reported fewer substance-related consequences.

Medications are often used as adjuncts to psychosocial treatment for substance use disorders in adults, but this area has been less studied among adolescents [24]. The most established medication to date in adolescents is buprenorphine-naloxone for opioid use disorder [25]. Amid mixed findings overall, some positive trials have been conducted with sustained-release bupropion or nicotine patch for tobacco use disorder, *N*-acetylcysteine for cannabis use disorder, and naltrexone for alcohol use disorder (for review, [24]). Given the limited literature overall to date on pharmacotherapies, it is generally suggested that they be reserved for treatment-refractory or high-severity cases and always as an adjunct to evidence-based psychosocial treatment.

Recent clinical research efforts have focused on devising strategies to more precisely match patients to treatment approaches that are most likely to be successful based on their presentation and characteristics [26]. To date, treatment matching has generally been managed clinically based on patient/family preference, clinician availability, and determination of risk/severity. However, it would be reasonable to suggest that additional characteristics may potentially predict the most well-suited treatment case-by-case. Another avenue of investigation is the development and testing of approach avoidance training (AAT), a computerized cognitive bias modification paradigm designed to train adolescents to implicitly override their habitual bias toward substance-related cues [27]. AAT, which targets neural pathways distinct from those affected by established interventions, has demonstrated long-term relapse prevention effects in adults with alcohol use disorder [28, 29]. It may be particularly well suited to adolescents, for whom substance-approach tendencies are strongly relevant to substance use [30]. If successfully translated to adolescent substance users, AAT could be incorporated as a complement to established treatments to enhance outcomes.

106.4 Addressing Comorbidities

A recent study indicated that 64% of adolescents ages 13–17 with a substance use disorder also meet criteria for a co-occurring psychiatric disorder, demonstrating that comorbidity may be the rule rather than the exception [31]. Among the most common comorbidities are mood disorder, conduct disorder, and attention-deficit/hyperactivity disorder (ADHD). With substance use and psychiatric services often delivered by separate providers and/or in separate facilities, systems have frequently attempted to address comorbidities in series rather than in parallel. However, given increased understanding of the complex interplay between psychiatric and substance use difficulties, as well as the overlap in psychotherapeutic approaches relevant to these conditions (e.g., cognitive-behavioral therapy across mood, anxiety, and substance use disorders), recent efforts have focused on developing and implementing integrated treatments [32, 33].

Clinical trials of pharmacotherapies for psychiatric conditions traditionally exclude individuals with co-occurring substance use disorders, limiting interpretability of findings for youth with comorbidities. Recent work has advanced the field, indicating that pharmacotherapies for ADHD [34–37] and major depressive disorder [38–41] may be safely administered to adolescents with co-occurring substance use disorders. While efficacy findings are mixed across these trials, there are positive findings for extended-release methylphenidate formulations for ADHD [35, 37] and for fluoxetine for MDD [38] in adolescents with co-occurring substance use disorders.

106.5 Conclusions

Given the high prevalence and known associated adverse consequences of adolescent substance use, clinicians are encouraged to embed routine screening into longitudinal and acute care while being equipped to provide detailed assessment and treatment (and/or treatment referral) in cases deemed to be high risk. A

number of psychosocial treatments, with individual and family components, have demonstrated efficacy in addressing substance use disorders in adolescents, and contingency management can be used as a treatment complement to enhance abstinence outcomes. Pharmacotherapy may play a role as an additional treatment complement, though beyond a handful of medications with positive trials, the evidence base is limited to date. Ongoing work is aimed at broadening the content, scope, and reach of assessment and treatment services for adolescents with substance use disorders, and delivery of services via electronic interfaces and mobile technology is among the most promising avenues of this research.

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Suicide and Substance Abuse in Adolescents

107

Dan Shlosberg and Gal Shoval

Contents

Abstract

Suicide is the second or third leading cause of death among adolescents in the industrialized world. Adolescent suicidal behaviors pose a major global public health concern since they are highly prevalent and associated with heavy mortality and morbidity. A plethora of accumulated data substantiate the connection between suicide and substance abuse in ado-

D. Shlosberg
Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
e-mail: Dan.shlosberg@tdhb.org.nz

G. Shoval (✉)
Geha Mental Health Center, Petah Tiqva, Israel

Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
e-mail: shovgal@tau.ac.il

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lescents and pose substance use disorders as a major risk factor for emergent suicidal behaviors. This chapter reviews recent patterns and trends of substance abuse, focusing mainly on alcohol and cannabis, which are most prevalent among adolescents, and presents the existing evidence linking adolescent suicidal behavior and substance abuse. We address the role of salient moderating factors such as comorbid psychiatric pathologies, age, and gender differences on this relationship and highlight vulnerable subpopulations such as sexual minorities that are predisposed to be affected by this connection. Perspectives on recent as well as future basic science research studying the connection between adolescent suicide and substance use as well as substance use trends are discussed. Treatment strategies for substance use disorders as well as for suicidal behaviors are presented, arguing in favor of an integrated approach.

107.1 Introduction

Suicidality is a broad term encompassing a wide range of self-injurious ideation or self-inflicted harmful behaviors executed with at least partial intent to die. These behaviors are a major global public health concern since they are highly prevalent and associated with heavy mortality and morbidity in the immediate as well as in long term. This issue is intensified when child and adolescent suicidality is concerned, and therefore, a pressing demand for efficient prevention plans and novel treatment strategies yet remains.

Suicide is a complex behavior and various pathways lead to suicidality. Numerous risk factors associated with suicidality have been described [12] and are frequently divided into several categorical groups. This reductionism in classification of suicidality risk factors can be misleading and, in many cases, not clinically pragmatic. In real-life situations, these risk factors are much too often interwoven, are mutually effective in a nonadditive and unpredictable manner, and ultimately pose a methodological conundrum in the clinical assessment of adolescent suicidality. Nevertheless, in epidemiological studies concerning suicidality, several risk factors including substance use disorders (SUD) stand out more prominently than others.

Much epidemiological data has been gathered in the past decades elucidating the diversity and extent of adolescent substance use. The information accumulated has been extensively used recently by various health services as well as clinicians to yield a plethora of studies substantiating the impact of SUD on adolescent suicidality. In recent years, one can witness a gradual transformation of the harnessed data from the descriptive to the operative form; suicide risk assessments and odds ratios are being translated into operational plans and large-scale screening and intervention efforts in schools and health facilities. The applicability and efficacy of some of these measures are yet to be ascertained and validated by evidence-based studies.

Since the scope of this chapter cannot encompass the specific effect of all illicit as well as legal substances on suicidality, we will focus mainly on alcohol and cannabis as these are the substances which are most widely used and studied worldwide [60, 89].

107.2 Adolescent Suicidality

There are multiple levels of severity and injury burden within the construct of "suicidality." The scope of suicidal behavior constrained in this term ranges from *suicidal ideation* with or without a specific plan through *suicide attempt* which is a nonfatal, self-inflicted destructive act with explicit or inferred intent to die and finally the fatal act of a completed suicide.

Suicide is the second or third leading cause of death among adolescents in the United States and Europe [22, 62], and suicidal behavior represents one of the greatest public health issues for this population**.** Lifetime estimates of suicide attempts among adolescents range from 1.3 to 3.8% in males and 1.5 to 10.1% in females [10]. These numbers should most probably be considered to underestimate the true extent of this mal-

ady; a large portion of suicidal attempts remains unnoticed and unreported since most data rely on self-report or emergency department (ED) admissions. Indeed, ED visits in the United States due to self-inflicted injury are highest among the 15- to 19-year-old age group. In the United States, youth risk behavior surveys (YRBS) assessing health risk behaviors among youth and young adults have been conducted among representative samples of high school students biennially since 1991. The latest survey reports disconcerting data describing teenage suicidal behavior. During the 12 months prior to the last survey, 17.2% of students had seriously considered attempting suicide, 13.6% had formulated a suicide attempt plan, and 7.4% had reportedly attempted suicide one or more times [41]. Adolescent suicidality has been identified as a nationwide health improvement priority in the United States, and consequently, the "healthy people 2020 (HP2020)" initiative has proposed the objective of reducing adolescent suicide attempt rate by 10% (http://www.healthypeople.gov) by the end of this decade. Given a 27% decrease in adolescent suicide rate in the previous decade, this goal seems far from unattainable.

In light of the above figures and those of previous years, numerous suicidality detection and prevention strategies have been proposed and implemented to various degrees of success worldwide. Most adolescents presenting with suicidal behavior do not end up committing suicide; nevertheless, suicidal ideation in adolescence has been shown to be a harbinger of compromised adult functioning and future Axis I diagnoses [69], stressing the need for early suicidality identification regardless the obvious dire consequences of suicide itself. In their review of the available suicidality screening tools applied in educational and health-related community facilities, Horowitz et al. [36] suggest that the implementation of targeted suicide screening in schools and universal suicide screening in primary care clinics and ED may be the most effective way to recognize and prevent suicidal behavior [36]. The leading screening tool used today in school settings is the Columbia-Suicide Severity Rating Scales (C-SSRS). This free, simple, and brief questionnaire addresses acute suicidal risks across the full range of suicidal behaviors, is readily available in more than 100 different languages, and can be tailored to specific populations and settings. Those who screen positive in the initial screen are referred for further clinical evaluation of suicidality. Another screening tool that is not specific to suicide or substance abuse is the Strengths and Difficulties Questionnaire (SDQ) which has the advantage that it can detect adolescent emotional and behavioral difficulties that are not necessarily strictly DSM-based and therefore may be more sensitive to detect distress and psychopathology [78].

Recent encouraging data suggest a decrease in global adolescent suicide rate. A significant linear decrease in the prevalence of US adolescents having made a suicide plan has been noted in the past 20 years (18.6% to 13.6%), although no significant change occurred in the prevalence of actual attempts [41]. During the past two decades, the crude death rate from suicide and intentional self-harm among adolescents aged 15–19 residing in the OECD countries has also steadily declined by more than 10% [62].

107.3 Adolescent Substance Use

107.3.1 Alcohol Use

Adolescent alcohol use is related to the three leading death causes in the young [58], namely, accidents, suicide, and homicide, and is therefore related to most premature death cases in the young. The use of alcohol increases the likelihood of suicide death in both direct (acute intoxication) as well as indirect (loss of inhibition, increased impulsivity) means although most of the cases are usually related to the latter causes.

Alcohol has been shown to be associated with elevated rates and increased risk for suicidal behavior [17] even after the effects of depression, impulsivity, peer delinquency, and parental monitoring are controlled for [82].

Patterns of alcohol use can vary widely in terms of time (e.g., how many days in a month) and volume (e.g., how many drinks each time), and so it may be more appropriate to examine the association with suicidality in instances in which alcohol is consumed in excess. Consuming five standard alcoholic drinks or more in the same drinking session ("binge drinking" or "heavy episodic drinking") would cause most adolescents to reach at least some degree of intoxication. Although no global or cultural consensus exists to define an alcohol volume of a standard drink or how many drinks constitute a "binge," binge drinking can generally be viewed as a rapid consumption of alcoholic beverages with the intention of becoming intoxicated. On average, nearly half of the students in the United States (45%) and a third in Europe (35%) reported that they had been intoxicated in this sense at least once during their lifetime [21].

Binge drinking is most prevalent among teenage alcohol consumers and is associated with many poor health outcomes [80] and increased risk for suicidal thoughts and attempts, even when compared to current alcohol drinkers who do not binge [55]. This connection is strongly correlated to frequency of binging; those who binge on more than ten monthly occasions attempt suicide more than those who binge six to nine times (30% vs. 16%) and almost three times as much as those who binge once a month (11.9%) [55].

Binge drinkers also tend to explore the use of other psychoactive substances. Not only does heavy episodic drinking show a significant correlation to lifetime use of cannabis, it also carries an odds ratio (OR) of 5 for concurrent marijuana use as compared to alcohol drinkers who do not binge and much more than when compared to nondrinkers (OR = 60) [55]. Adolescents reporting concurrent alcohol and marijuana use presenting to the ED following alcohol intoxication display heavier drinking patterns as compared to those who report alcohol use alone, including increased binge drinking instances as well as elevated alcohol consumption on each drinking occasion [14].

Archie et al. [1] suggested that binge drinking raises the risk for suicidality in youngsters only when depression is present [1]. Using a survey delivered to over 17,000 adolescents aged 15–24 years, they show that binge drinkers and non-binge drinkers shared the same risk for suicidality when no depression was present even when using more stringent definitions of binge drinking (at least once weekly). When the effect of depression was tested, they found that depressed binge drinkers had an increased risk for suicidality as compared to non-binge drinkers who were not depressed (OR = 6.3) [1].

107.3.2 Trends in Alcohol Use

Adolescent alcohol use in the United States is steadily declining. In 2017, 60.4% of high school students reported they had ever drunk alcohol, a substantial decrease from 81.6% in 1991. A drop of almost 40% in the corresponding years has been demonstrated in youth reporting current alcohol use, from 50.8% to 29.8%. Data from the large-scale Monitoring the Future (MTF) study corroborate these findings. The latest report presents adolescent alcohol use has reached an historic low, from 93% lifetime prevalence of use in senior year high school students 30 years ago down to 58.5% today. The situation in European countries is quite different, though, as adolescent alcohol use has remained relatively unchanged in the past 15 years. The European School Survey Project on Alcohol and Other Drugs (ESPAD), which is based on data gathered from 100,000 European students from 35 countries, reports that for youth between the ages of 15–16 years, lifetime use of alcoholic beverages has dropped only slightly from 89% in 1995 to 80% 20 years later [21]. As can be expected, substantial prevalence differences were found between countries in this study. Although these figures probably reflect different social and cultural norms in drinking patterns, the different rates of decline in adolescent alcohol consumption might also reflect the utility of various alcohol

use prevention plans locally employed. Many educational and preventive policies aimed to reduce the harmful use of alcohol have been formulated and utilized worldwide in the past three decades [90], and the use of alcohol in adolescents as aforementioned is since on the decline. Furthermore, temporal trend reports of American senior binge drinking prevalence present a substantial decrease of more than 50% between 1998 and 2018 (31.5%–13.8%), perhaps reflecting the success of educational preventive strategies focusing on the behavioral aspect of alcohol use (highlighting negative aspects of "drunkenness" instead of "drinking") and not of restrictive strategies (e.g., increased legal drinking age). It is also debatable whether restrictive measures for alcohol use are applicable, alcohol is perceived by youth to be easily available, and 87% of senior year adolescents find it fairly or very easy to get hold of an alcoholic beverage. Strict policies may also lead to rebellious behavior and an increased prevalence of binge drinking. A study exploring the drinking pattern and drunkenness among mid-adolescents in 40 European and North American countries found a trend whereby higher prices and stronger alcohol controls were associated with a lower proportion of weekly drinking but a higher proportion of drunkenness [26].

