

# Cannabis Use, Abuse, and Dependence

5 NASW Clinical, Substance Abuse Hours

## Audience

This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use cannabis, either illicitly or as an adjunct to medical treatment.

## Course Objective

The purpose of this course is to allow health and mental health professionals to effectively identify, diagnose, treat, and provide appropriate referrals for patients with cannabis use disorders.

## Learning Objectives

Upon completion of this course, you should be able to:

1. Review the history of cannabis use and define the concepts of cannabis abuse and dependence.
2. Discuss the epidemiology of cannabis use in the United States, including treatment utilization and risk factors for cannabis use disorders.
3. Outline the pharmacology of cannabis.
4. Review the established and investigational therapeutic uses of cannabis and delta-9-THC.
5. Identify acute effects of cannabis ingestion on both physical and psychological systems.
6. Describe long-term effects of cannabis ingestion and conditions associated with cannabis use, including the associated withdrawal syndrome.
7. Discuss the prognosis and treatment approaches for individuals who misuse cannabis, including considerations for non-English proficient patients.

## Faculty

**Mark Rose, BS, MA**, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has contributed to the authorship of several papers on addiction, as well as other medical disorders, and serves as an Expert Advisor and Expert Witness to various law firms on matters related to substance abuse. He is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine, and a member of several professional organizations.

## Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

## Division Planner

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## Division Planner Disclosure

The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

## Accreditation

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Social workers will receive 5 Clinical continuing education clock hours in participating in this intermediate to advanced course.

This course meets the qualifications for 5 hours of continuing education credit for MFTs and/or LCSWs as required by the California Board of Behavioral Sciences.

This course meets the requirements for 5 Clinical hours as required by the New Jersey Board of Social Work Examiners.

CME Resource designates this continuing education activity for 5 continuing education hours for addiction professionals.

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## INTRODUCTION

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Cannabis products such as marijuana and hashish comprise the most widely used recreational drugs both in the U.S. and worldwide [55]. Although, with a few exceptions, these drugs lack the liability of abuse and dependence seen with other illicit drugs, such as cocaine, methamphetamine, and heroin, physical and psychological withdrawal symptoms can occur with cannabis products, posing an additional consideration in the management of these patients. This course will provide the most pertinent up-to-date information regarding the demographics and characteristics of cannabis users, the history of therapeutic and recreational use of the drug, the pharmacology and clinical effects, adverse effects and conditions, and the management and treatment of overdose, toxicity, and abuse and dependence.

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## HISTORY OF CANNABIS USE

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Although the later part of the 20th century saw a rise in the use of cannabis for recreational, religious/spiritual, and medicinal purposes, humans have been consuming cannabis since prehistory. Cannabis, native to Central Asia, is one of the oldest known psychotropic drugs. Cultivated and consumed long before recorded history, archeological discovery indicates that it was used in China since around 4000 BCE. There are several species of cannabis, including *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. *Cannabis sativa* is the most widely used variety and can be cultivated in a variety of climates [1; 13].

The two main derivatives of cannabis are marijuana and hashish. The term marijuana originated in Mexico to describe cheap tobacco; today, it refers to the dried leaves and flowers of the *Cannabis* plant. Hashish, an Arabic term, is the viscous resin of the plant [1; 13].

The Chinese emperor Shen Nung is believed to be the first to describe the properties and therapeutic uses of cannabis, which appeared in his compendium of Chinese medicinal herbs written in 2737 BCE. Following this, cannabis was cultivated for its fiber, seeds, medicinal use, and recreational consumption, which then spread to India from China [1].

In 1839, William O'Shaughnessy, a British physician and surgeon working in India, was the first individual in Western medicine to discover the use of cannabis as an analgesic, appetite stimulant, antiemetic, muscle relaxant, or anticonvulsant. In 1854, cannabis was listed in the United States Dispensatory; however, after prohibition was repealed, American authorities condemned the use of cannabis, claim-

ing it responsible for insanity, intellectual deterioration, violence, and various crimes. In 1937, the U.S. Government introduced the Marihuana Tax Act. According to this legislation, a tax of \$1 per ounce was collected when cannabis was used for medical purposes and \$100 per ounce when it was used for unapproved purposes [13]. Cannabis was removed from the United States Pharmacopoeia in 1942 [1].

