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Comorbid Mood, Psychosis, and Marijuana Abuse Disorders: A Theoretical Review

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ABSTRACT. There is a need to bridge the gap between the fields of addiction psychiatry and general psychiatry to effectively treat co-morbid substance abuse and psychiatric disorders. This alarming epidemic transcends communities and severely impacts healthcare worldwide, yielding poor treatment outcomes and prognoses for afflicted patients. Because substance abuse can exacerbate or trigger psychosis and mood disorders, it is important to keep these issues in the forefront when evaluating patients. To address some of the complications stemming from not enough interactions between various groups of practitioners, this review addresses the neurobehavioral effects of cannabis use and their impact on patients who suffer from psychotic or affective disorders. The hope is that this article will serve as a spring board for further discussions among practitioners who treat these patients. Greater interactions between caretakers are bound to impact the care of our patients in a very positive way.

KEYWORDS. Addiction, cannabis, neuropsychiatry, depression, schizophrenia

INTRODUCTION

Substance abuse and dependence pose major clinical and public health concerns among psychiatric patients. Although epidemiological studies have documented the prevalence of co-morbid diagnoses in the general population, medical professionals and society remain ill-equipped to manage these problems. These issues are compounded by the high cost of treatment and relapse rates observed in patients. Fundamentally, an approach integrating pharmacologic, psychosocial, and psychotherapy is ideal; however, only recently have scientists begun to focus attention on the neurobiological underpinnings of co-morbidity. It has been reported that patients who suffer from either psychiatric diathesis or substance abuse disorders also show cognitive impairments that are associated with brain functional and morphological abnormalities. The aim of this article is to review the clinical neuropsychiatric underpinnings of the co-morbidity of marijuana abuse, affective, and psychotic disorders. This background is used to provide a theoretical framework from which to address the treatment of these co-morbid states.

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CANNABIS ABUSE

Introduction

Marijuana is the most prevalently used illicit substance with a minority of users indicating daily use and dependency.[1] In fact, 1.6 million marijuana users met the criteria for substance dependency according to the *Diagnostic and Statistical Manual for Mental Disorders* (DSM)-IV in 2000.[2–4] Marijuana dependence, like other substance dependence disorders, is associated with cognitive, behavioral, and physiological effects including the cannabis withdrawal syndrome.[4–7] The clinical effects of marijuana are due to the active ingredient, Δ^9 tetrahydocannabinol (THC), contained in marijuana.[5,8] THC mimics the action of natural cannabinoids that the body produces and binds to cannabinoid receptors, CB_1 and CB_2, but namely CB_1.[9] CB_1 and CB_2 are found in several brain regions including the frontal cortex, striatum, and hippocampus.[10–12] The localization of these receptors might account for the clinical presentation of marijuana abuse. Neuroanatomical findings show, that CB_1 interacts with dopamine, specifically D_2, coexists in several brain regions, and modulates the function of dopamine.[13–16] This interaction manipulates motor activity, endocrine regulation, appetite, learning, memory, cognition, mood, and pain perception.[17,18] However, the underlying molecular mechanisms of cannabinoid and dopaminergic interaction remain poorly understood.

Clinical Neuropsychiatry

Until recently, marijuana use was considered harmless and generally associated with feelings of euphoria, detachment, and relaxation.[19] However, the accumulated evidence suggests that chronic marijuana users experience acute adverse mental effects.[4–7,19] with a range of short-lived signs and symptoms that include depersonalization, derealization, irrational panic and paranoia, and feelings of loss of control and fear of dying.[20] Although many of these adverse reactions are usually transient, they tend to persist or recur among regular users.[20] Additional adverse effects include cannabis psychosis,[21] amotivational syndrome,[22] and cannabis withdrawal syndrome, which consists of anxiety, irritability, physical symptoms such as muscular pains, chills, and difficulty sleeping. Patients also suffer from decreased appetite, decreased food intake and weight loss.[23] Such withdrawal symptoms have been noted in several treatment projects.[24–28]