Despite the abovementioned positive trends, alcohol remains the substance most widely used today by teenagers. Given the close association to suicidality, this should warrant continuing efforts to decrease adolescent alcohol use and not to rejoice over the positive statistical data reporting its decrease.

107.3.3 Cannabis Use

Cannabis by far represents the most prevalent illicit substance used by adolescents use today. Data regarding the prevalence of other illicit drugs can be found elsewhere [21, 41, 60] and will not be elaborated here in detail. Briefly, about 4% of adolescents aged 12–17 years in the United States report last year use of illicit drugs excluding marijuana. Of the several illicit substance groups whose prevalence has been annually monitored, the misuse of psychotherapeutics (including amphetamines, sedatives, tranquilizers, and pain relievers) remains second to marijuana, whereas hallucinogens, inhalants, and other drugs are far less prevalent [60].

The US nationwide MTF study utilizes national annual surveyed samples of more than 40,000 students gathered since 1975. In 2017, the percentages of students indicating use of cannabis in the prior 12 months (representing current users) were 10.1%, 25.5%, and 37.1% in grades 8, 10, and 12, respectively. Data concerning drug use in European countries has also been gathered in the past two decades and summarized in the ESPAD report which reveals a 7% prevalence of use in the past month for the corresponding tenth grade age group [21]. The National Survey on Drug Use and Health (NSDUH) obtains information from approximately 70,000 US residents aged 12 years and older regarding several categories of illicit drug use. In the latest report relating to 2017, about half (46%) of youths aged 12 to 17 reported that it would be "fairly easy" or "very easy" for them to obtain marijuana if they wanted to [60].

It is worth mentioning that temporal changes in patterns of adolescent substance abuse clearly exist, stressing the importance of ongoing efforts to monitor drug use trends. For instance, the use of nonmedical analgesic opioids has become second in prevalence to marijuana, surpassing the use of inhalants and hallucinogens [94]. This trend appears to have changed in recent years, and a steady decrease has been observable since 2013 [54], which was recently corroborated by prescription data as well [24]. Another example can be found in the prevalence of synthetic cannabinoids use which has become a source of major concern at the beginning of this decade and was first monitored in the United States in the 2011 MTF survey. A comprehensive national US ban enacted in July 2012 and other enforcement efforts that were initiated might have contributed to the dramatic decrease evident in the use of this substance class from 11.4% in 2011 to just 3.7% in 2017 among 12th graders. Recent years have

witnessed a global trend of cannabis decriminalization and legalization to various extents, and this has led to initial concerns and speculations that a resultant increase in prevalence of adolescent cannabis use will follow [13, 96]. This is yet to be confirmed by ongoing monitoring and evaluation schemes [74] in light of the fact that trends of adolescent rates of cannabis use disapproval have recently reached the lowest levels in the past three decades.

107.4 Substance-Related Disorders as a Risk Factor for Suicidality

The link between substance use and suicide among adolescents is well established by evidence from clinical and epidemiological studies [93]. Postmortem examination studies lend further proof to this relationship; one of these studies reported that in pediatric decedents tested positive for illicit drugs, 93% died from violent causes, and of these 15% died by suicide [58]. Most recently, Gobbi et al. [27] presented an exhaustive meta-analysis of data pertaining to the association of adolescent cannabis use and subsequent adult emergent suicidality and psychiatric disorders. They report an OR of 1.5 to develop suicidal ideation and OR of 3.5 to attempt suicide among cannabis users as compared to nonusers [27]. Importantly, the strength of this association appears correlated to the severity level of suicidal behavior. Adolescent suicide attempters, for instance, are more likely to be substance dependent than suicidal ideators, suggesting that substance use may in fact facilitate the escalation from ideation to behavior. In a large study among 15,885 French adolescents [37], the risk for suicide attempt among cannabis users as compared to nonusers was reported to be 30% higher for "heavy users" than "occasional users" and almost 50% higher for "occasional users" as compared to "former users," clearly strengthening the notion of a positive correlation between cannabis use patterns and suicide attempts. In light of the general opinion that the adverse psychosocial effects of cannabis stem from frequent use alone, the finding that the risk for suicidality is also related to occasional and even sporadic use is noteworthy.

Regarding drug use habits associated with "more of others" as contrary to "more of the same" pattern, polydrug consumption is highly correlated to increased suicide risk. In a large European sample of over 45,000 adolescents from 16 countries, the percentage of respondents who reported at least one suicide attempt increased sharply with the number of substances used. Logistic regression analysis revealed that the risk for suicide attempt was OR = 4.5 for users of two substances and continued to increase thereafter with the use of additional substances as compared to nonusers [45]. Quite contrarily to popular belief, regular cannabis use does not substitute or protect from the use of other illicit drugs or alcohol; rather, it is strongly associated with their later use ("gateway drug") in an age- and frequency-of-use-dependent manners [84].

107.5 The Moderating Role of Psychiatric Morbidity

SUD and suicidality are both highly associated with psychiatric comorbidity [27]. Unfortunately, the moderating effect of psychiatric comorbidity on the relationship between them is highly complex and difficult to clarify. For instance, adolescent SUD patients display high psychiatric comorbidity most commonly associated with externalizing disorders [2], whereas suicidal adolescents also tend to display psychiatric comorbidity though mainly with internalizing disorders [43]. The presence of a psychotic disorder also displays a moderating effect on this relationship; Shoval et al. [76] presented a significant and strong association between suicide attempts and the use of illicit substances among adolescent suicidal inpatients diagnosed with schizophrenia or schizoaffective disorder as compared to nonsuicidal patients [76]. The existence of personality disorders or traits may further intricate the assessment of this connection.

Not only the nature of the psychiatric disorder present but also the number of concurrent psychi-

atric disorders may increase the risk for suicidality. In a prospective study investigating suicidal behavior among 180 discharged adolescent psychiatric inpatients followed for up to 13 years, most of those who were suicidal during the follow-up period had concurrent depressive disorders, and many had also displayed disruptive behavioral disorders either alone or concurrently [31]. In the same line of evidence, Vander Stoep et al. [87] have shown that co-occurring depression and conduct disorder symptoms increase the risk for subsequent suicidality as compared to a single diagnosis of either of these [87].

107.5.1 Mood Disorders as a Model

An estimated 3.2 million American youths suffered from a major depressive episode during 2017 [60], and depression is the strongest known risk factor for adolescent suicide [9, 93]. Some data suggest that even subthreshold depression, which is highly prevalent and can be found in up to 30% of adolescents, is associated with increased suicidality risk [4].

Adolescent depression displays high comorbidity with alcohol and substance abuse [2]. Adolescents suffering from major depressive episodes (MDE) were found to be more than twice as likely than those without past year MDE to have used illicit drugs in the past year (29% vs. 14.3%) or to be heavy alcohol users in the past month (1.2% vs. 0.6%). This disparity increases when comparing rates of substance dependence or abuse [60].

The combination of adolescent depression and substance abuse elevates the risk for suicidality. This may be true even for mild to moderate substance abuse, subthreshold to diagnostic criteria of SUD [37].

The causative relationship between substance abuse, depression, and suicidality remains unknown. Studies that address this relationship face many methodological challenges. A fundamental impediment is that both depression and substance abuse are independently highly associated with adolescent suicidality, and their co-occurrence is the rule rather than the exception in adolescents. Large-scale prospective studies addressing this causative connection may aid the construction of suicide screening and prevention strategies. For example, Goldstein et al. [28] used post hoc analyses on data from the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study to demonstrate that the level of substance-related impairments is reversely correlated to the response to antidepressive treatment [28], suggesting that treating substance abuse may by itself decrease depression and suicidality.

Data concerning suicidality in other mood disorders associated with substance use comorbidity are scarce in the adolescent population and usually hampered by a retrospective design. Most clinicians thus rely on adult studies and execute data extrapolation when considering risks and prevention plans. Nevertheless, the link between bipolar disorder (BD) and suicidality has been demonstrated in many retrospective studies [16, 18]. A study designed to assess predictors of prospectively observed suicide attempts among youth with bipolar disorder revealed a strong association of this disorder with high rates of suicide attempts [30]. This study utilized subjects enrolled in the Course and Outcome of Bipolar Youth (COBY) study and is the first prospective-designed study to test the BD-suicidality connection in adolescents. During the five-year follow-up period of 413 adolescents diagnosed with BD, 76 (18%) attempted suicide once or more. Of these, 31 attempted suicide more than once for a total of 163 suicide attempts during the follow-up period. Considering the early mean age of the study recruits (12.6 years), these figures may underscore the actual suicide attempt rate since most of these adolescents had yet to pass through the highest risk period for new onset of suicidal behavior which is in later adolescent years (see below).

The strength of the BD-suicidality connection may be correlated to the severity of suicidal behaviors. Brent et al. [8] described an extremely high prevalence of BD in adolescent suicide completers. The diagnosis of BD (either type I or II) in suicide completers (22%) was

found to be at least four times more prevalent than in suicidal inpatients admitted for attempted suicide or for having a suicidal ideation [8]. Surprisingly, suicide completers in this study did not display a higher frequency of the co-occurrence of mood disorder and substance abuse than non-completers. Though in a consequent larger sample study [9], they show that substance abuse is a more significant risk factor for suicide completion when comorbid with a mood disorder than when alone (OR = 17.0 vs. 3.3). Other studies describe the negative effect of substance use on suicidality in BD; Goldstein et al. [30] reveal a double risk for SUD and lifetime excessive drinking in BD-diagnosed adolescents who concomitantly performed a suicidal attempt as compared to those who did not. During the 8 weeks prior to the attempt, the risk for SUD was tripled [30]. The same group reported that in a large sample of bipolar adolescents in which lifetime prevalence of SUD was 16%, subjects with SUD demonstrated a significantly greater lifetime prevalence of suicide attempts as compared to those without SUD [29]. Interestingly, the effect of substance use and in particularly that of cannabinoids on suicidality in BD patients may be exacerbated by the emergence of increased psychotic features [93].

The psychological constructs underlying the relationship between substance use suicidality and mood disorders in adolescents are understudied when compared to the adult population and therefore less utilized in clinical practice. One model, for example, describes the constructs of adolescent behavioral disinhibition, which is frequently associated with self-injurious behavior, and ascribes personality traits such as impulsivity and sensation seeking as key structural elements [6]. In that line, a study utilizing a sample of adolescent self-reported questionnaires found significant associations between sensation-seeking behavior and depressive symptoms or the occurrence of substance use problems. Students with high sensation-seeking behaviors were three times more likely to have symptoms of depression or substance abuse than students with low sensation-seeking behavior [61]. Sensation seeking has also been shown to significantly increase risk for suicidality even when depression or substance abuse was controlled for [47, 61].

107.6 Gender Differences in Suicidality

The risk for suicidal behavior does not exhibit gender equality. This likely stems from multiple psychological, biological, and social between-gender distinctions that bear a dissimilar effect on mental states and behaviors associated with suicidal behavior. Trying to evaluate the moderating effect of gender on the SUD-suicidality connection is fraught with methodological challenges since gender is differentially associated with suicidality, depression, and substance use. For instance, female adolescents are more likely to be depressed; among American youth aged 12–17, females were more likely than males to have past year MDE (20% vs. 6.8%) or MDE with severe impairment (14.2% vs. 4.7%) [60]. Males, on the other hand, are more likely to use drugs and alcohol. On average, boys report illicit substance use to a larger extent than girls do (21% vs. 15% in Europe and 14.5% vs. 13.3% in the United States) [21, 41]. Adolescent males initiate alcohol consumption earlier in life, drink more alcohol, and report more frequent heavy episodic drinking [21, 41, 88]; additionally, females are more sensitive to alcohol-induced effects due to biological factors.

Regarding suicidality, adolescent females are more likely to have suicidal ideation, to make suicidal plans, and to attempt suicide [41, 49, 88], whereas males are more likely to complete suicide [73].

107.6.1 Sexual Minority Youth (SMY)

Adolescents belonging to sexual minority groups include mainly, but not exclusively, youths who identify themselves as lesbian, gay, bisexual, or transgender (LGBT). Among high school youth in the United States, more than 10% identify

themselves as nonheterosexual [42]. This population is gradually and increasingly being exposed to the public eye and to scientific studies that suggest that they suffer from increased rates of environmental stress which may lead to social isolation and interfere with normal adolescent development.

Assessing data regarding this subpopulation in the adolescent age group is not a simple task. Most SMY do not openly present themselves as such and many are not without doubt regarding their sexual preferences, and a substantial part of them go on to change their sexual orientation throughout this transitional period [59]. This task is made even harder when trying to retrospectively assess whether same-gender sexual affiliation was present, requiring the differentiation of self-defined sexual orientation from practiced sexual relationships which may or may not be in accordance to the sexual affiliation.

SMY display higher prevalence of binge drinking and report a higher rate of current marijuana use [41]. A meta-analysis exploring the connection between nonheterosexual sex orientation and substance abuse found an increased risk for SUD among SMY, including lifetime use of alcohol (OR = 2.23) and marijuana (OR = 2.58) [53]. Data gathered from a national longitudinal study of adolescent health in the United States revealed that SMY reported higher rates of suicidal ideation and suicide attempts than did non-SMY, even after controlling for race, gender, and age [79]. Risk factors analyses exposed different patterns of suicide-related risk factors for SMY. Problem drug use was more strongly associated with suicidal ideation among non-SMY, as was the association between depression and suicide attempts. The authors suggest that different treatment targets should be sought for this population following the elucidation of specific suicidal risk factors relevant to SMY.