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## DEFINITION OF CANNABIS ABUSE AND DEPENDENCE

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Although severe problems associated with abuse and dependence are less common among cannabis users than among other drug users, they do occur. Furthermore, cannabis had the highest rate of past year dependence or abuse in 2007 of all illicit drugs [5].

Cannabis dependence is best described as a chronic relapsing disease characterized by compulsive seeking and use of cannabis, accompanied by functional and molecular changes to the brain [2]. The single most defining aspect of cannabis dependence is the salience of the relationship with the drug. The stronger the relationship, the more likely the patient will continue problematic use despite internal and external consequences. Psychological dependence, whereby the patient believes cannabis is necessary to get through daily activities, alleviate stress, and cope with problems, is a symptom of cannabis dependence. Physiological adaptation, evidenced by tolerance and withdrawal, is often present but is not sufficient for a diagnosis of dependence. Cannabis dependence is diagnosed behaviorally and is evidenced by cravings for cannabis, preoccupation with use of the drug, sneaking and concealing ingestion, loss of the ability to control cannabis use, and continued use despite significant physical, psychological, social, occupational, or legal consequences [3].

Cannabis abuse is a condition of frequent or binge-type use and continued use despite failure to meet work, school, or domestic obligations or legal consequences. However, abuse is characterized by less severity and fewer behavioral symptoms than with the dependence syndrome [3].

Identifying patients with a cannabis-related disorder can be difficult, as abuse and associated problems are typically slow to develop. Patients frequently do not recognize they have a problem or do not want to give up their drug use. They may also be attempting to conceal their drug use from parents, physicians, and other authority figures. Unexplained deterioration in academic or work performance, problems with or changes in social relationships, and changes in recreational activities are signs of a possible problem [4].

## EPIDEMIOLOGY OF CANNABIS USE

The 2007 National Household Survey on Drug Abuse found that more than 100 million (40.6%) of Americans 12 years of age and older had tried cannabis at least once in their lifetimes, and 14.4 million (5.8%) had used cannabis in the past month [5]. Twelfth grade boys in all ethnic groups are more likely than girls to have used cannabis in the last 30 days [57]. Among ethnic groups, Asian adolescents are the least likely to have used cannabis within the last month; Native American teens are the most likely [57].

Of the 19.9 million illicit drug users in the United States, 72.8% were current (past month) users of cannabis, with the majority (53.3%) exclusively using cannabis [5; 6]. In 2007, the National Household Survey on Drug Abuse found that 3.9 million Americans met the criteria for cannabis dependence [5]. Approximately 6% of those who have used cannabis in the past year meet the *Diagnostic and Statistical Manual of Mental Disorders* 4th edition (DSM-IV) criteria for cannabis dependence [7].

Approximately 10% of persons who have ever tried cannabis become daily users, and cannabis dependence affects 1.6% of the population, a higher rate than any other illicit drug [5]. This rate is mainly attributable to the greater numbers of cannabis users relative to users of other substances [8]. When examining the risk of dependence among those who have ever used a particular substance (referred to as conditional dependence), the rates for cocaine (17%), heroin (23%), and tobacco (32%) are significantly higher [8].

The rate of cannabis use by children and adolescents doubled during the 1990s [9]. Occasional cannabis use, while illegal, is often considered normative behavior for adolescents and is not strongly correlated with emotional or behavioral disorders by the general public. Unfortunately, although the exact threshold is unclear, approximately one-half of those who use cannabis more than monthly exhibit behavioral or emotional difficulties [9].

## TREATMENT UTILIZATION

Increases in both the prevalence of cannabis use and the potency of cannabis have contributed to the 139% increase in cannabis-related emergency department episodes reported from 1995 to 2002 [10]. Cannabis-related conditions that may be seen in an emergency department include chronic addiction to cannabis, acute cannabis psychosis, and cannabis-related schizophrenia.