Cognitive Effects

Imaging data correlating cognitive performance with marijuana show decreased cerebral blood flow in the auditory cortex and left superior temporal gyrus regions on task of dichotic listening for meaningless syllables in individuals with a history of moderate use.[29] On a visual attention paradigm, decreased activation in the right prefrontal, medial, and dorsal parietal cortices and medial vermis of the cerebellum were detected in both abstaining and active marijuana users when compared to control subjects.[30] Additional data show that marijuana use is associated with subtle cognitive impairments and the activation of the frontal lobe, dorsolateral prefrontal cortex, and the hippocampus, which are brain regions linked to executive function, working memory, and manual dexterity.[31–35] Conversely, data exist that show no cognitive deficits associated with marijuana use. For example, Jager et al.[36] found no evidence of working memory or selective attention deficits among cannabis users during 1 week of abstinence. In fact, no significant differences on tasks of visuoauditory and verbal working memory were observed between users and non-users.[36] Moreover, research is uncertain regarding the long-term cognitive effects of marijuana use. For instance, some studies show no recovery after a month of abstinence,[35,37–38] whereas others report full recovery[39] or show partial recovery.[40]

Neuroimaging Studies

CB_1 receptors are distributed heterogeneously in the central nervous system,[41] with elevated concentrations found in the neocortex, thalamic nuclei, limbic regions, basal ganglia, and cerebellar cortex.[10] Thus, by activating the presynaptic cannabinoid receptor CB_1,

a spectrum of functions are manipulated.[17,18] Global cortical effects of marijuana have been documented, including global cerebral glucose metabolism after infusion of THC,[42] increased cerebral blood flow in frontal regions with greater increases detected in the right hemisphere among individuals reporting a history of use,[43] lower volumes of ventricular cerebrospinal fluid among users when compared to controls,[44] denser grey matter in the parahippocampal gyrus, denser white matter in the left parietal lobe among heavy users compared to non-users,[45] elevated systolic and mean blood flow velocity in the middle cerebral artery and the anterior cerebral artery, and higher pulsatility index in both the middle cerebral artery and anterior cerebral artery.[46]

BIPOLAR DISORDER

Overview

Bipolar disorder is a chronic psychiatric condition; 2% of Canadians and 3% of Americans meet formal criteria for the disorder.[47,48] Current estimates of lifetime prevalence of bipolar disorder range from 3% to 6.5%.[49] Prevalence rates are higher among women, individuals with comorbid neurological conditions, and adults who are separated, divorced, or widowed.[49] This disease is often associated with premature mortality,[50] profound functional impairments,[51] and substantial treatment cost.[52] However, with proper treatment and diagnosis, bipolar patients are more likely to adhere to medication regiments, respond to short-term treatment, and experience fewer relapse episodes.[53]

Clinical Neuropsychiatry

Bipolar disorder is characterized by recurrent episodes of acute mania, depression, and mixed emotions. Depressive signs include unintentional weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, loss of feelings of worthlessness or excessive guilt, impaired concentration or indecisiveness, and recurrent thoughts of death or suicide ideation.[6] Manic signs include inflated self-esteem, decreased need for sleep, talkative or pressured speech, flight of ideas, distractibility, psychomotor agitation, and increased probability of risking behaviors resulting in pain.[6] Typically manifesting during late adolescence or early adulthood, bipolar disorder is often triggered by stress.

Cognitive Effects

Cognitive deficits in patients diagnosed as bipolar include psychomotor slowing and memory and concentration impairments.[54] These patients also have difficulties encoding information on verbal learning tasks.[55] Patients diagnosed as bipolar performed poorer and made more errors of omission than unipolar patients on sustaining attentional measures.[56] Additional differences have also been observed among the various episodic states. For example, visuospatial deficits and other cognitive impairments observed among patients diagnosed as bipolar have been attributed to mood state.[57] However, research is unable to consistently link cognitive deficits to state factors in patients diagnosed as bipolar.[58]

Neuroimaging Studies

Abnormalities in the anterior limbic networks including the dorsolateral prefrontal cortex, anterior cingulate, amygdala, hippocampus, striatal enlargement, cerebellar atrophy, and ventriculomegaly have been reported in the brains of patients diagnosed as bipolar.[59–61] Smaller subgenual prefrontal cortex has been reported in bipolar patients with a family history of affective illness.[62] This region works in concert with cingulated and other anterior limbic regions to perform integration of cognitive and emotional information integration.[62] Functional imaging data show regional hyperfusion in left frontal and temporal lobes[63] and increased metabolism. Perfusion in temporal structures and prefrontal cortex have been documented in patients functioning in various episodic states.[64,65] Recently, Agarwal et al.[63] have reported that patients diagnosed as bipolar show inverse frontal asymmetry index.