A meta-analytic review comparing suicidality and depressive symptoms in sexual minority and heterosexual youth has also found increased suicidal behavior (OR = 2.9) and depressive symptoms in this population [52]. Of note in this analysis was the description of an increase in the level of disparity between both populations as the severity of suicidal behavior increased (OR = 1.96, 2.2, 3.18, 4.17 for suicidal ideation, intent, attempt, serious attempt requiring medical attention accordingly) stressing the need for health-care personnel to pay heightened attention to suicidal behavior when encountered in SMY and when performing a suicide risk assessment. In the United States, the most current surveys show that SMY have an almost fourfold risk for formulating a suicide plan and almost a fivefold risk for attempting suicide as compared to heterosexual peers [41]. Furthermore, SMY are more likely than their peers to have been victimized and threatened and to have been engaged in a variety of risky behaviors [41].

Prospective studies are in demand to promote the identification of distinct attributes concerned with suicidality in this population through their transition into adulthood and maturation of sexual preference as major risk factors such as depression remain elevated even in young adulthood [50]. In a large longitudinal study following a cohort of over 1000 children from birth to age 21, the sexual orientation was studied at age 21 retrospectively from the age of 16. The correlation analyses between sexual orientation and suicidality revealed a fivefold risk for such behavior in SMY through the cohort period. The risk for SMY substance dependence was almost double, although not statistically significant ($p = 0.086$) [23]. The prospective nature of this study allowed for the evaluation of social and familial backgrounds of the subjects, and indeed, some differences were found between SMY and other cohort members in their familial background, suggesting a more troubled childhood for SMY. Interestingly, controlling for these differences in the statistical analyses had a negligible effect on the unadjusted results and thus might reflect a need to focus on developmental and behavioral factors instead.

107.7 Age Differences in Suicidality

Zalsman [95] has speculated that the timing of onset of gene-environment interactions leading to adolescent suicidality is crucial. He postu-

lates that specific brain development time windows may be critical for this interplay to emerge as behavioral phenotypes [95]. Clinical observations of age influences on suicidal behavior are evident, and the risk for suicidal behavior has been shown to increase through the transition from childhood to adolescence in such a way that late adolescents (generally defined as over 15 years old) exhibit increased risks for suicidal attempts and completion as compared to early adolescents [92]. Indeed, in early adolescence, suicide is the tenth cause of mortality worldwide, and at age 15–19 years, there is a dramatic leap to second place [64]. In older adolescents, the perception of risk from using alcohol and marijuana is lower and the use of drugs and alcohol as well as practicing binge drinking is increased. For instance, in a study by Rey et al. [71], the lifetime use of cannabis tripled between ages 13–15 years and a further increase of about 60% occurred between 15 and 17 years [71]. Furthermore, late adolescents' suicidal behavior is more associated with increased alcohol and drug use [38] even though cannabis use [7] or heavy episodic drinking [3] may have a more prominent effect on suicidal behavior in school-aged children as compared to older adolescent users. These data clearly strengthen the notion that public health leaders should prioritize suicide and substance use prevention schemes directed at younger school-aged adolescents.

107.8 Future Studies

Whereas the epidemiological and clinical data linking substance abuse to suicidality are compelling, basic science research encounters many difficulties in establishing this connection. Several problems arise to hamper the fundamental demand to minimize heterogeneity in the studied variables. First, there is no consensus as to the exact age span of adolescence and to the transitional phases of childhood and young adulthood. Furthermore, adolescence encompasses developmental stages such as puberty and post-puberty, associated with dramatic hormonal and physiological changes (e.g., the menarche) which cannot be constrained by strict temporal limits. Second, adolescence is a period of a dramatic psychosocial transition from childhood to adulthood, and this change is anatomically supported by a profound increase in brain plasticity including rostro-caudal white matter increase (myelinization) and accelerated dendritic pruning [25] leaving few brain regions and neurochemical pathways unchanged. Suicidal behavior or even thoughts might turn out to variably modify brain activity and plasticity in a similar way as does substance abuse [15] or depression [83]. Trying to account for this variability in brain connectivity in time and space over the full adolescent period seems presently impractical. Third, for obvious reasons, studying human brain morphology and activity, particularly those of children and adolescents, should be undertaken by employing noninvasive means. These means are presently scarce, and thus, most studies rely on comparative neuroimaging techniques alone.

These methodological challenges are demonstrated in a comprehensive overview of the relationship between alcohol and suicide by Pompili et al. [67]. They describe this causal relationship as being inconclusive and highly suggestible at best in light of the many neurotransmitter systems which are affected by ethanol, with varying spatial and temporal modifications regarding target brain regions [67].

Nevertheless, in the molecular level, a substantial volume of research has been accumulated relating to neurobiological changes associated with suicidality in adolescents. While these studies present convincing data regarding a genetic predisposition to suicidality [95] as well as altered receptor and signal transduction pathways associated with suicidality [63], they seldom address the role of substance abuse as a modifier to these neurobiological changes.

Suicidality is undoubtedly a complex behavioral phenotype. Currently, researchers studying the heritability of suicidal behavior are increasingly concerned with endophenotypes or biomarkers [81] of suicidal behavior and less so with single genes, although in distinct cases, a direct

connection can be drawn between single genes and suicide-related features such as impulsivity [5]. A seminal workshop convened for the purpose of the identification of candidate biological and clinical endophenotypes associated with suicidality found the most promising endophenotypes to be aggression/impulsivity trait, early onset major depression, neurocognitive function, and cortisol social stress response [51]. Specific endophenotypes for drug dependence have also been described [20] as well as inherited alterations in regulatory mechanisms of the hypothalamic-pituitary-adrenal (HPA) axis in the development of alcoholism [75]. It has been recently suggested that these endophenotypes as well as others can and should be translated into animal models that will help elucidate how genetic and epigenetic factors contribute to emerging suicidality [32].

It will be interesting to explore how relevant are these newly defined endophenotypes and biomarkers to the adolescent age group and to what extent do they overlap in specific individuals. This might pave the path for early targeted detection of high-risk suicidal patients and enable the utilization of individualized biological-based suicide prevention schemes.

107.9 Treatment and Prevention

How effective are drug prevention programs? Recent surveys portray an optimistic dramatic decrease in the past decade in adolescent alcohol as well as illicit substance use for all substances tested excluding cannabis and including ecstasy, methamphetamine, heroin, inhalants, cocaine, and synthetic cannabis [34, 41, 46].

The increasing global trend to legalize or decriminalize cannabis-related products has also been raised as an issue of concern when considering the effect this might have on adolescent exposure and availability to cannabis products. Although studies addressing correlation trends to study the effect of cannabis decriminalization are scarce, a recent meta-analysis suggested that permissive medical marijuana laws do not lead to increased prevalence of cannabis use among adolescents [74]. Indeed, although adolescent perception of harmful effects of regular cannabis smoking has significantly decreased in past decade, the percentage of regular adolescent users remains the same [60]. The explanation for this positive trend despite growing public approval of cannabis is most probably multifactorial and can not only be the result of timely use of campaigns and programs addressing the negative effects of cannabis.

A straightforward example of a successful nationwide campaign to decrease the use and subsequent harm of substances can be seen in the effort of the US government to curb the opioid use epidemic in the recent years [40]. It is evident that widespread state- and federal-level legislations and interventions schemes have already resulted in favorable outcomes. In 2017, a 10% decrease in pain relief medication misuse was noted as compared to 2016 in adolescents aged 12–17 [60]. The percentage of senior year adolescents using narcotics has decreased from 13.2% a decade ago to an all-time low of 6% in 2018 as monitored since 1991. The ongoing funding and maintaining of large-scale surveillance programs to monitor and decrease prescription drug misuse are imperative as this recently highlighted that mode of substance use is also strongly associated with adolescent suicidality [33].

Despite the somewhat reassuring trend in substance use prevalence in the last decade, youth perception of drug prevention efforts is still far from encouraging. In the past 15 years, the percentages of adolescents reporting recent exposure to drug or alcohol use prevention messages through media and school sources have steadily declined, and also almost half of adolescents do not talk with their parents about potential dangers of substance use [60].

Efforts should also be directed to improve available treatment options since data from recent US surveys display dismal reports of severe undertreatment of adolescent illicit drug and alcohol use problems particularly in specialized centers. The most recent NSDUH report from 2017 reported that 770,000 adolescents were deemed in need for an illicit drug use problem

specialized treatment. Of these, only 7.3% received appropriate treatment, representing a significant decrease from the situation 6 years prior to that (10.5 percent) and a long-term negative trend displaying a lack of specialty treatment resources available to those youth who need it. This low availability of specialized resources further stands out when compared to adults who are more than three times likely to receive such treatments. The situation is very much similar for alcohol use disorders with only 8.4% of youth who are deemed to be of need for specialty alcohol treatment services actually receiving them [60]. These statistics are presumed to be even worse in many other countries due to stigma, underdiagnosis, and shortage of relevant clinical facilities or funding.

Treatment strategies for adolescent SUD are abundant, multidimensional in time and setting, and incorporate a variable degree of pharmacological, psychosocial, and behavioral tools in a wide spectrum of modalities. The full scope of the treatment options available is far beyond the scope of this chapter [56], and it has not yet been shown that adolescent SUD treatments have a suicide-lowering effect at all. The efficacy of substance use-targeted treatments in lowering suicidal rates remains largely unknown and demands a prospective controlled study sufficiently powered to capture these relatively infrequent events. Recently, a suicide-lowering effect has been shown for methadone substitution therapy in a mainly adult population seeking help for opioid use disorders [57]. Other reports imply that treating substance use may decrease suicidality for youth with comorbid depression ([28]).

Treatment options for alcohol disorders are markedly more abundant today than were in the past and are generally individual-focused, family/community centered or school-based in structure. In a review of the various assessment instruments and treatment options in use for alcohol use disorders in youth, Perepletchikova et al. [66] suggest Multidimensional Family Therapy (MDFT) and group-administered Cognitive Behavioral Therapies (CBT) in combination with brief individual Motivational Enhancement Therapy (MET) as the most evidence-based supported treatment strategies of adolescent alcohol use disorders [66]. Further meta-analyses of available treatment schemes suggested that behavior-based treatments are most beneficial in maintaining long-term changes [86] and that motivational-based brief interventions administered in health-care facilities offer the strongest proof of efficacy in alcohol use reduction [65]. Recently, school-based programs focusing on personality factors of targeted high-risk students seem promising in reducing alcohol use and transition to substance use disorders [19].

Suicide prevention programs and treatment strategies are also abundant, and a multidimensional approach is generally encouraged although hard to be implemented using evidence-based approaches. A major challenge to be overcome for the successful implementation of prevention and treatment strategies stems from the fact that most suicidal adolescents do not reach for help prior to their suicidal acts. Only 14% of young people in the United Kingdom who completed suicide were in contact with mental health services in the year prior to their death, and incidentally, 71% of these reported concomitant substance abuse [92]. Also, in a case-control study on the utilization of health-care services among Canadian adolescents aged 11–18 years prior to completed suicide, Renaud et al. [70] described that although 95% of suicide completers suffered from mental disorders, over two-thirds of them had no treatment contact within the month prior to the act, while only 12.7% were in contact with psychiatric services during that same period [70]. Psychoeducational suicide prevention programs have generally shown to positively affect knowledge and certain attitudes concerning suicide [68] although a paucity of large-scale controlled trials limits a clear-cut conclusion regarding their efficacy. Other prevention strategies, such as screening efforts, gatekeepers training, means restriction, family-based treatments, and cognitive- as well as dialectic-based behavioral therapies, have also been described [44] and their efficacy reviewed elsewhere [35]. An NIH Pathways to Prevention

(P2P) workshop was convened in 2016 to explore expert-led evidence-based means to promote adolescent suicide preventive measures. This governmental-funded workshop highlighted data systems improvement, data collection enhancement and improvement of analysis methods, and strengthening the research and clinical community as key strategies to enable improvement of current practice [48].

Finally, the exposure of youth to suicidal behaviors through the traditional and, more so in recent years, through social media may carry a substantial impact on the prevalence of suicidal behavior which should not be underestimated (suicide contagion or "Werther effect") [11, 77]. Despite this, media sources and particularly Internet sites and smartphone applications may also lend real-time, confidential, and easy-to-access sources for suicidality counseling and support and provide an accessible route for treatment referral [44, 72, 85].

107.10Conclusions

Although the act of completed suicide is extremely challenging to predict, many risk factors have been well established and studied. Efforts to further maximize the accurate assessment of high-risk individuals based on these should be encouraged. Reducing suicide attempts in these individuals remains a major challenge since it is not yet clear to what extent eliminating the associated risk factors will in effect result in the reduction of the risk for suicidal behaviors. In this context, efforts to strengthen anti-suicidal resiliency [39] through local or national initiatives have gathered interest, although their effectiveness remains to be proven.

It is apparent that both suicidality and SUD are highly prevalent in the young population and that both carry an increased risk for morbidity and mortality, increasing with older age. The counter-effect of these two complex behavioral states on each other increases the risk for suicidal behavior in adolescents with SUD as opposed to those without. This may largely be due to the fact that both are associated with decreased inhibition and increased impulsivity that lead to impaired decision-making manifested in risk-taking and reckless behaviors. In the proximal timescale, co-occurring SUD may facilitate the transition of ideation to action, whereas in the distal timescale, it may contribute to increased stress by adversely affecting the adolescent's environment and circumstances.

The ongoing efforts of large-scale initiatives that monitor teenage substance use trends and suicidality should also be supported. Relevant data gathered from these facilitate the analysis of global as well as local trends in substance use and their correlation with suicidality. Future clinical studies should follow these changes in temporal trends to provide rapid and relevant reports of the usefulness of prevention efforts utilized. To date, available treatment options only partially rely on evidence-based knowledge due to a lack of studies on the one hand and methodological difficulties on the other. Carefully planned large-scale prospective studies are in need to provide a stronger evidence base for assessing clinical benefits of prevention and treatment plans. A major goal for basic science research remains to discover a low-cost, minimally invasive, and highly specific endophenotype marker for suicide. Such a marker may be more pronounced or relevant in adolescents with SUD due to the strong association between the two phenomena.