Utilization of treatment services for cannabis dependence has also increased. Patients entering substance abuse treatment programs with cannabis-related problems doubled between 1992 and 1998. The percentage of treatment admissions (23%) is now roughly equivalent to that of cocaine and heroin [11].

However, these statistics are dramatically higher among adolescents. In 2000, cannabis accounted for 61% of all adolescent treatment admissions in the U.S., and the majority of all patients admitted to substance abuse treatment programs as adolescents report cannabis as their primary substance. Between 1992 and 2000, the number of adolescents receiving treatment at public treatment centers for cannabis abuse or dependence doubled [12].

Overall, the proportion of those seeking treatment for cannabis dependence is relatively low in the United States. This may be partially due to the perception of cannabis as a relatively innocuous drug [13]. A sample of 243 long-term cannabis users who reported smoking 3 to 4 times a week found a lifetime prevalence of cannabis dependence of 57%. However, only one-quarter of the sample believed that they had a cannabis problem [14].

## RISK FACTORS FOR CANNABIS USE DISORDERS

Cannabis use typically begins in early to middle adolescence, and use tends to peak during late adolescence and young adulthood [13]. Many people first use cannabis out of curiosity, peer pressure, or both, and continue to use it for the desired effects of euphoria, relaxation, heightened sensations and perceptions, and socialization with other users. Factors that contribute to chronic use include easy access, the expectation of few or no legal consequences for use, and attempts to self-medicate physical and emotional problems. For some, chronic use develops into cannabis dependence [4].

A major risk factor for adolescent substance abuse, including cannabis use, is the presence of conduct problems in childhood. This may be because family conflict, poor parental monitoring, parental substance use, academic problems, and association with deviant peers are all risk factors for both substance abuse and conduct problems. More than one-half of adolescents with substance abuse problems also exhibit conduct problems [12]. Co-occurrence of these problems is a strong predictor of poor outcome following substance abuse treatment [12]. Factors associated with cannabis dependence include male gender, ethnic minority status, and evidence of adolescent risk-taking behaviors, such as cigarette smoking, conduct problems, and involvement in a delinquent peer group [14].

Early subjective response to cannabis is associated with later risk of dependence. Participants in a survey reporting 5 positive reactions to the drug had 20 times greater risk of later dependence than those who did not experience positive reactions, even after controlling for confounding factors. These findings suggest that early subjective and physiological reactions to cannabis are predictive of later dependence and possibly reflect underlying genetic differences in vulnerability to dependence. These possible genetic predispositions are likely mediated by individual differences in the responsiveness of the mesolimbic dopamine system to substance use [16].

Several factors associated with successful cessation of cannabis use have been identified. These factors include older age, female gender, married marital status, infrequent cannabis use, absence of delinquent behavior, and high school completion [17].

### Genetic Vulnerability

A summary of the genetic studies examining the relationship between cannabis use and other drugs use has found that the association between the use of cannabis and other drugs is due in part to two factors: genetic vulnerability and an overlap of environmental influences. An individual's vulnerability to cannabis abuse is shaped by this common susceptibility to multiple drug involvement and also by risk factors unique to cannabis [18]. A summary of numerous studies has concluded that there are substantial genetic influences on measures of cannabis involvement [18].

### ESCALATION OF CANNABIS USE TO OTHER ILLICIT DRUGS

Early onset and frequency of cannabis use are strong predictors of escalation in other illicit drug use across sexes, populations, ethnicities, and socioeconomic strata. Frequent cannabis use during young adulthood significantly increases the risk of polysubstance abuse, earlier onset of substance dependence, poorer educational and occupational outcomes, multiple health and psychiatric problems, and criminal justice system involvement [15].

Cannabis and other illicit drug use may be correlated. Studies have shown that cannabis is a potential "gateway drug," leading to the use and abuse of more dangerous drugs, such as cocaine and heroin [18]. However, it should be noted that evidence of a causal relationship between cannabis use and progression to other drug use has been speculative at best [18].