SCHIZOPHRENIC DISORDER

Overview

Schizophrenia is a complex disorder affecting nearly 1.1% of Americans a year.[66] It is among the most expensive diagnosis in medicine, accounting for 2.5% of U.S. healthcare expenditure.[67,68] Per patient, treatment has been estimated to cost $25,940 USD annually, with the majority of monies allocated for nursing home care while the residual expenditure funds ambulatory services, psychotherapy, acute hospital care, prescription drugs, and psychiatric hospital care.[69] In fact, patients with schizophrenia occupy 20% to 25% of available beds in psychiatric hospitals.[68] The dopaminergic hypothesis implicates the dopaminergic system in the pathophysiology of schizophrenia.[69] Currently, the schizophrenia disorder paradigm speculates that the mesolimbic, mesocortical, and nigrostrial dopamine neurons are slightly overactive, increasing delusional and hallucinating symptoms and various cognitive deficits in patients with schizophrenia.[70]

Clinical Neuropsychiatry

Schizophrenia disorder usually manifests during late adolescence and young adulthood. Clinical signs and symptoms are categorized as either positive or negative. Positive symptoms encompass auditory hallucinations, delusions, disorganization of speech, and movement disorders, whereas negative symptoms encompass flat affect, poverty of speech, and other deficits.[6] Negative symptoms are often misinterpreted as laziness or depression.[66] In severe cases, the disease fuels the most basic functions and allows the individual to feel quintessential possessing irrational beliefs without any basis in reality.[71] Given this, many schizophrenic patients experience adverse social and emotional consequences.

Cognitive Effects

Several studies have documented cognitive deficits in patients who suffer from schizophrenia.[72–79] These include problems with language comprehension, learning and reasoning,[72–74] deficits in tests of visuospatial performance.[75] Schizophrenic patients also have deficits in tests of attention, concentration, set shifting as well as concept formation.[76–79] Additional studies have linked performance deficits to disorganization syndrome in patients with schizophrenia on task of cognitive deficits with shifting set and interference tasks.[80–82] Syndrome dimensions reflecting psychomotor deficits have been linked to verbal fluency and memory measures.[81,83–85] O'Leary et al.[86] showed a relationship between cognitive deficits and disorganization and negative syndrome. However, the patterns of negative syndrome were significantly different from patterns of disorganization syndrome, which suggest different neurobiological substrates between the two dimensions.[86] When correlating cognitive performance on executive functioning tasks and cerebral blood flow, data show lower cerebral blood flow in the prefrontal regions on the Wisconsin Card Sorting Task,[87] lower frontal activation,[88] and alterations in mean flow velocity in patients with schizophrenia during the Wisconsin Card Sorting Task,[89–91] Tower of Hanoi,[89] and Stockings of Cambridge.[92]

Neuroimaging Studies

Converging neuroanatomical evidence presently suggests that schizophrenic patients suffer from major morphological abnormalities in their temporal lobes.[93] In addition, other studies implicate the enlargement of lateral ventricles,[94] reduction in prefrontal lobe volumes,[93] altered inferior parietal cortex, basal ganglia, thalamus, corpus collosum or enlargement of septum pellicidum,[95–96] reduced cortical folding, and loss of normal asymmetry.[95] Although the nature of the underlying mechanism involved in the pathophysiology is unclear, evidence suggests neurodevelopmental lesions resulting in brain abnormalities, neurodevelopmental abnormalities interacting with biochemical factors such as hypothalamopituitary-adrenal (HPA) axis dysregulation,[97] adverse effects of stress,[98] poor diet and exercise,[97] and brain alterations attributed to antipsychotic extrapyramidal effects.[99] Additional neuroimaging studies show left dominance

hyperperfusion in both the middle and anterior cerebral arteries in acute schizophrenia[99] and increased global cerebral perfusion,[100] increased cerebral blood flow volume in first episode acute schizophrenia,[101] and impairment of frontal regional cerebral blood flow or regional glucose metabolism when compared to controls.[102–104] Abnormal regional cerebral blood flow has also been reported in the temporal lobes[99]; while some report increased metabolism in the basal ganglia,[102,104] others report no difference.[99,105]

COMORBIDITY OF MARIJUANA ABUSE AND PSYCHIATRIC DISORDERS

Overview

The prevalence of substance abuse among individuals with pervasive psychiatric diagnosis is an increasing concern.[106–108] In the United States alone, aproximately 47% of patients with schizophrenia and 61% patients diagnosed as being bipolar report higher rates of substance abuse than the general public.[109] Among individuals living with a psychiatric diagnosis or at risk for developing a psychiatric diagnosis, a spectrum of negative symptoms are generally associated with illicit drug use.[110] Moreover, evidence suggests increasing mortality rates among comorbid patients associated with obesity, cardiovascular, and respiratory issues.[111–114] Comorbidity is associated with poor treatment compliance, higher rates of drug relapse, violent behaviors, unstable housing, and homelessness.[115–118] Thus, developing reliable and accurate methods of assessing and treating comorbidity is critical when developing effective paradigms for patient care.