In defined high-risk populations, such as the SMY, in which the SUD-suicidality association is more pronounced, efforts for early detection must be increased by the health system and careful evaluation of suicidality should be made based on validated assessment scales and established risk factors while avoiding stigmatization. Wide gaps appear between therapeutic strategies in different countries and even within countries. This may reflect the paucity of evidence-based proven efficacy of current therapies targeted either for SUD or suicidality. The association between SUD and adolescent suicidality is highly influenced by other psychiatric comorbidities, primarily but not exclusively mood disorders, which are most prevalent among these patients and confer an increased risk for additional psychopathology and completed suicide. SUD adolescents with suicidal behaviors are increas-

ingly diagnosed as suffering from "dual diagnosis" or "coexisting problems" without a concomitant referral to specialized treatment facilities. Regretfully, in most countries, the therapy for SUD is not part of the "mainstream" psychiatric health system, and this artificial dichotomy most probably hampers the integrative treatment effort which suicidal adolescents and their families require. We propose that for these patients, a holistic treatment approach is needed to be implemented in specialty facilities. SUD as well as other psychiatric comorbidities and emergent suicidal behaviors should be addressed concurrently as mutual effective connections between these conditions, although not yet well understood, are most evident.

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Risk and Protective Factors for Substance Use and Addiction

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Philip A. Spechler, Alexandra Ivanciu, and Hugh Garavan

Contents

Abstract

Studies on the predictors of substance use disorders have typically focused on psychosocial predictors, whereas the neurobiological predictors are still being elucidated. While psychosocial predictors such as peer influences and personality measures may be considered robust predictors of drug use, understanding neurobiological associations is crucial to uncovering biomarkers, which inform mechanistic models of addiction and treatment options. This review briefly surveys key psychosocial findings and focuses on the predictors of drug use identified from genetic and neuroimaging research. Special attention is given to cannabis use in adolescence, as cannabis is the most commonly used illicit substance, and adults with substance use disorders are likely to have initiated drug use in adolescence. This chapter concludes with a commentary on the future directions for substance use prediction studies.

Keywords

Prediction · Risk · Adolescence · Cannabis Addiction · Neuroimaging

P. A. Spechler (✉) · A. Ivanciu · H. Garavan
Department of Psychiatry, University of Vermont, Burlington, VT, USA
e-mail: philip.spechler@uvm.edu

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108.1 Introduction

Problematic drug use is one of the most common and chronic behavioral health issues facing society [15], yet little is known about the neurobiological predictors of use. It is important to study the predictors of drug use within the context of adolescence as individuals who struggle with substance use disorders typically initiate use during this developmental period. An epidemiological survey estimated that 74% of young adults admitted to substance use treatment programs had initiated drug use by age 17 or younger [59]. Furthermore, early initiation of cannabis use is related to outcomes like lower socioeconomic status (SES) [22, 38] and jeopardized mental health including risk for mood disorders [25], schizophrenia, and other psychotic-like disorders [23, 40].

Despite known risks associated with its use, recreational cannabis use for adults is now legal or decriminalized in many parts of the United States and abroad. Global estimates indicate that cannabis use disorder is currently the second most prevalent substance use disorder behind alcohol [15]. In line with this finding, epidemiological studies of adolescent drug use indicated cannabis is also the second most popular drug (following alcohol) used by adolescents, surpassing cigarettes in 2011 [30].

In this chapter, we review what is known about the predictors that increase (risk factors) or decrease (protective factors) the likelihood of cannabis use in adolescence with a focus on the psychosocial and neurobiological changes that occur during adolescence. Special focus will be given to longitudinal neuroimaging studies reporting predictors and correlates of cannabis use in adolescence. The identification of these predictors will inform pathways to cannabis initiation, stratify risk in vulnerable adolescents, and supply targets for proactive interventions tailored to mitigate use and attenuate the consequences of use.

108.2 Psychosocial Risk Factors

The World Health Organization defines adolescence as the period of development between ages 10 and 19 (www.who.init) and is characterized by substantial psychosocial and neurobiological changes [51]. An increase in risk-taking and sensation-seeking behaviors is a common feature of adolescence. For instance, novelty-seeking personality levels typically peak during adolescence [35, 44] and are highly predictive of substance use [14, 26, 37]. Adolescents also tend to discount delayed rewards in favor of immediate rewards [57] and display insensitivities to the aversive properties of some drugs [9, 18, 46]. Together, these behavioral characteristics are thought to contribute to an adolescent's increased propensity for drug use.

Numerous studies have also identified relationships between environmental factors, such as traumatic and stressful life events, and risk for drug use in adolescence. Frequency of early life stress [5] and perceived level of stress [4, 17, 29, 61] are robust predictors of drug use in adolescence. While these findings predict drug use later in life for both sexes, physical and/or sexual abuse during childhood was more common in females than in males [34]. For males, severity of later-in-life drug use was inversely correlated with age at first abuse, such that younger males experiencing physical and/or sexual abuse showed more severe substance abuse problems later in life. This dose-response relationship was not evident in females, where any history of abuse during childhood strongly predicted substance use problems in adulthood [34].

Early life stress might promote the generation of maladaptive coping strategies including substance use. And while stress generally precipitates drug use [16, 49, 61, 66], the exact mechanism driving this association is actively being studied [39]. Drugs and drug-seeking behaviors may potentiate perceptual and biological reactivity to stress [11, 12, 19, 27] and drive self-medicating behaviors. Stress may impair the capacity for impulse control, which is thought to contribute to the maintenance of a substance use disorder [49]. Thus, while we might conclude that a variety of life stressors are reliable predictors of use, understanding the neurobiological mechanisms mediating the effects of these stressors remains an important research focus.

108.2.1 Peer and Parental Influences

A wealth of research supports the concept that parents' lifetime cannabis use predicts adolescent cannabis use [21, 31]. A recent paper by Sokol and colleagues reported that age of cannabis initiation was shifted 2 years earlier in children with a mother reporting any lifetime cannabis use, relative to children of cannabis-naive parents [50]. Furthermore, O'Loughlin and colleagues reported adolescents with *one* parent who endorsed any lifetime use were roughly twice as likely to use cannabis, while adolescents with *two* parents who endorsed any lifetime use were eight times more likely to use cannabis, relative to peers with cannabis-naive parents [42]. While many factors may contribute to parent-offspring transmission of drug use (e.g., exposure, drug availability), possible mechanisms include shared environmental factors as well as genetic and neurobiological predispositions.

An adolescent's peer group also influences cannabis use. Numerous studies indicate that an adolescent is more likely to use cannabis if their peer network uses cannabis [3, 20, 32]. Mechanisms contributing to this effect are thought to relate to the reinforcing properties of both the drug and the social context [8]. For instance, some adolescents may not find drug use itself pleasurable. Thus, the social context involved in cannabis use may prove reinforcing in those who may not find the cannabis itself rewarding. In contrast, some adolescents may not enjoy the social context, but it is a necessary means to obtaining the reinforcing drug. Evidence for both these scenarios are reported in the literature. Lee and colleagues reported that 26% of high school graduates who used cannabis endorsed social enhancement and bonding as their primary motive for cannabis use [33]. Buckner and colleagues measured the likelihood of cannabis use in different social situations and reported that adolescents with social anxieties avoided social situations where cannabis was unavailable [7].

In reviewing the preceding psychosocial risk factors for cannabis use, it should be noted that the research tends to focus on specific factors in isolation. As a result, much less is known about how risk factors accumulate or interact with one another to facilitate or impede cannabis use behaviors. For example, the likelihood of early life stress to confer risk for cannabis use might be moderated by differences in personality traits, peer, or parental influences. Further, although these psychosocial predictors inform pathways to drug use, they offer limited insight into the biological processes related to drug use. Next, the literature concerning the biological predictors of cannabis use will be surveyed starting with a brief overview of the genetic predictors identified from genome-wide association studies (GWAS), followed by human neuroimaging studies.

108.3 Biological Risk Factors

108.3.1 Genetic Associations

Genetic studies seek to identify preexisting genetic risk factors associated with a drug using phenotype. These studies require very large samples in order to detect and, ideally, replicate effects which are typically small in magnitude. Two GWAS studies on cannabis use failed to detect any single nucleotide polymorphisms (SNPs) that passed significance thresholds [2, 58]. Conversely, two other GWAS studies found significant genetic variants associated with cannabis use. The first such study identified three SNPs associated with cannabis use dependence [48]. One SNP was found on an antisense transcription region (rs143244591) whose function is unknown. The other SNPs were found on a gene coding for a protein that regulates extracellular calcium concentrations (rs146091982) and a gene coding for a protein that regulates neuronal inflammation (rs77378271). In another recent GWAS using a very large sample ($N = 184{,}765$), researchers identified eight SNPs that explained 11% of the variance in lifetime cannabis use. The three most significant SNPs were on a gene coding for CADM2, a cell adhesion molecule expressed widely in the brain. This gene has been previously linked to alcohol consumption and risk-taking behaviors [43].

It is hypothesized that different genetic profiles relate to the pharmacological actions of cannabis. For example, Agrawal and Lynskey proposed studying genes coding for various neurotransmitter receptors (CNR1, CB2, TRPV1, GPR55) and ligand enzymes (FAAH, MGLL) [1]. Spechler and colleagues used this approach as an exploratory analysis within the context of a larger machine learning prediction study (described further below) [54]. Here, the search for genetic associations with cannabis use was restricted to 108 SNPs chosen as they were previously reported to have relationships with substance use phenotypes. Results from that study yielded ten SNPs that modestly predicted cannabis use initiation in adolescence. Five of those SNPs were located on genes coding for the primary mu-opioid neurotransmitter receptor, three SNPs in genes coding for norepinephrine receptors, and two SNPs in genes coding for the D1-dopamine receptor. While these findings, like all genetic studies, require replication, they suggest that genetic variation on the opioid and catecholamine receptors might constitute a genetic profile conferring risk for cannabis use.

108.3.2 Neuroimaging Predictors

Structural and functional magnetic resonance imaging (fMRI) studies on substance-using populations typically use cross-sectional designs. Given the interpretational challenges posed by such designs, more studies using carefully controlled longitudinal and prospective designs are needed to make claims related to predictors of use. For example, Cheetham and colleagues studied gray matter volumes (GMV) in an adolescent sample pre- and post-cannabis use. Findings indicated that less GMV in the orbital frontal cortex (OFC) at age 12 predicted cannabis use by age 16 [10]. The OFC is commonly implicated in addiction. Early work by Volkow and Fowler reported converging evidence for hypoactivity in this region using fMRI and positron emission tomography (PET) to characterize individuals with drug dependence [62]. These studies suggest a propensity for drug use is partially predicted by differences in structure and function of the OFC, a region putatively involved in functions relevant to substance use, such as reinforcer evaluation [41] and behavioral regulation [6].

Jacobus and colleagues studied cortical thickness in a sample of adolescents before (age 13) and after (age 19) initiating alcohol-only, or alcohol and cannabis, and compared them to drug-naive peers. Less cortical thickness across many prefrontal regions, including the left precentral and superior frontal gyri, predicted the future alcohol + cannabis group relative to alcohol-only. Less thickness in right middle frontal gyrus predicted the alcohol + cannabis group relative to controls [28]. This study also included repeated measures on neurocognitive and mental health surveys. Results indicated that worse performance on working memory tasks and higher externalizing scores at baseline predicted the alcohol + cannabis initiating group relative to the others. These results suggest a preexisting working memory deficit is sustained (if not exacerbated) through prolonged cannabis exposure in adolescence. Consequently, a combination of behavioral and neuroimaging measures may yield a predictive profile of cannabis use in adolescence.

These two structural MRI studies suggest that less gray matter in prefrontal regions preceded cannabis use in adolescence. Normative adolescent neurodevelopment is characterized by volume reductions, so interpreting these effects is challenging. One possibility is that they might signal precocious development [24]. Hence, adolescents exhibiting less gray matter relative to their peers at the same age might indicate accelerated neurodevelopment – a possible marker of or risk factor for maladaptive psychosocial development and drug-seeking behaviors.

Prospective functional MRI studies investigating adolescent cannabis use are even more scarce than structural MRI studies. A forthcoming prospective report by Spechler and colleagues identified amygdala hyperactivity to threat signals (angry faces) in cannabis-naive adolescents predicted the level of cannabis use by age 19 [52]. This study informs previous work which demonstrated that amygdala hyperactivity correlated

with cannabis use by age 14 [55] and also suggests a dose-response relationship between pre-existing amygdala hyperactivity and future cannabis use.

In another prospective fMRI study by Tervo-Clemmens and colleagues, researchers scanned children at ages 12 and 15 using a working memory paradigm [60]. In children who were cannabis-naive at age 12, higher frontoparietal activations and lower visual cortex activations during high task load predicted cannabis use by age 15. A dose-response effect was also found in the cuneus, such that lower activations predicted heavier use. Additionally, lower spatial planning scores from a cognitive test battery (CANTAB) also predicted use. These results add to the literature despite being limited by a small outcome group ($n = 22$ future cannabis users): Replication with larger samples is needed. More refined predictive modeling strategies can be applied to larger samples, including cross-validation schemes testing for generalizability of models on external samples to further evaluate prediction accuracy [64].

108.4 Prediction Analyses with Machine Learning

Prediction analyses aim to yield models that accurately predict novel observations. As large longitudinal research projects like IMAGEN [47] and ABCD [63] become more prevalent, study sample sizes approach epidemiological levels and make external- or cross-validation procedures possible. These large research projects provide feature-rich characterizations of participants. Machine learning approaches may then be utilized to uncover multi-domain data-driven predictors of phenotypes, while testing the generalizability of a predictive model on novel observations using an external validation set or cross-validation [45, 64].

Despite recent large-scale projects, few studies have specifically identified neurobiological predictors of drug use. Whelan and colleagues used cross-validated regularized regressions to classify adolescent binge drinkers at age 14 and to predict binge drinking by age 16 from age 14 data [65]. These methods, applied to a wealth of neuroimaging, psychometric, and candidate SNP data, indicated highly significant classification (Area Under the receiver operating characteristic Curve (AUC) = 0.90) and prediction (AUC = 0.75). Hence, these methods yielded models that performed well in classifying and predicting independent samples.

