Chapter 24

Adverse effects of marijuana

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ABSTRACT

Marijuana is a complex substance with many potential physical and neuropsychiatric adverse effects. Acute physical effects include tachycardia, decreased task performance, and reduced cerebral blood flow. These effects may be particularly dangerous if the user is driving a car, operating machinery, or has certain pre-existing medical problems (such as cardiovascular disease). Acute neuropsychiatric effects may include paranoia, changes in libido, altered time and sensory perceptions, and others. Chronic marijuana use may lead to adverse effects on the respiratory system (due to tar, carbon monoxide, carcinogens and other chemicals), reproduction system, motivation, memory and other systems. Chemical dependence to cannabinoids may insidiously develop and marijuana use can be a "gate way" to use of other substances of potential abuse. Although human studies on marijuana have many limitations, adverse effects of marijuana is of considerable clinical and social importance.

Key Words: marijuana, cannabinoids, chemical dependence, amotivation syndrome, task performance, neuropsychiatric effects, cardiovascular effects, reproduction system, respiratory effects

INTRODUCTION

Marijuana is typically used for recreational purposes to achieve a dream-like state or "high". Peer pressure may motivate use not only in adolescents and teenagers, but in sub-populations of adults as well. In some cases, people use marijuana in attempts at self-medication for anxiety and other emotional problems, nausea (such as from medications to fight cancer), chronic pain, and for other purposes (Hubbard *et al*., 1999). The use of marijuana peaked in the 1960s, but is still very high (Hubbard *et al*., 1999), because marijuana is the most commonly used illicit drug in the United States and is used in some states for medical purposes, understanding its potential adverse effects is of significant clinical and social interest.

Adverse effects of marijuana may occur with or without the knowledge of the user. For example, long-term use of marijuana may cause changes too slowly to be noticed or to be certain of the cause. Even with acute use, an adverse effect may not be obvious to the user because they are "high" or because the effect occurs

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significantly after the intoxicating effect is over. Also an adverse effect may not be observed because it is internal (such as brain blood flow or hormonal changes) or because a measurement instrument is needed to observe the change. In one survey 10–15% of chronic cannabis users noticed adverse effects to marijuana (Halibo *et al*., 1971). Others have reported that 40–60% of marijuana users have undesired side effects (Smart and Adlaf, 1982). In this chapter we will review scientific and clinical information on the adverse effects of marijuana and related cannabinoid containing substances.

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LIMITATIONS OF HUMAN STUDIES ON MARIJUANA

Marijuana has been an area of significant social and scientific interest for many years, yet many questions remain unanswered or not fully answered. In part, this is due to the inherent difficulties of human research on any illegal substance and in part it is due to special characteristics of marijuana. For example, marijuana has a very long half-life making the cause and effect less obvious, and marijuana is not a specific chemical, but rather a substance derived from the cannabis sativa plant that contains numerous active and inert chemicals. In general, studies on acute exposure to marijuana are better controlled than studies on long-term use. However most acute exposure studies using human subjects were done decades ago. Many of these older studies may underestimate adverse effects of current marijuana preparations since marijuana is now generally much more potent than that used in the past. Investigations on the adverse effects of chronic marijuana are very important, but most of these studies are limited by necessity to naturalistic and retrospective designs.

Results and interpretation of investigations of marijuana therefore depend on many factors that vary between studies. Some of these differences include:

(a) the content of the active chemicals in the marijuana preparation used [particularly the major psychoactive chemical Δ^9-tetrahydrocannabinol (THC)]
(b) acute vs. chronic exposure
(c) frequency of use
(d) concomitant use of other alcohol or drugs of abuse
(e) psychological and biological differences between subjects
(f) controlled vs. uncontrolled investigations
(g) prospective vs. retrospective investigation
(h) time(s) of adverse effect measurement (i.e. too late, too early, or optimal time to observe the change)

ACUTE ADVERSE EFFECTS OF MARIJUANA

Many acute adverse effects of marijuana have been reported after recent use as shown in Table 24.1. Some of these effects include headache, dry mouth, decreased coordination, tachycardia, changes in pulmonary functioning, altered body tem-

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Table 24.1 Acute adverse physical effects of marijuana

Dry mouth	Tachycardia
Decreased coordination/task performance	Changes in pulmonary functioning
Altered body temperature	Reduced muscle strength
Appetite	Decreased cerebral blood flow

References 1, 4–9, 13–20

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perature, reduced muscle strength, increased appetite, decreased cerebral blood flow, task performance and others (Hubbard *et al*., 1999).