Clinical Neuropsychiatry

Data suggest a kindred relationship between neurologic conditions and substance abuse, more specifically the cannabinoid system.[119,120] In fact, the endogenous cannabinoid system modulates the dopaminergic system, which is involved with the networks regulating motor control, emotional response, and cognitive processes in schizophrenia disorder[121–122] and characteristics of depression.[123] Comorbidity is associated with increased suicidal risks,[124] impulsive or aggressive behavior,[125] and poor clinical prognosis,[126] with marijuana use exacerbating psychopathology in both schizophrenia and bipolar disorder.[127–128] However, depressed patients report using marijuana to reduce duration of depression[129] and counteract adverse antidepressant effects.[130,131] Schizophrenic patients report using marijuana to "self-medicate" extrapyramidial effects of neuroleptics and to relax, feel good, and stimulate social interaction.[132–135] These explanations for self-medicating are extremely subjective, biased, and rely on self-reports, which is ironic because denial and rationalization both play a crucial role in drug abuse.[136,137]

Cognitive Effects

Liraud and Verdoux[138] concluded that comorbid marijuana use and psychotic or mood disorders compromised cognitive functioning on a test of inhibition. Pencer and Addington[139] found during a 1-year follow-up that marijuana use correlated with poor performance on category naming among first psychotic episodic patients. Conversely, first psychotic episode patients with a history of marijuana use outperformed non-using first psychotic episode patients on task measuring memory, verbal fluency, visual spatial construction, sequencing, and facial recognition[140,141] and on tasks of emotion-based decision making.[142] Although marijuana use in bipolar patients has not been extensively researched, it is believed that marijuana use would exacerbate cognitive deficits.[143]

Neuroimaging Studies

Studies show less anterior grey matter in first episode patients with schizophrenia who used marijuana compared to non-using and healthy controls.[144] More prominent gray matter density and volume reduction in the right posterior cingulated cortex have been reported in first episode schizophrenics who used marijuana when compared to controls and marijuana naïve patients with schizophrenic.[145] Pronounced reduced brain volume over a 5-year follow-up have

been reported in patients with schizophrenia who are using marijuana compared to their non-using counterparts.[146] Higher serum of nerve growth factor have also been reported in patients with schizophrenia who used marijuana compared to non-using patients with schizophrenia.[147]

Marijuana use increases the risk of developing schizophrenia disorder or depressive mood disorders later in life.[148,149] Given this, age of initial use may be critical in understanding structural abnormalities in comorbid patients. However, this possible relationship between early use and diagnosis poses obstacles when determining whether functional abnormalities in comorbid adults should be attributed to substance use or to biological predisposition of the psychiatric disorders. Additionally, to generalize adolescent findings to adults, researchers must consider adolescent neuromaturation. Nonetheless, it is quite likely that marijuana abuse might exacerbate the functional and structural brain abnormalities that have been documented in psychiatric patients.

CONCLUSION

Over the past two decades, a high prevalence of marijuana use has been reported among individuals suffering with psychotic and affective disorders. The present review of the literature on co-morbid diagnoses suggests that there are major problems in elucidating the specific relationships between psychiatric disorders and substance use disorders when applying DSM-IV guidelines for diagnosing co-morbid disorders and pharmacological approaches to the treatment of these disorders.[150–152] Despite substantial research gathered on co-morbid diagnoses, much remains to be done to understand the neuropathological substrates of these disorders. Because experts from various fields have not come together, it has been somewhat difficult to understand the initial impact that marijuana use might have on affective and schizophrenic disorders. For example, how does marijuana exacerbate clinical symptoms like psychosis and depression? Are these related to cannabis-induced compromised neurobehavioral performances, cerebral perfusion, and electrophysiological alterations.[153,154] Unfortunately, there is little written on the underlying mechanisms that contribute to the functional impairments of patients with comorbid diagnoses. Possibly, this gap has a lot to do with bridging diagnoses and treatment effectiveness. Thus, allocating more research funds to this major public health issue will heighten awareness and, potentially, revolutionize the care of these patients.

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