Several features from the Whelan et al. [65] study both classified and predicted adolescent binge drinking: more frequent sexual life experiences, higher novelty seeking, disorderly and extravagant personalities, and lower conscientiousness. With regard to neurobiological features, lower activation in the left putamen and hippocampus during reward anticipation and less GMV in the ventromedial prefrontal cortex classified age 14 binge drinking. Lower activation in pre- and post-central gyri during failed response inhibitions predicted future binge drinking. In sum, the classification was driven by lower activity in regions serving appetitive processing, while the prediction was driven by lower activity in sensory motor areas during failed response inhibitions.

Spechler and colleagues implemented a similar approach using machine learning to generate cross-validated models that predicted cannabis use initiation in males and female adolescents [54]. Multi-domain data measured prior to any reported cannabis use were modeled together to uncover a sparse set of brain and behavioral predictors. Cross-validated prediction accuracy was robust (males AUC = 0.74; females AUC = 0.82). Psychosocial predictors observed in both sexes included higher lifetime alcohol or tobacco use, parental cannabis use, and novelty-seeking personality features.

Brain predictors from the Spechler et al. [54] study were found to be sex-specific. Generally, lower brain activations during a response inhibition task characterized future cannabis use in males and females, but the specific locations of these effects differed between the sexes. For example, males exhibited lower activation in the cerebellum, whereas females exhibited lower activation in prefrontal and temporal cortex, rela-

tive to their cannabis-naive peers. Brain activation during face processing and reward processing also predicted future cannabis use in females. The authors demonstrated that sex-specific predictors did not predict future cannabis use in the opposite sex, nor did they generalize to predict binge drinking in a related sample of same-sex adolescents. Lastly, hierarchical regressions demonstrated that the inclusion of each set of domain-specific predictors significantly improved model fits. Therefore, behavioral and brain data explain unique portions of the variance in future cannabis use initiation.

A caveat of the Spechler et al. [54] report was that the future cannabis users also reported future binge drinking. Even though the cannabis predictors identified in the 2018 report did not predict an independent sample of future binge drinkers, a stricter test of drug specificity would be welcome to help uncover the predictors unique to cannabis use. Therefore, in a forthcoming report by Spechler and colleagues, machine learning techniques were used to differentially predict future cannabis use vs. future binge drinking [53]. In that study, all individuals were cannabis-naive at baseline, but the comparison sample was chosen to be matched to the future cannabis-using group on their future binge drinking levels.

Results indicated prediction was still highly significant (males AUC = 0.63; females AUC = 0.66), although lower than when discriminating future cannabis users from cannabis and binge drinking naive controls. The identified predictors were also fewer in number. Higher rate of baseline cigarette use was the only feature that consistently predicted future cannabis use across the sexes. However, future cannabis use in males was also predicted by less negative feelings toward deviant behaviors and more regional GMV in the right inferior temporal lobe relative to future binge drinking peers. Future cannabis use in females was also predicted by a set of lower brain activations during response inhibitions, including the left middle frontal gyrus, right inferior temporal gyrus and right paracentral lobule during successful response inhibitions, and the left inferior frontal gyrus during failed response inhibitions.

Lastly, Squeglia and colleagues recently published a machine learning study predicting the initiation of alcohol use in adolescence [56]. In that report, researchers used random forests on data collected at age 12–14 to predict moderate to heavy alcohol use by age 18, relative to a sample of consistently alcohol-naive peers. Three separate models were generated by increasing the number of feature domains (demographics only; demographics + neurocognitive; demographics + neurocognitive + neuroimaging). Prediction accuracies increased with the inclusion of each domain, as indexed by sensitivity (0.60, 0.67, and 0.74, respectively) and specificity (0.64, 0.70, and 0.73, respectively) to alcohol initiation. The best predictors were from the neuroimaging data, including lower thickness of the left supramarginal gyrus and lower activations in the right posterior cingulate and superior temporal gyrus during a working memory task.

Aside from the neuroimaging data, sex, SES, and cognitive measures were also identified as predictors of adolescent alcohol use. The lack of consistency with Whelan and colleagues is likely due to differences in measurement (Whelan used voxel-wise data; Squeglia used regions of interest). Nonetheless, results indicated that the best prediction was achieved with a combination of behavioral and neuroimaging data. In keeping with the prediction studies by Whelan and colleagues [65] and Spechler et al. [54], machine learning approaches can be used to leverage multi-domain data, resulting in meaningful predictions and uncovering profiles predicting drug use in adolescence.

108.5 Discussion

Identifying risk for substance use and disorders is an active area of research spanning biological and behavioral domains. Uncovering risk for early initiation and problematic cannabis use is paramount in light of the prevalence of those who initiate as adolescents [30], the global estimates of cannabis use disorder [15], and the ongoing shift in legal status for adult recreational cannabis use. Generally, the psychosocial findings high-

light the role of novelty-seeking personality traits, alcohol and cigarette use, and peer and parental relationships as key predictors of drug use in adolescence. The neuroimaging studies, though still nascent, point to structural and functional differences in prefrontal regions as preexisting differences that increase risk for future cannabis use.

Machine learning approaches are novel and insightful tools for leveraging large datasets to identify predictors of drug use. Robust prediction models should generalize to predict independent observations and may identify predictors from multiple domains. Indeed, as demonstrated by Spechler et al. [54], modeling the combined psychosocial and neuroimaging predictors returned superior model fits relative to models containing only psychosocial data. Therefore, it is important to consider the contribution of risk from multiple domains in order to identify a comprehensive risk profile that can be used to infer etiological mechanisms and possible treatment strategies.

Of course, existing findings require replication, and future research should examine how predictors relate to each other. The majority of the research methods discussed thus far employed the general linear model, assuming a linear relationship among predictor variables. These methods also assumed predictors were independent from one another and their effects summed together to model a group average. Incorporating nonlinear interaction terms or other nonlinear modeling procedures might yield new insights into the joint contribution of multi-domain predictors explaining drug-using phenotypes. Therefore, new hypotheses to be investigated should model cross-domain interactions. For instance, some individuals may possess genetic risk variants, yet their personality traits or environmental factors moderate these effects to either magnify risk or protect against cannabis use. Moreover, researchers should explore the extent to which genetic and psychosocial features interact with neurobiology to influence the likelihood of drug use or substance use disorders.

One eventual goal would be for the findings of prediction studies to help develop and validate strategies that might disrupt a risk phenotype. Some of the predictors discussed in this chapter could be incorporated into treatments (e.g., augmenting executive control functions subserved by the OFC), whereas others may be incorporated by targeting the individual's environment including their parent and peers. As it stands, the psychosocial domain might be more accessible than the biological domain. For example, there is evidence for the efficacy of personality-targeted interventions [13] in reducing the likelihood of cannabis use in adolescents by targeting a sensation-seeking personality [36].

Central to all the research discussed in this chapter is the assumption that preexisting differences confer risk for drug use. However, it is worth noting that it would be incautious to assert that these preexisting differences caused drug use. Even with carefully designed and controlled longitudinal studies, it is difficult to assert causal relationships between risk factors and a complex behavioral phenotype. Treatment (intervention) studies are one method to approach causality if the modification of a risk factor is found to attenuate the phenotype. Conversely, if a protective factor is disrupted, say, by a shift in the social environment of the adolescent, that would also help illuminate causal mechanisms. The combination of longitudinal observational studies and experimental intervention studies should, in time, identify etiological mechanisms and identify which elements of those mechanisms are modifiable.

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Perinatal Substance Use Disorders: Intrauterine Exposure

109

Martha L. Velez, Chloe J. Jordan,
and Lauren M. Jansson

Contents

M. L. Velez (✉) · L. M. Jansson
The Johns Hopkins University School of Medicine,
Baltimore, MD, USA
e-mail: mvelez@jhmi.edu

C. J. Jordan
National Institute on Drug Abuse,
Baltimore, MD, USA

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Abstract

Substance use disorders (SUDs) among childbearing-aged women are a significant public health problem. With advances in fields such as genetics, epigenetics, and neuroimaging as well as improved research methodologies, it is now established that prenatal exposure to psychoactive substances is a major preventable cause of disorders of fetal and infant/child growth and neurodevelopment. The effects of these neurodevelopmental alterations can appear at any time of the individual's life and can affect a variety of domains including developmental, behavioral, cognitive, and adaptive functioning. Problems related to prenatal substance exposure can be transient and start during the neonatal period (i.e., neonatal abstinence syndrome) or can appear at any age and compromise specific areas of functioning for a lifetime (i.e., deficit in executive functioning). Moreover, maternal chronic substance use can compromise the maternal neural circuitries that subserve executive functioning and regulation of stress responses, impairing their ability to appropriately parent. Expression of the teratogenic effects of perinatal exposure to substances can be exacerbated by a toxic or unstable prenatal and/or postnatal environment and ameliorated by a nurturing and stable one. Health-care providers play a crucial role in the prevention, early detection, and intervention for perinatal SUD. This chapter will describe the effects of maternal SUD on the mother, child, and mother/child dyad functioning and provide recommendations for screening and interventions for families affected by perinatal SUD.

Keywords

Prenatal substance exposure · Maternal substance use disorder · Perinatal · Parenting Child development · Intrauterine exposure

109.1 Introduction

The use and misuse of psychoactive substances among pregnant and postpartum women is of great concern for health professionals and policy makers. Prenatal substance exposure (PSE) affects more newborns than other common medical conditions and is linked to a variety of adverse outcomes for the pregnancy, the fetus/child, and/or the mother. Furthermore, an SUD can compromise maternal neural circuitries regulating stress responses and behavior, challenging her ability to care for the child and increasing risk for child abuse and neglect. The physiological, behavioral, and neurodevelopmental problems associated with PSE can appear in the fetus, at birth, or at any later age. These problems can be transient or persist throughout life, causing serious emotional and financial burdens to individuals, families, and society. The management of pregnant women with substance use disorder and their children is an opportunity and a challenge for the patients, their families, and their health-care providers. Failing to identify and treat this group of mothers and children comprehensively may bring undesirable consequences for the dyad and for society. The purpose of this chapter is to review the (1) scope of the problem, (2) challenges faced by pregnant women with SUD, (3) effects of substances on fetal/child neurodevelopment, (4) identification of pregnant women with SUD and their children, and (5) interventions to help this population of women and children.

109.1.1 Epidemiology at Different Developmental Periods Related to Perinatal SUD

The use/misuse of licit and illicit substances during pregnancy is a major cause of preventable disorders in fetal growth and neurodevelopment. Greater understanding of the epidemiology and factors contributing to substance use prior to, during, and after pregnancy, and of the mechanisms through which those factors exert their

effects, is a prerequisite to detecting and treating affected children and their families.

109.1.1.1 Preconceptional Period

In the US, 55% of childbearing-age women report alcohol use, with 24.5% reporting binge drinking in the past month. The use of tobacco among nonpregnant women aged 15–44 is 24%, and the use of illicit substances is 11.4% [42]. After marijuana use, prescription drug misuse/abuse is the most common type of problematic substance use.

Although pregnancy is frequently a motivation for women to decrease or stop substance use, a high percentage of pregnancies are unplanned, and late pregnancy recognition (≥7 weeks) occurs in 23% of women of childbearing age. In women with SUD, further failure to recognize a pregnancy can occur for many reasons, including chaotic lifestyles and amenorrhea associated with substance use, putting the exposed fetus at increased risk during a critical period of early brain development.

While the effects of maternal substance use on infant outcomes have been the focus of extensive research, the role of paternal substance use prior to conception has been limited. Epidemiological and animal studies indicate that chronic paternal substance use prior to conception may have a negative impact on the offspring's development [1]. Paternal alcohol, nicotine, cocaine, or opioid use has been found to influence infant birth weight, congenital malformations, and cognitive functioning, as well as increased risk for SUD in adulthood [35]. Although the mechanisms underlying the impact of paternal substance use on physical and developmental outcomes of the offspring remain unclear, preliminary studies suggest that paternal preconceptional substance use can produce heritable changes in genomic expression and phenotype in offspring via epigenetic transmission [15].

109.1.1.2 Prenatal Period

Tobacco, alcohol, marijuana, cocaine, amphetamines, opioids, and benzodiazepines are the most commonly used substances during gestation, with polysubstance use being more common than monosubstance use. The prevalence of disorders related to PSE varies by ethnicity, geographic location, and temporal and population factors. Globally, in a systematic review and meta-analysis published in 2017, approximately 10–15% of women consumed alcohol during pregnancy [34]. In the US, it is estimated that 9.4% of pregnant women use alcohol regularly with 2.3% reporting binge alcohol drinking, 15% smoking tobacco, and 5.4% current illicit substance use. Adolescents in particular are of concern; the rate of illicit substance use among pregnant women between 15 and 17 years old was 14.6% in 2012–2013 [42]. In a population-based US survey, 4.2% of women reported cannabis use during pregnancy and 6.8% after pregnancy [25]. Past-month cannabis use among pregnant women in the US increased up to 62% between 2002 and 2014 [6] and may continue rising with increased acceptance and efforts toward decriminalization and legalization. Concurrent use of cannabis and nicotine is also increasing. During the last decade, the overprescription, diversion, and misuse of opioid medications and subsequent increase in heroin use and fentanyl misuse have also become a major public health burden for maternal and child care. Finally, the use of benzodiazepines is estimated at 1–11% pregnant women, with 3.9% of a privately insured population of pregnant women being prescribed a benzodiazepine. Among pregnant women with opioid use disorder, 9.2% also reported concurrent benzodiazepine use [37].

109.1.1.3 Postnatal Period and Epidemiology of the Effects of PSE

Prenatal smoking is one of the most common preventable causes of infant morbidity and mortality. Approximately 5–8% of preterm births, 13–19% of term low birth weight infants, 23–34% cases of sudden infant death syndrome (SIDS), and 5–7% of preterm-related infant deaths are attributable to prenatal maternal smoking [11]. In the US, the proportion of infants developing neonatal abstinence syndrome (NAS) due to opioids increased fivefold between 2000 and 2012. The global prevalence of fetal alcohol spectrum

disorder (FASD) is 7.7 per 1000 population [26]. Within the US, FASD estimates range from 3% to 5% [34]. FASD risk is higher in disadvantaged groups, with rates of up to 68.0–89.2 per 1000 in the wine-producing regions of South Africa [30].