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## PHARMACOLOGY

Cannabis contains more than 460 known chemicals, more than 60 of which are grouped under the category of cannabinoids [1]. The primary psychoactive ingredient is delta 9-tetrahydrocannabinol (delta-9-THC). Other cannabinoids, including delta-8-THC, cannabinal, cannabidiol, cannabicyclol, cannabichromene, and cannabigerol, are present in small quantities and have no significant psychotropic effects compared to THC. It is unknown whether these compounds may have an impact on the overall effect of cannabis [1].

Cannabis is ingested in many forms, but it is most often smoked in the form of a cigarette ("joint") or out of a pipe, water pipe ("bong"), or improvised vessel (e.g., sawn-off plastic bottle). It may also be added as an ingredient in baked goods, eaten, or drunk as an extract. Because of its relative water insolubility, it is unsuitable for intravenous use [21].

Cannabinoids are present in the stalks, leaves, flowers, and seeds of the plant, but they are particularly abundant in the resin secreted by the female plant. THC content varies among the available sources and preparations of cannabis. Advances in cultivation (such as hydroponic farming) and plant-breeding techniques have increased the potency of cannabis products [21].

During the 1960s and 1970s, an average joint contained about 10 mg of THC. Today, a joint made of a potent subspecies of *Cannabis sativa* may contain 60–150 mg of THC. This can increase to 300 mg if the joint is laced with hashish oil. The substantial increase in potency in cannabis products today exposes cannabis smokers to many times the THC dose compared to their counterparts in the 1960s and 1970s. This is an important fact, as the effects of THC are dose-related and most research on cannabis was conducted in the 1970s using doses of 5–25 mg THC. Some researchers consider the research published on cannabis use during the 1960s and 1970s to be obsolete [21; 22].

### PHARMACOKINETICS OF CANNABINOIDS

Approximately 50% of the THC and other cannabinoids present in a cannabis cigarette enter the mainstream smoke and are inhaled [22]. Smoking style affects the amount absorbed through the lungs, with experienced smokers who inhale deeply and hold the smoke in the lungs for some seconds before exhaling ingesting virtually all of the cannabinoids present in the mainstream smoke [22].

The onset of cannabis effects is within seconds of ingestion, with full effect within minutes. The bioavailability after oral ingestion is lower than that seen with smoking; blood concentrations are as low as 25% to 30% of those obtained by smoking the same dose, partly due to hepatic first-pass metabolism [21]. The onset of effect is delayed (0.5 to 2 hours) after oral ingestion, but the duration is prolonged because of continued slow absorption from the gut [21].

As little as 2.5 mg THC is enough to produce measurable psychological and physical effects in the occasional cannabis user. Upon transferring to the bloodstream, cannabinoids are distributed rapidly systemically, first reaching the tissues with the highest blood flow, such as the brain, lungs, and liver [22]. Within the brain, cannabinoids are differentially distributed, reaching high concentrations in the neocortical areas, especially the frontal cortex; the limbic areas, including the hippocampus and amygdala; sensory areas, such as the visual and auditory cortex; motor areas, including the basal ganglia and cerebellum; and the pons [22].

Cannabinoids are highly fat soluble and accumulate in fatty tissues. From these tissues, the compounds are very slowly released into other parts of the body. In occasional users, the plasma elimination half-life of THC is approximately 56 hours; in chronic users it is shortened to 28 hours. However,

due to its sequestration in fat, the tissue half-life is approximately 7 days and complete elimination of one dose may take as long as 30 days [22].

Cannabinoids are metabolized in the liver, where they produce more than 20 metabolites, some of which are psychoactive and many of which have plasma elimination half-lives of the order of 50 hours. A major metabolite is 11-hydroxy-THC. This metabolite may be more potent than the parent compound and may be responsible for some of the effects of cannabis. Further metabolism produces inactive metabolites, of which 15% to 30% are excreted in urine. Active and inactive metabolites are also excreted into the intestine and bile. Approximately 15% are reabsorbed back into the body, prolonging the action of cannabis, while 35% to 65% are finally eliminated in the feces [22].

### PHARMACODYNAMICS

Cannabinoids act by binding to cannabinoid receptors type 1 and 2 (CB1 and CB2). Both of these receptors are part of the G-protein coupled class, and their activation results in inhibition of adenylate cyclase activity. Identification of agonists and antagonists of these receptors has stimulated interest in medical uses of cannabis [1; 13].