Acute neuropsychiatric adverse effects to marijuana have been reported. Some of these side effects include anxiety, paranoia, hallucinations, time perception distortion, sensory (color/sound), altered libido, derealization, poor memory, decreased motivation and others (Table 24.2).

The potency of the preparation, the rate and duration of exposure, use of other drugs or alcohol, the setting of use, the psychological state of the individual and many other factors all influence the occurrence and severity of the acute adverse effect(s).

Task performance

Marijuana exposure can reduce physical motor performance. This has been demonstrated using many different measurements such as hand-eye coordination, tracking ability, body sway, reaction time, muscle strength tests and others (Ashton, 1999). The effect of marijuana on coordination lasts considerably longer than on the feeling of intoxication (Hubbard *et al*., 1999; Losken *et al*., 1996). The prolonged disruptive effect of marijuana on motor skills may be particularly important with regard to automobile driving, or in operating other vehicles or machinery (Klonoff, 1974; Smiley, 1986; Peck *et al*., 1986; Gold, 1994). For example, driving on an obstacle course was shown to be more difficult during cannabis intoxication (Peck *et al*., 1986). After an initial increase in motor activity, subjects often have ataxia, poor coordination, and psychomotor retardation (Ashton, 1999).

Performance of simulated airplane operating skills has also been shown to be reduced in pilots both during, and many hours after, marijuana intoxication (Gold, 1994; Janowsky *et al*., 1976; Hollister, 1998). For example, in a study by Leirer and Yesavag, (1991) marijuana exposure worsened simulated landings one hour after smoking a 19 mg THC marijuana cigarette. In addition, some deficiencies

Table 24.2 Acute psychiatric adverse effects of marijuana

Paranoia	Depersonalization
Anxiety	Altered time perception
Dysphoria	Worsened memory
Hallucinations	Altered motivation
Changes in libido	Possible increased suicidal ideation
Derealization	Sensory perception

References 1, 3, 4, 9, 13, 15, 16, 19, 21–25, 27, 28

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were noted 24 h later even though the pilots were unaware of their decreased performance (Leirer and Yesavag, 1991).

Task performance may be diminished with marijuana use not only due to the physical effects, but by the additional effect of marijuana on sensory perception (Ashton, 1999). For example, time, space, color and sound experiences may be altered (Ashton, 1999). Even after low dose exposure to marijuana subjects often overestimate the amount of time that has gone by.

Human position emission tomography (PET) studies show that cannabinoids change frontal lobe, parietal lobe, and cerebellum lobe metabolism of glucose for several hours (Nahas and Latour, 1992). These changes in metabolism may be related to the effects of marijuana on task performance (Nahas and Latour, 1992).

Cardiovascular

Marijuana has many affects on the cardiovascular system, such as increasing heart rate and cardiac work load (Hubbard *et al*., 1999). Tachycardia appears to be primarily due to decreased vagel tone (Clark *et al*., 1974). The cardiac output has been reported to be increased up to 30% (Ashton, 1999). Peripheral vasodilatation and postural hypotension have also been reported (Ashton, 1999).

The acute effect of marijuana on stimulating heart rate and cardiac output may be dangerous to some users due to increased myocardial demand, especially those with preexisting cardiovascular disease (Hubbard *et al*., 1999; Ashton, 1999; Schuckit, 1989; Hollister, 1988; Lu *et al*., 1993; Benowitz and Jones, 1975; Gottschalk *et al*., 1977). Marijuana has been shown to decrease cardiac oxygen and yet to increase myocardial demand in patients with angina (Gottschalk *et al*., 1977; Aronow and Cassidy, 1974). A 18 mg THC cigarette reduced exercise time to develop angina by 48% in cardiac patients (Gottschalk *et al*., 1977; Aronow and Cassidy, 1974). Heart attacks and transient ischemic attacks have been reported even in young healthy marijuana users (Ashton, 1999).