In addition to the effects of PSE on the offspring, resumption of maternal substance use following delivery is frequent and can further impact the infant via exposure through breast milk, as well as impair the mother's parenting abilities. Compared with use during the third trimester of pregnancy, cigarette, alcohol, binge alcohol, and marijuana use rates were higher in women with a child younger than three months of age [41].

109.2 Problems Faced by the Pregnant Women with SUD

In the mother, chronic substance use can lead to morphological and functional brain changes that produce compulsive craving and drug seeking, impairing daily functioning. Substance-induced brain changes result in heightened stress, which may amplify negative affect states and increase drug-seeking and neglectful or abusive parenting behavior. Drug use is further associated with impairment of memory and attention, inhibitory control, interoception, and self-awareness, all processes required to support the demands of adequate parenting practices, self-care, and healthy decision-making. Poor decision-making skills can lead to risky sex, violence exposure, higher stress, and homelessness. Many pregnant women with SUD seek prenatal care late or not at all even if they have chronic health concerns, further increasing the risk of poor perinatal outcomes. Dental problems are very common due to poor dental hygiene, lack of dental care, opioid exposure, and inadequate nutrition.

A significant proportion of pregnant women with SUDs have one or more psychiatric diagnoses, with comorbidity ranging from 45% to 75%, depending on the sample. Moreover, they commonly have histories of multiple adverse experiences. A past and/or current history of abuse (physical, sexual, or emotional), neglect, abandonment, and family violence is common condition. Many women with SUD grow up in multigenerational drug-using families with significant mental health problems or environments where multigenerational substance use, chaos, inconsistency, mistrust, and aggression are the norm. The perceptual, cognitive, and emotional capabilities of the mother and her parenting skills are built upon the scaffolding provided by her earlier life experiences. Life trauma may lead to maladaptive and recurring unhealthy behaviors that have a negative impact on general functioning and pregnancy well-being. Unaddressed maternal psychosocial issues can contribute to mother-infant interaction problems and alter developmental trajectories of children. Socioenvironmental problems have been found to affect the severity of neonatal abstinence syndrome expression in opioid-exposed infants [32].

109.3 Effects of Drugs on Fetal Neurodevelopment

The environment encountered in fetal and neonatal life exerts a profound influence on physiological function and risk of disease in later and adult life. The foundations of brain architecture and function are established early in pregnancy through dynamic interactions between genetic influences and the prenatal environment.

Most substances cross the placenta and have a longer half-life in the fetus than in adults, resulting in higher concentrations in fetal than maternal blood. Substances may affect biologic functions either through binding to receptors in the CNS or by affecting the release and reuptake of neurotransmitters. Neurotransmitters and neuromodulators appear early during embryogenesis, and their signaling serves key functions during neurodevelopment, including neurogenesis, neural progenitor proliferation, lineage segregation, and the migration and phenotypic specification of immature neurons and glial cells. Alterations in these processes can change neurodevelopmental trajectories via a variety of actions depending on the substance, timing and patterns of exposure, and the system affected. For

example, prenatal alcohol exposure alters gene expression and disrupts neural development by interfering with myelination, synaptogenesis, and cell migration and by enhancing cell death [50]. Similarly, opioid exposure disrupts neuronal maturation, alters the development of dopamine and serotonin transmitter systems, and suppresses myelination, resulting in reduced brain volume and connectivity [8]. While endogenous cannabinoid signaling tightly regulates neural development and migration during the prenatal period, exposure to exogenous cannabinoids (e.g., through marijuana) prenatally disrupts neuronal maturation, connectivity, and transmitter signaling [19]. Adverse prenatal environments created by substance exposures may result in long-term epigenetic modifications (i.e., heritable alterations in gene expression due to drugs, toxins, stress, and inflammatory responses), altered hypothalamic-pituitary-adrenal (HPA) axis activity, and elevated corticosteroid levels in the mother and fetus. These changes alter the programming of the fetal neuroendocrine environment and predispose the child to behavioral and emotional dysregulation, compromising physical and mental health and developmental trajectories.

109.3.1 Substance-Related Adverse Birth Outcomes

SUD during pregnancy is linked to perinatal complications related to the direct effects of the drugs or, secondarily, due to the environment associated with compulsive drug use and seeking. Substances used during pregnancy have been associated with adverse outcomes such as preterm birth (e.g., nicotine, alcohol, cocaine, benzodiazepines) and low birth weight (e.g., nicotine, alcohol, cocaine, methamphetamine) [49]. Medical and obstetrical complications associated with substance use include miscarriage, premature rupture of membranes, premature delivery, placental abruption, intrauterine growth restriction, chorioamnionitis, stillbirth, hypertension, and increased rate of infections, including sexually transmitted diseases. Intravenous substance use carries the additional risk of cellulitis and abscess formation, sepsis, endocarditis, hepatitis B, hepatitis C, and HIV infection. Small-for-gestational age rather than preterm birth is the main mechanism through which smoking causes excess infant mortality. Some studies suggest that infant mortality is 40% higher in infants exposed to smoking during pregnancy compared to those born to nonsmoking mothers, with variations by race/ethnicity [36].

109.3.2 Congenital Malformations

Malformations associated with prenatal alcohol use include the dysmorphic facial features (short palpebral features, smooth philtrum, and thin vermillion border) seen in fetal alcohol syndrome (FAS) or partial fetal alcohol syndrome (pFAS) and the congenital malformations seen in alcohol-related birth defects (ARBD), which include cardiac defects, eyesight and hearing issues, urinary problems, joint abnormalities, and skeletal problems. Reports from autopsies of infants with FAS and human imaging studies demonstrate abnormalities in overall brain size and shape particularly in the cerebellum, basal ganglia, and corpus callosum [28].

Aside from alcohol, which has a clearly defined pattern of birth defects, studies evaluating the correlation between congenital anomalies and other prenatal substance exposures are inconsistent [46]. While a few case reports, retrospective studies, and studies with small samples describe associations of some substances with particular anomalies, large-scale and prospective studies do not generally confirm these associations [4]. A systematic literature review of studies carried out between 1959 and 2010 found a significant positive association between maternal prenatal smoking and cardiovascular/heart defects, musculoskeletal defects, limb reduction defects, missing/extra digits, clubfoot, craniosynostosis, facial defects, eye defects, orofacial clefts, gastrointestinal defects, and undescended testicles [17]. However, these associations have not been reported by others. Minor physical anomalies such as true ocular hypertelorism and

severe epicanthus have been reported in heavy users of cannabis, but there is a lack of a definitive relationship between physical anomalies and prenatal cannabis exposure in general [2]. Congenital anomalies had been reported in some cocaine-exposed infants, but larger recent studies have not documented those associations [48]. Infants exposed in utero to PCP have been reported to display microcephaly and alterations in facial features [40]. Isolated cases of cardiac defects, cleft lip, and biliary atresia have been reported in neonates exposed to methamphetamine [33], but these findings have not been found in other samples. There has also been inconstant reporting on the relative risk of congenital anomalies (orofacial clefts) among infants exposed to benzodiazepines [23]. Recent meta-analyses of maternal opioid use reported mixed associations between prenatal opioid exposure and congenital malformations [29]. Cardiac defects and oral clefts may be more common in opioid-exposed infants, although results of larger meta-analyses are inconclusive [29].

109.3.3 Neurobehavioral Effects of Substance Exposures

Neonates prenatally exposed to substances are at increased risk for a variety of conditions that can make adaptation to extrauterine life a challenge for the neonate and caregivers and can negatively alter the mother-infant interaction and/or the trajectory of development if not recognized and properly treated. There exist several conditions associated with prenatal substance exposure that become apparent during the neonatal period, such as the neurobehavioral alterations associated with NAS in opioid-exposed pregnancies. Developmental effects secondary to disruptions in brain maturation may not become clinically apparent until later in life and can be produced in the fetus at dose levels that are relatively harmless for adults. Postnatal factors such as nutrition, socioeconomic conditions, parenting practices, and exposure to adversity can further alter gene expression and modify infant brain development. Regardless of mechanisms of harm, children exposed to substances during pregnancy are at increased risk for a variety of conditions that portend future consequences. It is easy to comprehend the wide variation in infant outcomes from substance-exposed pregnancies with the myriad factors at play in these pregnancies (Fig. 109.1).

109.3.3.1 Neurobehavioral and Regulatory Problems

Each newborn has a particular repertoire of physiological and behavioral characteristics that depend on the maturation, organization, and regulation of at least four different interactive systems: (1) sleep/awake state control and attention,

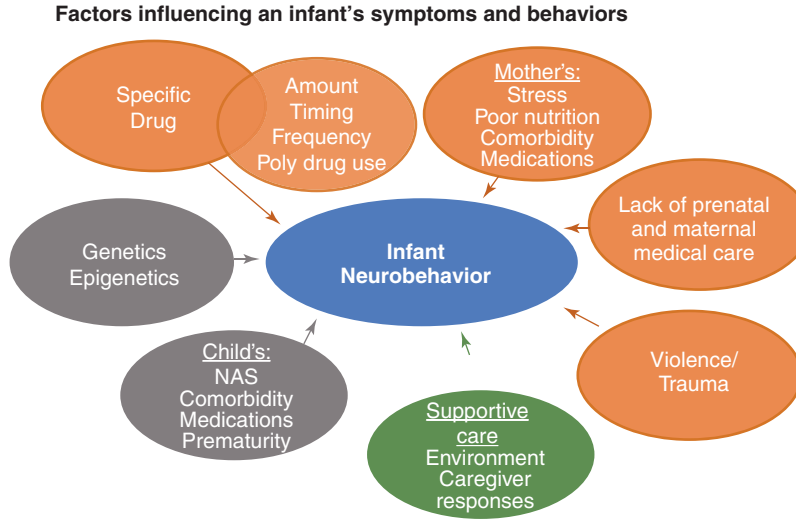

Fig. 109.1 Factors determining the effects of the prenatally exposed individual. These include maternal factors (drug use, medical care, stress), infant factors (including NAS and comorbid pediatric conditions such as preterm birth), and genetic/epigenetic and placental factors

(2) sensory integration, (3) motor/tone performance, and (4) autonomic control. The direct and/or indirect effects of substances on the fetus can negatively impact the newborn's functioning in one or more of these domains in an individualized way. The regulatory difficulties experienced by neonates can be assessed using the NICU Network Neurobehavioral Scale (NNNS) [45]. This scale, developed as neurobehavioral assessment tool for normal and at-risk infants, has been used to describe and evaluate how stressors, such as in utero substance exposure (cocaine, nicotine, marijuana, alcohol, methamphetamine, methadone, buprenorphine), affect infant self-organizing neurobehavioral capacities. Infants with compromised neurobehavioral functioning require early recognition and appropriate interventions for each domain of dysfunction to prevent problems related to feeding and organization of sleep-wake patterns, growth, acquisition of developmental milestones, and healthy child/caregiver interactions and communication. Such early recognition and intervention are crucial to facilitating a developmental trajectory toward more regulated, adaptive, and rewarding interactions.

109.3.3.2 Neonatal Abstinence Syndrome (NAS)

NAS is a group of signs and neurobehaviors experienced by the infant after discontinuation of gestational exposure to psychoactive substances taken by the mother. The symptoms associated with NAS include high-pitched cry/irritability, sleep-wake disturbances, alterations in motor tone and movement, feeding difficulties, gastrointestinal disturbances (vomiting, loose stools), autonomic dysfunction (sweating, sneezing, fever, stuffiness, and yawning), and failure to thrive. NAS is variable in its onset, severity, and types of symptoms presented, and typically associated with opioid withdrawal, yet other substances can produce an independent or synergistic withdrawal phenomenon (e.g., benzodiazepines). Opioid-induced NAS symptoms usually begin during the first four days of life with the clinical signs escalating over time as the drug is eliminated by the newborn. Polysubstance exposure, particularly opioids in combination with benzodiazepines, can result in more severe NAS expression that is induced by opioids alone [22].

109.3.4 Problems Related to Individual Substance Exposures

While consideration for the effects of individual substances may be important, most substance-exposed infants are polysubstance exposed, making these distinctions somewhat artificial. It should be noted that all of these substances pass through the placenta to the fetus, and all can be found in breast milk.