Cannabinoids exert many of their effects by combining with specific receptors in the central nervous system (CNS) and peripheral nervous system. The discovery of cannabinoid receptors led to a search for the endogenous ligand with which the receptors naturally interact. This substance was eventually isolated and named anandamide after the Sanskrit word for bliss, *ananda*. Anandamides are derivatives of arachidonic acid, related to prostaglandins [22].

Both anandamides and their receptors lie in neuronal lipid membranes and modulate neuronal activity through intracellular G-proteins that control cyclic adenosine monophosphate formation and calcium and potassium ion transport [21]. The physiological function of the cannabinoid system is not fully understood, but it is thought to have important interactions with opioid, GABAergic, dopaminergic, noradrenergic, serotonergic, cholinergic, glucocorticoid, and prostaglandin systems [22]. A number of the cannabinoids' pharmacological effects can be explained on the basis of these interactions, examples being tachycardia and xenostomia, which are caused by the effects of THC on acetylcholine [23].

CB2 receptors are primarily found in immune cells, suggesting that cannabinoids may play a role in the immune response. CB1 receptors are found throughout the body but are concentrated in the brain, with the highest density in the basal ganglia. Other brain regions with high CB1 receptor density include the cerebellum, hippocampus, cerebral cortex, and nucleus accumbens. The distribution of CB receptors suggests that the endogenous cannabinoid system may have effects on a broad range of behaviors [13].

### TOXICITY

The median lethal dose of oral THC in rats is 80–1900 mg/kg, depending on the sex of the rat and the strain of cannabis [21]. There are no cases of death due to toxicity following the maximum oral THC dose in animal studies. No deaths directly attributable to acute cannabis use have ever been reported [21].

### TOLERANCE

Tolerance to most of the THC effects eventually develops in regular users. In a 30-day study, volunteers developed tolerance both to the associated cognitive and psychomotor impairment and to the subjective high by the end of the study. The increased heart rate present upon acute ingestion of the drug at the beginning of the study was replaced by a normal or a slowed heart rate after several days. Tolerance to cannabis is attributable to pharmacodynamic changes, presumably based on receptor down-regulation and/or receptor desensitization, although the rate and duration of tolerance varies with different effects [23].

### DRUG-DRUG INTERACTIONS

As with many drugs, THC can enhance or attenuate the effects of other medications. A combination of dronabinol (a cannabinoid) and prochlorperazine is more effective in reducing chemotherapy-associated nausea and vomiting than prochlorperazine alone [33]. Cannabis can also augment the sedating effects of other psychotropic substances, such as alcohol and benzodiazepines. A number of synergistic effects may be therapeutically desirable, such as the enhancement of:

- Muscle relaxants, bronchodilators, and antiglaucoma medication
- Opiate analgesia
- Phenothiazines' antiemetic effect
- Benzodiazepines' antiepileptic action

The cyclooxygenase inhibitors, indomethacin, acetylsalicylic acid, and other nonsteroidal anti-inflammatory drugs antagonize THC effects, reflecting the involvement of cyclooxygenase activity in several THC effects [23].

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## THERAPEUTIC USE OF CANNABIS

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Use of cannabis for medical purposes was first documented in China thousands of years ago, where it was reportedly used to treat malaria, constipation, rheumatism, and childbirth [33]. There are also reports of cannabis mixed with wine being used as an analgesic. Throughout history, the medical use of cannabis has been found in records from Asia, the Middle East, Southern Africa, and South America [33].

Despite being categorized as illegal, cannabis has continued to be an attractive option for self-medication among some patients. In 1978, a compassionate program for medicinal cannabis was established by the U.S. government; this program stopped accepting new candidates in 1991 [1]. Since then, 13 states have enacted laws to ensure that patients may use cannabis for medical purposes without criminal penalties [60]. It is important to note that many of the effects discussed in this section result from THC in prescription forms, not smoked cannabis. These effects are generally categorized according to the strength of available evidence.