Neuropsychiatric

The human brain contains numerous cannabinoid receptors which may in part account for the many neuropsychiatric effects of marijuana (Hubbard *et al*., 1999). Some common neuropsychiatric side effects of marijuana include paranoia, anxiety, dysphoria, aggressiveness, hallucinations, changes in libido, derealization, depersonalization, altered time perception, worsened short-term memory, altered motivation, possible increased suicidal ideation (Hubbard *et al*., 1999; Smart and Adlaf, 1982; Ashton, 1999; Nahas and Latour, 1992; Schuckit, 1989; Hollister, 1988; Hubbard *et al*., 1993; Gottschalk *et al*., 1977; Nahas, 1977; Weil, 1970; Tunving, 1985). Most of the acute adverse neuropsychiatric effects appear to be anxiety reactions (Tunving, 1985). Sedation often occurs after the initial feeling of intoxication (Ashton, 1999).

The detrimental effect of marijuana on short-term memory is well known (Nahas and Latour, 1992). Interestingly, however, it can persist long after cessation of use. For example, in 1989 Schwartz *et al*. (Schwartz *et al*., 1989) reported short-term memory deficits in middle-class youths (median age 16 and matched

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for age and intelligence) who were dependent on cannabis both initially and after six weeks of controlled abstinence.

Paranoia, panic reactions and anxiety are unpleasant effects that can occur with marijuana exposure especially in those with a history of psychiatric disturbances (Weil, 1970; Hubbard *et al*., 1993). Acute psychosis, melancholia and manic episodes have been described for many years (Tunving, 1985). Rapid thoughts, often considered by the user to be "profound" may occur, and confusion can develop at high doses (Ashton, 1999).

Patients with Schizophrenia are at increased risk of marijuana-induced psychosis (Gold, 1994; Nahas and Latour, 1992). In a study by Hubbard *et al*. (1993), patients with Schizophrenia and Bipolar disorders reported being particularly prone to paranoia with marijuana use.

ADVERSE EFFECTS OF CHRONIC MARIJUANA ABUSE

Evidence for adverse effects from chronic marijuana is difficult to establish in both research studies and anecdotally because of the numerous uncontrolled variables over a long period of time. Overall, however, available data suggests that long-term marijuana abuse may adversely effect behavior, mental functioning, the cardiovascular system, immune system, respiratory system, reproductive system and others as discussed below (Tables 24.3 and 24.4). In addition, chronic abuse of marijuana can lead to a clinical state of cannabis dependence.

Neuropsychiatric

Although there is no clear demonstration of structural brain damage caused by marijuana, evidence suggests that cannabis has neurotoxic effects on the animal and human brains. The hippocampus appears to be particularly susceptible to marijuana exposure, which may help explain apparent deficits in memory and learning skills (Ashton, 1999; Gold, 1994; Janowsky *et al*., 1976; Nahas and Latour, 1992; Tunving, 1985). In some cases, changes resemble that of accelerated brain aging (Hollister, 1998). The changes tend to be slow and subtle, which may not be readily noticed by the users without repeated measurements (Gold, 1994; Hollister, 1998). Memory and learning deficits were not initially found in a cohort of heavy marijuana users in Costa Rica, yet abnormalities in short-term memory were observed 10 years later (Nahas and Latour, 1992; Page *et al*., 1988). Other studies have shown effects on short-term memory as well (Nahas and Latour, 1992).

Table 24.3 Neuropsychiatric effects of chronic marijuana use

Memory deficits	Cognitive deficits/Learning deficits
Worsening of Psychosis	Judgement problem
Low motivation	Lower math/verbal testing
Chemical dependence	

References 1, 4, 9, 10, 13, 25, 30–32, 46

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Table 24.4 Physical effects of chronic marijuana use

Alteration of sex hormones	Risk to patients with coronary artery disease
Fetal decrease in weight and length	Worsening emphysema/bronchitis
Duration of labor	Squamous cell metaplasia
Immune system deficits	Weight gain

References 4, 9–11, 13, 25, 32, 35–37, 41–44

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In a study of 23 chronic cannabis users compared to non-using controls, differences in judgement, communication, verbalization and compromised were noted using the Wechsler Adult Intelligence Scale (Gold, 1994; Corrion, 1990). In a separate investigation of 144, 12th grade chronic marijuana users and 72 non-users (matched for IQ in the 4th grade), marijuana users scored poorer on verbal, math and memory testing (Ashton, 1999; Black and Ghanesia, 1993). Other studies did not notice differences (Gold, 1994). Studies on prenatal exposure to marijuana are preliminary but suggest possible development of subtle cognitive deficits in children (Walker *et al*., 1999).