109.3.4.1 Alcohol

Alcohol is acknowledged as one of the leading human teratogens and is the top known cause of preventable neurodevelopmental disorders in Western society. Alcohol's effects vary depending upon timing of exposure, blood alcohol concentration, and patterns of maternal use. Although dose-related severity has been found, there are no evidence-based studies to suggest that any amount of alcohol use is safe during pregnancy. Women should be advised to abstain from drinking during pregnancy or while attempting to conceive, because it is not possible to predict which children will be affected by maternal alcohol use and how severely. The different categories of effects related to prenatal alcohol exposure are grouped under the nondiagnostic umbrella term "FASD." Four different groups of symptoms constitute FASD: fetal alcohol syndrome (FAS), partial FAS (pFAS), alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental disorder (ARND) (Fig. 109.2). If early detection and intervention for the neurocognitive and behavioral (e.g., self-regulation, adaptive, cognitive) deficits associated to FASD are not provided, secondary disabilities may arise during school/adolescence and adult life. In affected adults, the implications and effects of the disabilities resulting from prenatal alcohol exposure may involve troubles with the law, mental health problems, inappropriate sexual behaviors,

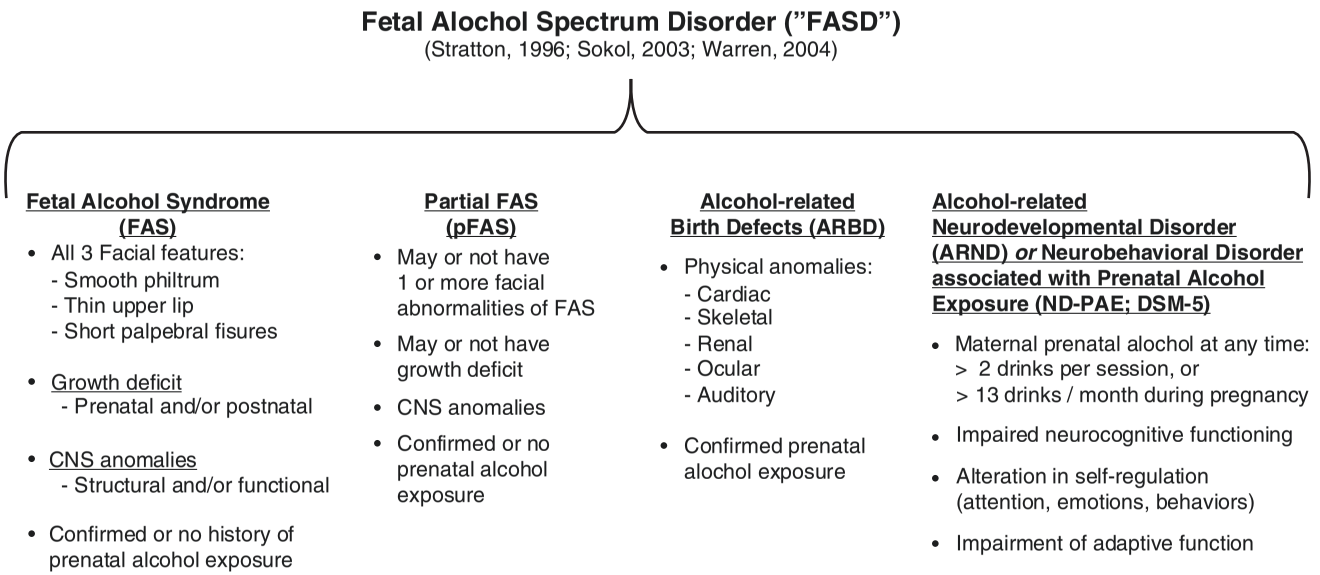

Fig. 109.2 Categories of effects related to prenatal alcohol exposure under the umbrella term of fetal alcohol spectrum disorder

SUDs, and problems with employment and dependent living. The magnitude of the health burden combined with the high prevalence of FASD makes the early diagnosis of and intervention for maternal prenatal alcohol use, in an effort to prevent damage to the developing fetal brain, a research and public health priority.

109.3.4.2 Cocaine, Methamphetamine, and PCP

Cocaine and methamphetamine are popular illicit stimulant drugs used recreationally worldwide, particularly among young adults in the US, Europe, and Australia. During the neonatal period, cocaine-exposed neonates display signs of disrupted neurobehavioral regulation including state lability, poor quality of movement and reflexes, hypertonia, deficits in orienting and attention, and increased irritability. Beyond the neonatal period, deficits in arousal regulation, hyperreactivity, and reduced emotional modulation and physiological responses to environmental stimulation during challenging tasks have been noted in cocaine-exposed infants. Other studies have reported behavior, language, cognition (including poor sustained attention), and motor function problems (for review, see Smith and Santos [39]). Some studies associate prenatal cocaine exposure with ADHD, oppositional defiance disorder, and future substance use.

Prenatal methamphetamine exposure has been associated with decreased arousal, increased physiological stress (e.g., difficulty maintaining normal respiration), and poor quality of movement. Neonates exposed to methamphetamine show reduced striatal and thalamus brain volumes and lower connectivity between the striatum, midbrain, orbitofrontal cortex, and limbic regions [48]. While research on the long-term effects of methamphetamine remains limited, similar to cocaine, ongoing longitudinal studies indicate that children at three and five years of age display more behavioral and emotional problems, including heightened emotional reactivity, anxiety, depression, and social withdrawal. Five-year-old children had more attention deficit-hyperactivity and externalizing behaviors, and by ages six to seven, methamphetamine-exposed children show reduced IQ and deficits in learning, memory, and motor coordination [39].

Neonatal neurobehavioral signs associated with antenatal PCP exposure consist of decreased attention, high-pitched cry, poor visual tracking, tremors, lethargy, nystagmus/roving eye movements, poor feeding, and altered reflexes [40]. Animal studies indicate that prenatal PCP exposure compromises neural proliferation and induces dysfunction in the brain's inhibitory GABAergic system, particularly in the prefrontal cortex, which may contribute to long-term behavioral consequences [44].

109.3.4.3 Nicotine

Neurobehavioral symptoms described in neonates exposed to nicotine include impairment of arousal, irritability and hyperexcitability, hypertonicity, and signs of stress/abstinence [27]. Smoking during pregnancy has been associated with increased risk of abruption, placenta previa, prematurity, low birth weight, and neonatal respiratory problems. Co-use of cannabis and tobacco smoking has been associated with smaller head circumference. Neurobehaviorally, prenatal nicotine exposure is linked to irritability and difficult temperament during infancy and poor self-regulation during childhood. Disorders of attention, externalizing behavior problems, and deficits in self-regulation, such as aggressive behavior and a higher risk of smoking, also occur in later childhood and adolescence [16].

109.3.4.4 Opioids

Long-term studies of children exposed to opioids are scarce, and most lack adequate control groups and have small sample sizes. Prenatal opioid exposure is linked to reduced brain volume in the striatum, thalamus, and cerebellum [38]. Hyperactivity and short attention span have been noted in toddlers prenatally exposed to opiates, and preschool children exposed to heroin demonstrated memory and perceptual problems. There is no consensus from available studies about the effects of opioids on cognition. Among infants born to women on methadone and buprenorphine treatment for opioid use disorder, no differences were observed in self-regulation or in sensory profiles compared to healthy controls [3].

109.3.4.5 Cannabis

Cannabis is the world's third most popular recreational drug used during pregnancy after alcohol and tobacco, and it is the most frequently used illegal substance during pregnancy in the Western world. Despite its popular use, there are few studies exploring the long-term effects of THC on the developing brain. Recent research has found that the endocannabinoid system plays a key role in prenatal and postnatal brain development, and activation by exogenous cannabinoids can permanently alter brain development. Use of cannabis during pregnancy is associated with low birth weight, increased need for neonatal intensive care, and abnormal infant cortical thickness [12]. Neonatal neurobehavioral effects of in utero cannabis exposure include changes in visual functioning, tremors, startling, jitteriness, difficulties with arousal, self-regulation, irritability, and excitability [10]. During the preschool years, deficits in verbal reasoning and short-term memory have been reported following prenatal THC exposure [9]. Adolescents prenatally exposed to THC may have impaired executive functioning (deficits in problem-solving, inattention, and impulsivity) [13].

109.3.4.6 Benzodiazepines

One of the most frequently prescribed classes of drugs during pregnancy, benzodiazepines also are commonly abused licit drugs, and exposure in infants often is unrecognized or ignored due to inconsistent screening policies. Signs of benzodiazepine withdrawal include hypoventilation, irritability, hypotonicity, and feeding difficulties, particularly after use in late gestation [37]. These symptoms can appear within a few days to three weeks after birth and can last for several months. Studies evaluating the neurodevelopmental effects on exposed children have yielded mixed results, with some reporting delayed motor development and neuropsychological symptoms [14]. More recently, protracted prenatal exposure to benzodiazepines (2+ trimesters) was associated with increased internalizing behaviors at 1.5 years and 3 years, suggesting long-term impact [5].

109.4 Identification of Pregnant Women with SUD

The periconceptual identification of the women with SUDs is necessary to provide SUD treatment and gynecologic/obstetric and other care as early as possible to prevent and/or mitigate the effects of substance exposures. The US Preventive Services Task Force, the American College of Obstetrics and Gynecology, and the American Academy of Pediatrics recommend that universal screening for substance use or misuse become a routine at any encounter with sexually active women and men of childbearing age. Stigma surrounding SUD creates enormous barriers to the treatment of pregnant women. Women often have difficulty acknowledging their problems with substance use, and professionals are reluctant to ask women about drug and alcohol use for many reasons, including lack of training or resources to adequately address an identified SUD. Pregnant women using substances are stigmatized by society and are perceived (and often view themselves) as having deviated from the traditional societal norms expected of women in their suitability as mothers and caregivers. Health-care providers may be explicitly or passively judgmental toward the woman causing her to be unreceptive to needed health care. Many states have punitive laws in place for pregnant women who use drugs. Such policies often contribute to patient unwillingness to admit substance use and missed opportunities for identification, education, support, and intervention. As a result, such women are likely to continue to use alcohol/drugs during their pregnancy, arriving at labor and delivery unregistered, with an increased risk of adverse maternal and infant consequences. Women face practical and financial barriers to accessing treatments that are gender specific, such as the need for adequate child care.

109.4.1 Identification of Women at Risk for SUD During Pregnancy

There are essentially two methods of screening for SUDs that can be used during the preconcep-

tion and prenatal periods: maternal interview/self-report and biologic specimen testing.

109.4.1.1 Maternal Interview Screening

All pregnant women, regardless of socioeconomic status and/or any perceived risk, should be asked about past and current licit and illicit substance use or misuse. A high index of sensitivity for substance use combined with an open-ended, nonjudgmental, and repeated questioning of pregnant women is therefore necessary to reduce reluctance to admission to use. There are several structured questionnaires that can be used during the prenatal period, although a majority are specific to alcohol (see Table 109.1). For example, the full AUDIT instrument, the abbreviated AUDIT-C, and single-question screening ("How many times in the past year have you had five [for men] or four [for women] or more drinks in a day?") have the best performance characteristics for detecting the full spectrum of alcohol misuse. Screening, Brief Intervention, and Referral to Treatment (SBIRT) is an evidence-based practice used to identify, reduce, and prevent SUDs in different settings.

Table 109.1 Screening tools for maternal substance use during the prenatal period

Instrument	Purpose
Alcohol use disorders identification test (AUDIT-C)	Screening for excessive alcohol use or alcohol use disorder
Cut down, annoyed, guilty, eye-opener (CAGE)	Potential problems with alcohol
Cannabis use disorder identification test (CUDIT-R)	Screening for excessive cannabis use or cannabis use disorder
Drug abuse screening test (DAST)	Screening for abuse of drugs other than alcohol
Michigan alcohol screening test (MAST)	Identification of heavy drinking or alcohol dependence
Pregnancy information program (PIP)	Assessment of stress, diet, alcohol, tobacco, and illicit drug use during pregnancy
Substance use risk profile-pregnancy (SURP-P)	Detection of alcohol or illicit drug use during pregnancy
Tolerance, annoyance, cut down, eye-opener (T-ACE)	Identification of risk drinking during pregnancy
Ten-question drinking history (TQDH)	Brief questionnaire for identification of alcohol abuse
Tolerance, worry about drinking, eye-opener, amnesia, K/Cut down (tweak)	Brief questionnaire for detecting alcohol problems during pregnancy
4P plus (parents, partner, past, pregnancy)	Screening for tobacco, alcohol, or illicit drug use risk during pregnancy

109.4.1.2 Biologic Specimens

The use of biologic specimens to screen for substance use or misuse has inherent difficulties. These methods do not give information about use patterns, are variably accurate depending on substances screened for and type of testing used, and can cause unintended legal consequences. Maternal and neonatal urine screenings obtained at the time of birth are most commonly used and have the lowest cost but only provide information about use in the last part of gestation (exceptions to this are chronic marijuana exposures; the metabolites of which can be excreted for as long as ten days in the urine of regular users and 15 or up to 60+ days in chronic, heavy users; and benzodiazepines, which can be present in urine up to 30 days), have low sensitivity, and have no role in mitigating the effects of substance exposures during pregnancy. Meconium analysis is more sensitive and supplies information about use in the second and third trimesters when meconium is formed but does not reflect periods of drug abstinence closer to delivery and as such may be harmful to women who access treatment and avoid use in the third trimester. Meconium may be difficult to collect and has high false-positive rates, and its passage may be delayed, particularly in premature infants, delaying the diagnosis. Umbilical cord testing is available but may be less sensitive than meconium [7]. Prior to testing, clinicians must be aware of legal requirements and the need for consent, which vary by state in the US. Hospital policies should comply with local laws and avoid discriminatory practices.

109.5 Identification of the Individual Exposed Prenatally to Substances

To date, there are no biologic markers to confirm or refute with certainty a syndrome or phenotype of children with problems related to PSE. This is a diagnosis of exclusion based on medical and alcohol/drug exposure history together with suggestive clinical signs. Infants with a suspected diagnosis of substance exposure and/or NAS should be evaluated using a scoring system such as the Finnegan Neonatal Scoring System (for opioid exposure) [24]. For children beyond the neonatal period, there are nonspecific situations that can indicate suspicion of PSE in the absence of known causes, which include developmental delays, sensory integration problems, emotional and behavioral problems, poor academic performance, or specific deficits in functioning of the child (Fig. 109.3). The diagnosis of problems related to PSE is complex. Because it carries life-long consequences, early recognition and treatment can result in a better outcome for the child that receives a diagnosis.

Underdiagnoses or overdiagnoses of any condition related to prenatal substance exposure are not beneficial for the child or the family. The clinician should rule out alternative or coexisting diagnoses of any suspected problem related to prenatal exposure to substances. Individuals with FASD are frequently misdiagnosed. There are other disorders such as ADHD, ADD, ODD that can have similar symptoms or can co-occur with any of the FASD categories. The formal identification of an FASD requires a qualified team and/or dysmorphologist. Individuals with an FASD group of symptoms require an early diagnosis to obtain the intensive and personalized services that may improve the outcomes and avoid secondary disabilities. For a review of guidelines for diagnosing FASD, see the recent update by Hoyme and colleagues [21].