### ESTABLISHED EFFECTS

Dronabinol, the medicinal form of THC, is approved for the treatment of refractory nausea and vomiting caused by antineoplastic drugs used for the treatment of cancer and for appetite loss in anorexia and cachexia of patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) [23]. Delta-9-THC and nabilone, the synthetic version, are generally considered effective antiemetics. However, comparisons with 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) antagonists are lacking, and their role in modern antiemetic regimens remains to be determined [33].

### RELATIVELY WELL-CONFIRMED EFFECTS

Patients with multiple sclerosis have reported an improvement in symptoms associated with cannabis use, and small controlled trials support this use, although the effect upon posture and balance requires clarification [33]. There is also mounting support for the use of THC and cannabinoid extracts in the treatment of spasticity due to spinal cord injury, chronic pain, and Tourette's syndrome. Clinical effects in the treatment of asthma and glaucoma are also relatively well-confirmed [23]. The mechanism for cannabis bronchodilation likely differs from that of beta-2-stimulants, indicating that synergistic combinations may be possible. Additionally, the effectiveness of cannabis and THC as appetite stimulants, coupled with their antiemetic, analgesic, anxiolytic, hypnotic, and antipyretic properties, suggests a unique role in alleviating symptoms in selected patients with cancer or AIDS [33].

### POSSIBLE EFFECTS

Several indications suggest benefits in patients with epilepsy, intractable hiccups, depression, bipolar disorder, anxiety disorder, opiate or alcohol dependence, and disturbed behavior in Alzheimer's disease [23]. These possible uses have been mainly supported through case reports.

### BASIC RESEARCH STAGE

Several promising areas of possible future therapeutic uses of cannabis are in the basic research stage. Neuroprotection is an important physiological role of endocannabinoids, and a clinical study investigating the therapeutic potential of a nonpsychotropic derivative of THC in hypoxia and ischemia resulting from traumatic injury has yielded positive prelimi-

nary results. Other areas of promising investigation related to neuroprotection include nerve gas damage and stroke.

The immunological mechanisms of THC indicate that the compound may be helpful in treating autoimmune diseases. Possible antineoplastic activity of THC was discovered in an animal study designed to investigate the potential carcinogenicity of THC; long-term treatment of rats with THC resulted in improved survival due to the lower incidence of several types of cancer compared to control rats. Subsequent studies have found that cannabinoids have antineoplastic activity on malignant gliomas and skin tumors and inhibit angiogenesis of malignant gliomas. Other conditions of possible cannabis utility include cardiovascular disease and hypertension [23].

Because cannabis has an extensive history of use for a variety of purposes, it is very unlikely that unknown adverse events will develop, as occasionally occurs with newly designed synthetic drugs [23].

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## ACUTE CANNABIS EFFECTS

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Similar to other drugs with an abuse liability, such as heroin, cocaine, amphetamines, and nicotine, the pleasurable effects of cannabis are the result of the release of dopamine in the reward circuitry, comprised of the subcortical ventral tegmentum, nucleus accumbens, striatum, and medial prefrontal cortex [9; 24]. Transmission of dopamine is increased in the nucleus accumbens following acute administration of cannabinoid agonists. This effect may be blocked by the CB<sub>1</sub> receptor antagonist rimonabant, a drug that had been available in Europe until 2008 [13; 58].

### BEHAVIORAL AND PSYCHOLOGICAL EFFECTS

The pharmacological actions of cannabinoids are very complex. The resulting effects are a unique combination of those found with the use of depressants and hallucinogens. Because cannabinoid receptors are widely distributed through the body, numerous body systems are affected [22]. The experience of intoxication is highly variable and is influenced by the dose, the environment, and the experience and expectations of the user [24].

#### Effects on Mood

The euphoriant potential of cannabis is probably the single most important characteristic in sustaining its widespread and often chronic recreational use. This effect varies greatly with dose, route of administration, expectation, environment, and personality of the user. However, dysphoric reactions to cannabis are not uncommon. In some cases, use may result in severe anxiety and panic, unpleasant somatic sensations, and paranoia. Anxiety-panic reactions are the most common adverse psychological effects of cannabis use. Flashbacks, whereby the original drug experience (usually dysphoria) is

re-experienced weeks or months later, are possible and may represent a psychological reaction similar to that of post-traumatic stress disorder [22].