In addition to causing acute decompensation of patients with schizophrenia, high associations between marijuana use and schizophrenia have been noted (Hollister, 1998; Gersten, 1980). For example, a sixfold increase in the diagnosis of schizophrenia was reported in marijuana users in a study of about 55,000 Swedish military recruits (Andreasean *et al*., 1987). Flashbacks of sensations similar to the original drug exposure have been reported, but are rare (Halibo *et al*., 1971; Ashton, 1999). They most often occur weeks to months after heavy use (Ashton, 1999).

Concerns about marijuana abuse leading to an "amotivational syndrome" have been an area of considerable clinical concern and scientific debate. Low motivation and drive is often observed in marijuana abusers, however, it is uncertain if use of the drug leads to this condition, if people with lower drive tend to use marijuana, or both. Apparent low motivation may also be due to frequent states of intoxication (Ashton, 1999).

Reproduction system, hormone system and the fetus

Many investigations suggest that marijuana has adverse effects on the reproduction system and may be harmful to the fetus (Nahas and Latour, 1992; Witorsch *et al*., 1995). By necessity, most studies on the reproductive system have been done in animals, however, human data has been collected as well. For example, marijuana appears to alter the menstrual cycle and decrease ovulation (Ashton, 1999; Nahas and Latour, 1992; Witorsch *et al*., 1995). This may be due to effects of cannabinoids on sex hormones (Witorsch *et al*., 1995). While acute marijuana exposure tends to decrease prolactin levels, chronic use may increase prolactin and lead to gynecomastia in males and galactorrhea in females (Ashton, 1999). Duration of labor may also be affected by marijuana use (Gold, 1994; Martin and Hubbard, 2000).

Epidemiological investigations suggest that marijuana may affect fetus weight gain, growth in length, and possibly behavioral characteristics of the child (Ashton,

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1999; Gold, 1994; Martin and Hubbard, 2000). In a large study of 1,200 mothers, the children of the 10% that had a positive urinalysis for marijuana had reduced birth weight by 79 g, averaged shorter length by 0.5 cm, and had smaller head size (Gersten, 1980; Zuckerman *et al*., 1989). Children of mothers who used marijuana during pregnancy were reported to more frequently have deficits in language skills, visual perception tasks, memory and attention at four years of age (Ashton, 1999; Janowsky *et al*., 1976). High-speed computerized voice analysis of newborns showed voice abnormalities in babies of Jamaican women who smoked marijuana compared to controls (Lester and Dreher, 1989). Also, cannabinoids have been reported to cause hypotonicity, lethargy, tremor, and increased startle in newborns (Walker *et al*., 1999).

In males, cannabinoids are anti-androgenic and appears to decrease sperm mobility, sperm count and may alter sperm shape (Ashton, 1999). Decreased testosterone has also been noted in marijuana users (Witorsch *et al*., 1995). Effects on fertility are uncertain (Ashton, 1999).

Cancer

Tissue culture and Ames tests showed that marijuana smoke may be mutagenic (Nahas and Latour, 1992). However, teratological effects have not been clearly demonstrated. In a 204 pair case-controlled study Robinson *et al*. (1989) reported a 10 times increase in the risk of non-lymphoblastic leukemia in children of mothers who used marijuana just before or during pregnancy. Leukemia was not increased by other drugs such as alcohol or tobacco (Nahas and Latour, 1992; Robinson *et al*., 1989). Children of marijuana smoking mothers were also reported to have a threefold greater risk of rhabdomyosarcoma (Janowsky *et al*., 1976). With regard to the respiratory system, squamous cell hyperplasia has been shown even in young adults (20–26 years old) who are heavy hashish users (Tennani and Guerny, 1980).

Immune system

Numerous changes in the immune system to marijuana and THC have been reported in *in vitro* and *in vivo* systems (Ashton, 1999; Hollister, 1998). However, the clinical medical significance of these alterations is not certain (Ashton, 1999; Hollister, 1998). Marijuana use did not appear to alter progression of AIDS in a study of nearly 5,000 HIV-positive homosexual men (Ashton, 1999; Hollister, 1998; Kaslow *et al*., 1989).

Cardiovascular system (CVS)

The effect of chronic marijuana use on the CVS has not been well demonstrated (Hollister, 1998). However, some clinicians report concern over the potential dangers of the large quantities of carbon monoxide in cannabis smoke (Ashton, 1999). Possible dangers of marijuana use on the CVS may be more important in the elderly, and those with hypertension, coronary artery disease, and/or other cardiovascular diseases (Janowsky *et al*., 1976).