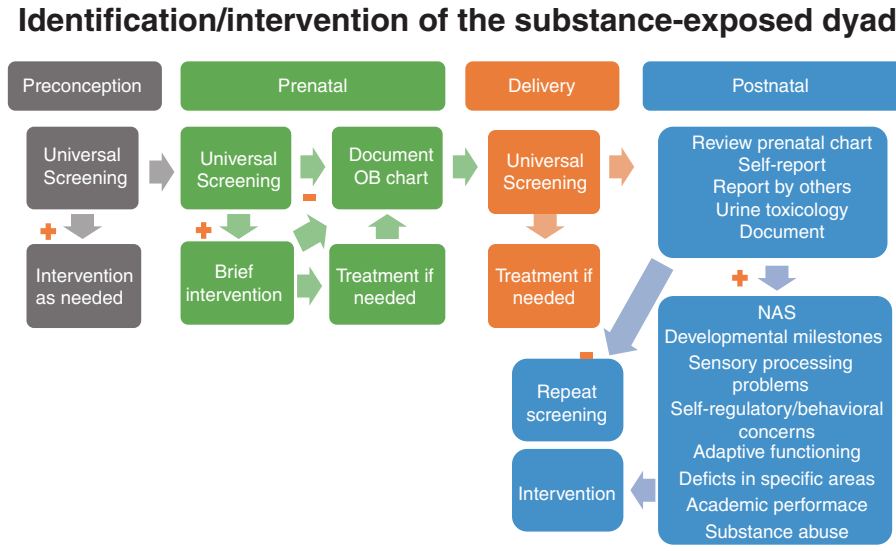

Fig. 109.3 Identification of the childbearing woman who uses/abuses substances should occur at several points during preconception, gestation, and at birth and be multipronged to include universal screening, review of the medical and social history, and maternal interview screening (Table 109.1), as well as evaluation of the infant/child

109.6 Interventions for Pregnant Women with SUD and Their Children

109.6.1 Preconception and Prenatal Counseling

Early pregnancy detection and first trimester prenatal care increase the chances of having a healthy pregnancy and baby. Women with a positive screening for substance use or misuse can receive brief intervention(s) or be referred to a comprehensive diagnostic evaluation and intervention. This process can be facilitated by using the principles of motivational interviewing. Brief interventions include short counseling sessions, feedback, advice, and goal setting conducted by health-care providers. Brief counseling has demonstrated efficacy in reducing the amount of drinking in pregnant women.

Pregnant women with SUD should receive a multistep management approach that includes comprehensive individual and/or group therapy concerning the adverse maternal and fetal/newborn impact of continued substance use. Referral to a multidisciplinary team for drug rehabilitation and a high-risk pregnancy specialist for ongoing fetal surveillance should occur; referrals may include counseling to deal with preexisting trauma and/or psychiatric comorbidity and assistance with other social determinants of health (e.g., housing; Fig. 109.4). Partner and/or family participation in prenatal care and SUD treatment is important to the woman's recovery; partner active drug use has been associated with delayed treatment time for pregnant women seeking care. Comprehensive care that is trauma informed and gender specific, including medical health care and developmental and behavioral assessments for existing children, should additionally be incorporated into the care plan for any parenting woman.

109.6.2 Treatment During Pregnancy

SBIRT gives health-care providers skills to discuss health behavior changes with their patients and can be effective at motivating individuals to

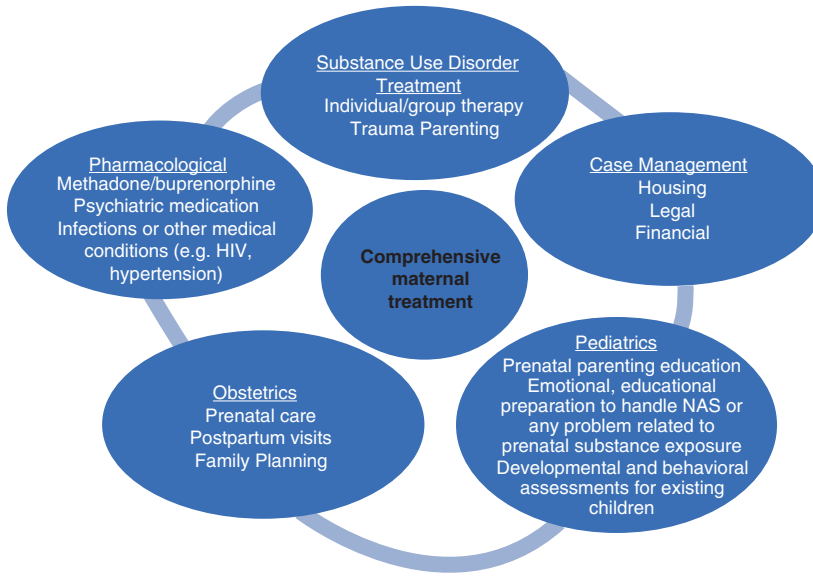

Fig. 109.4 Comprehensive treatment of the pregnant woman with an SUD. Treatment of the pregnant woman who uses/misuses substances should be comprehensive, trauma informed, and gender specific in nature and incorporate behavioral treatment; medical/obstetric/psychiatric care with pharmacologic treatment, including methadone or buprenorphine maintenance, as warranted; and the identification and provision of social support structures

change harmful substance use. SBIRT has three components: (1) screening to determine the severity of substance use, (2) brief intervention to build motivation through supportive conversation, and (3) referral to treatment directly linking the patient with needed services. Documentation of the interview and confirmation or not of maternal substance use should be recorded and transferred to appropriate health-care providers (i.e., anesthesiologist, pediatrician) to ensure a continuum of care.

Any pharmacologic treatment during pregnancy requires a clear and thorough discussion of the risk-benefits of the medication between the health-care provider, the mother, and the significant other when appropriate. Pharmacologic treatment for pregnant women with SUD includes medications for medical problems (i.e., HIV, hypertension), psychiatric comorbidities, and medications for opioid use disorders (OUDs). Daily methadone or buprenorphine treatment reduces the risk of relapse, increases retention in obstetric and SUD treatment, and may improve lifestyle for women with OUD by reducing criminal activity and avoiding risks associated with a drug culture, including those associated with drug seeking, overdose, and death. Both medications must be viewed as a central aspect to treatment but should be given as part of a comprehensive treatment approach that also includes obstetrical care, medical care, case management, life and parenting skills, and counseling. Although the benefits of treatment with methadone and buprenorphine are well known, many infants exposed to these medications develop NAS.

New non-pharmacologic treatment options for pregnant women with SUD have begun to emerge. These treatment options convey the advantage of not directly impacting perinatal development via exposure in utero or during breastfeeding, but studies to date are limited and efficacy remains to be demonstrated in large sample sizes. One such option is repetitive transcranial magnetic stimulation to the prefrontal cortex (rTMS), which has shown promise in the treatment of cocaine, alcohol, and nicotine use disorders [18] as well as depression during pregnancy [20].

Digital interventions, delivered via cell phones, computer software, Web pages, and "telepsychiatry" or social media, have also shown efficacy in reducing substance use [31], but these interventions have not yet been tested in pregnant women with SUD, and larger studies with adequate control groups are needed.

109.6.3 Postpartum Care of the Woman with an SUD

Comprehensive postpartum follow-up for pregnant women with SUD is necessary, with appropriate referrals to a primary care provider (OB providers for postpartum check and contraception, pediatric providers for the infant and existing children, and general medicine provider for the mother), psychiatrist if needed, and social services when warranted to ensure that the newborn has a safe home environment. While opioid overdose rates decrease during the second and third trimesters due to the availability of prenatal care for pregnant women with SUD, overdose deaths increase significantly within the first 7–12 months after birth, in part due to the paucity of health-care resources available for postpartum women as well as the stressors involved in caring for an infant. Working to ensure that women with SUD engage in safe sex practices and have acceptable contraception is a constant challenge; this population is disproportionately overrepresented among women with unplanned pregnancies and sexual violence.

109.6.4 The Mother/Child Dyad: Postnatal Period

All substance-exposed dyads should receive non-pharmacologic supportive management beginning at the time of infant birth and continuing throughout the hospitalization and beyond regardless of the infant's need for medication for NAS. These interventions are designed to (1) individualize the understanding and care of the infant, based on behavioral observations, with the goal of promoting organi-

zation, physiological stability, and competence; (2) modify the environment to support organized sleep/awake patterns and autonomic, sensory, motor, and attention/interactive development; and (3) encourage parental involvement with their infant [47].

An infant with opioid exposure should be hospitalized for a minimum of 72 hours for evaluation and identification of symptoms that may need pharmacologic treatment for NAS. This evaluation can be done using the Finnegan scoring system or a variant of it. These tools are applied every 3–4 hours for the infant's entire hospitalization. Medications most frequently used to treat the opioid-exposed infant are morphine sulfate and methadone. Breastfeeding is not contraindicated in many women with SUD who are able to access treatment, which may include methadone or buprenorphine maintenance, and who achieve sobriety and have no other medical contraindications to lactation. Each dyad should be individually assessed regarding their suitability for breastfeeding [24].

The primary care pediatrician has an important role in addressing PSE, which includes ongoing assessment of the infant, his caregivers, and his environment. This includes (1) assistance with maternal difficulties surrounding her substance use/misuse and awareness of how those difficulties impact the health and development of the child; (2) identification of infant/child difficulties related to exposures or parenting styles; (3) evaluation and interventions of the child for situations related to current or past parental SUDs such as violence exposure, relapse, and untreated psychiatric comorbidity; and (4) frequent and careful medical and developmental follow-up of the substance-exposed infant to child to teen. Mothers of substance-exposed children may be afraid to seek evaluations of the child when they have concerns (i.e., assessment for problems related to FASD) for fear of being labeled a "bad" or incompetent parent or due to her own difficulties dealing with guilt if the child's problem might be due to PSE. Judgmental or punitive health-care provider attitudes will cause further reluctance on the mother's part to engage in necessary health care. Neurodevelopmental, behavioral, academic, and emotional problems in childhood related to PSE can have both lifelong and intergenerational effects. Identifying and addressing these concerns early in life is essential, not only for the individual child and his/her parent(s) but to break the multigenerational cycle of SUD and victimization that often exists in substance-using families. In these cases, pediatricians must be able to step out of their traditional role as health-care provider to the child only to recognize and address the issues that are of critical importance to pediatric health, namely, issues that involve principally the parent and the environment created by parental difficulties with SUD.

Substance-exposed children and their mothers may have disabilities that can range from subtle to serious, with affected individuals presenting variable combinations of emotional regulatory deficits; deficits in memory, information processing, social skills (including pragmatic language and social communication skills), attention, and executive functioning; as well as significant emotional-behavioral and mental health issues. As a result, the interventions for a child, adolescent, or adult affected by prenatal exposure and his/her family vary according to these factors. Interventions designed to address neurodevelopmental problems associated with substance exposure require multidisciplinary assessment and care that is individualized and unique to the dyad, coordinated, compassionate, and comprehensive.

109.6.5 Parenting by the Mother with an SUD

The promotion of resilience in a substance-exposed child faced with the biologic vulnerability created by prenatal exposures depends upon the availability of parenting adults who can help children develop effective coping skills necessary to restore physiological and behavioral homeostasis and reduce disruptions in their developing brain circuitries. Essential to this process is the capacity of the parent to provide buffering protection for the children's developmental progress

through their own skills which include parental self-awareness, self-control, problem-solving, empathy, monitoring, and self-regulation. These skills areas are frequently underdeveloped or altered in one or both parents with SUD. The likelihood is, therefore, relatively low that these skills will be sufficiently strengthened by the simple education about child development or parenting recommendations. Training or coaching strategies that center on the parental skill set that includes executive functioning, emotion regulation, and social abilities offer a promising new direction that is worthy of investigation, especially for parents whose needs are not sufficiently addressed by existing support. An example of this mother/child model may be found in the "Mothering from the Inside Out" program [43]. In this model, mothers struggling to manage their SUD as they also parent their children participate in therapy focusing on problem-solving and coping emotionally with the everyday stresses of being a mother. This program is founded on an attachment-based intervention, which focuses on building reflective functioning in the mother and her capacity to attend to her own and her child's mental states, in order to promote secure attachment and emotional development in the dyad. These services are offered in conjunction with outpatient SUD treatment for the mother. Mother/child interaction is facilitated by a developmentally trained child care team, and the treatment center functions as a milieu that facilitates the dyad's regulatory functions.

109.7 Summary and Conclusions

In summary, the prevalence of use/misuse of substances among women before, during, and after pregnancy remains a major public health concern and constitutes one of the most common preventable causes of child morbidity. There are several key points the reader should take away from this chapter.

- PSE can disrupt fetal neurotransmitter systems, brain circuitry, and other important regulatory systems in ways that continue to influence physiology, behavior, and health at birth or decades later.
- It is of extreme importance to raise awareness of the impact of prenatal alcohol/substance use and to encourage the use of effective screening tools to reduce the incidence of problems related to PSE, which can profoundly impact not only the individual and the family but the health-care, education, and legal systems in our society.
- Any health-care professional in contact with a childbearing-age or pregnant/parenting woman and/or her child plays a critical role in screening for substance use during pregnancy and initiating appropriate interventions, as well as in the early diagnosis and ongoing treatment of children affected by PSE both biologically and environmentally.
- Although identification and intervention for women and children affected by PSE is critical, primary preventions (reducing the number of women of childbearing age who abuse legal and illegal drugs) and secondary preventions (recognizing and reducing the use of drugs substances among pregnant women) are also necessary. Inclusion of repetitive counseling to abstain from alcohol and other substances, including marijuana, nicotine, and misuse of prescribed drugs for women in the perinatal (preconception, pregnancy, parenting mother) health examinations is essential.
- Women of childbearing age and the general population must be informed that no safe level of alcohol or illicit drug consumption during pregnancy has been established and educated about the risks of misuse of licit substances.
- Services that enhance the mental health, executive function skills, and self-regulation capacities of vulnerable mothers should exist, with a focus on de-stigmatization. Few inclusive services exist, and such programs must include the child or at a minimum consideration for the child.
- A gold standard of care for the substance-exposed dyad must be established beyond the postpartum period, from the prenatal period through the first several years of the child's life. Only through the cooperative investment

of providers of all specialties in the well-being of the dyad can truly meaningful intervention take place for these high-cost, high-risk families. SUD treatment that is available, non-stigmatized, gender specific, and trauma informed that includes the child(ren) should exist for all pregnant women with SUD.

- Research funding should seek to prioritize the examination of optimal care for both mothers and children, examine the short- and long-term outcomes for the substance-exposed dyad, and establish effective measures to maximize healthy trajectories for both maternal recovery and the infant's neurodevelopment.

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