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Respiratory system

Smoking marijuana is believed to have several dangerous effects on the respiratory system. Like tobacco smoke, cannabis smoke contains both tar carbon monoxide and carcinogens (Gold, 1994; Nahas and Latour, 1992). Unlike cigarettes, marijuana joints do not have filters, and smokers often inhale deeply and keep the smoke in their lungs for extended time to get the full euphoric effect. Marijuana smoke has about three times more tar and five to six times more carbon monoxide than cigarette smoke (Ashton, 1999; Janowsky *et al*., 1976; Walker *et al*., 1999; Wu *et al*., 1988). Chronic use of marijuana has been associated with worsening emphysema, bronchitis, airway obstruction and squamous cell metaplasia (Ashton, 1999; Nahas and Latour, 1992). Case reports of chronic marijuana users developing large lung bullae are also of potential concern (Johnson *et al*., 2000).

Weight gain

Users of marijuana generally agree that marijuana increases appetite (Hollister, 1970). However, many regular marijuana smokers may not think about the effect of marijuana on their weight. In a study of 10 controls (non-users), 12 "casual" users, and 15 "heavy" marijuana users, significant weight gain was found in both casual and heavy marijuana users after 3 weeks of use (Greenberg *et al*., 1976). Casual users (use of about 12 times per month) gained 2.8 lbs on average, heavy users (use of about 42 times per month) 3.7 lbs, and non-users gained only 0.2 lbs in the 21-day interval. Weight gain did not appear to be water retention. Weight gain over a longer period of time may be of significant importance to some patients, especially those with diabetes or other health related problems.

Chemical dependence

Dependence to cannabinoids appears to occur in humans and develop slowly with increased risk at higher doses and frequency of use (Gold, 1994; Martin and Hubbard, 2000). Compulsive use has been reported antidotally and in survey studies (Ashton, 1999). Like other drugs of abuse, cannabinoids has been shown to stimulate release of dopamine in neuroanatomical reward centers of the brain (Gardner and Lowinson, 1991). Cannabis dependence is estimated to be about 4% of the population (Gold, 1994; Martin and Hubbard, 2000). Tolerance to marijuana often develops and craving and compulsive urges to use are often reported. In clinical practice, patients often report being surprised to discover how difficult it can be to stop marijuana use. Some people resume marijuana use after initial attempts to quit despite significant personal consequences at home, school or work and yet many deny that they have a chemical dependence problem.

Although the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) does not include cannabinoid withdrawal as a diagnostic category, withdrawal symptoms from cannabis have been reported in human and animal studies (Ashton, 1999; Tunving, 1985). For example, withdrawal symptoms have been observed in a laboratory setting when cannabis was used every day for 10 days or more and then abruptly stopped (Tunving, 1985). Anxiety, tremor, irrit-

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ability, perspiration, nausea, muscle cramps, and insomnia are some of the reported withdrawal symptoms (Hubbard *et al*., 1999; Ashton, 1999; Tunving, 1985). More often withdrawal symptoms do not occur or are mild due to the long half-life of THC (Hubbard *et al*., 1999). In chronic users withdrawal symptoms are reported to occur in about 16–29% of subjects (Ashton, 1999).

It has also been a great concern that marijuana is a "gateway" drug to other illicit substances of abuse for some people (Hubbard *et al*., 1999; Gold, 1994). For example, it was reported in 1985 that one of the best predictors of cocaine use in adolescents is marijuana use (Gold, 1994; Kandel *et al*., 1985). The common gateway pattern of drug abuse generally begins with legal substances such as alcohol and cigarettes prior to marijuana use.

CONCLUSIONS

Overall, it appears that marijuana has potential for significant acute and long-term impact on the mental and physical health of users. Some adverse effects of marijuana are disturbing to the user (such as anxiety and paranoid states), while others (such as effects on memory and motivation) may not be noticed because they develop slowly and the association with marijuana use is not recognized. Marijuana does not appear to be directly life threatening (unlike alcohol, opiates and many other drugs of abuse) but may increase risk of harm during intoxication (such as during driving or doing other potentially dangerous activities).

The potential short-term and long-term risks of marijuana should be considered prior to medical use or for recreational purposes. Clearly this is an area where more research on the potential benefits and adverse effects is of significant social, scientific, and medical interest.

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