### Sedative and Anxiolytic Effects

Following an initial period of excitement after acute ingestion of cannabis, a generalized CNS depressant effect is observed. This may lead to drowsiness and sleep toward the end of a period of intoxication [22].

### Effects on Perception

The changes in perception that result from cannabis and THC affect all sensory modalities. Color and sound perception may be heightened, and musical appreciation may be increased. Temporal and spatial perception is distorted, impairing judgment of distance and time. Even after small doses, persons under the influence of cannabis consistently overestimate the passage of time. Persistent visual changes, some lasting for months, have been documented [22].

### Effects on Motor Function

As noted, the initial period of excitement and increased motor activity after cannabis ingestion is followed by a state of physical inertia, with ataxia, dysarthria, and general incoordination possibly lasting for several hours. Motor performance, including measurements of body sway, tracking ability, pursuit motor performance, hand-eye coordination, reaction time, and physical strength, is demonstrably impaired [22].

### Effects on Cognition and Memory

The effects of cannabis on cognitive processes are characterized initially by subjective feelings of accelerated speed of thought, flight of ideas that may seem unusually profound, and a crowding of perceptions. Higher doses can result in out-of-control thoughts, fragmented thinking, and mental confusion. Cannabis is associated with short-term memory deficits; it is believed that these deficits may be caused by an attention deficit combined with an inability to filter out irrelevant information and the intrusion of extraneous thoughts. Memory lapses may contribute to the distortion in the perception of time and poor psychomotor performance in complex tasks [22].

### Psychomotor Performance

Even low doses of THC (5–15 mg) can significantly impair an individual's ability to perform complex or demanding tasks, including those involved in fine hand-eye coordination, complex tracking, divided attention tasks, visual information processing, digit code tests, and alternate addition-subtraction tasks [22]. Psychomotor performance further deteriorates at higher doses, and impairment can persist several hours following a single dose [22].

### Aggression and Violence

Cannabis typically decreases aggression and increases sociability. However, in rare cases, individuals, particularly those under stress and predisposed to violence, become aggressive after taking cannabis. It has also been suggested that violent behavior may be more common among those with acute paranoid or manic psychosis induced by cannabis and polydrug use [22].

### Psychiatric Symptoms

Cannabis use can lead to a range of short-lived psychiatric symptoms, including depersonalization, derealization, a feeling of loss of control, fear of dying, irrational panic, and paranoid ideas [14]. After taking a large dose of cannabis, vulnerable users may temporarily experience a form of drug-induced psychosis. Cannabis-induced psychosis has the potential to require hospital admission. During the initial diagnosis, this psychosis may be misidentified as schizophrenia, as patients may display characteristic schizophrenic symptoms, such as delusions of control, grandiose identity, persecution, thought insertion, auditory hallucinations, altered perception, and blunted affect [24].

## PHYSICAL EFFECTS

### Cardiovascular Effects

Acute doses of cannabis may induce tachycardia with peripheral vasodilatation, which can result in postural hypotension and a slight decrease in body temperature. Cardiac output may be increased by as much as 30%, accompanied by increased cardiac work and oxygen demand. Because of this, cannabis can aggravate pre-existing heart disease. The absorption of relatively large amounts of carbon monoxide from smoking cannabis also contributes to the long-term cardiovascular risk of chronic cannabis use [22]. Reddening of the conjunctivae, a characteristic sign of cannabis use, is the result of widespread vasodilation [21].

### Respiratory Effects

Cannabis smoke contains many of the same constituents as tobacco smoke (minus the nicotine), including bronchial irritants, tumor initiators (mutagens), tumor promoters, and carcinogens. The tar from cannabis smoke also contains higher concentrations of the carcinogens benzanthracenes and benzpyrenes than tobacco smoke tar. Smoking a cannabis cigarette results in inhalation of three times the amount of tar of a tobacco cigarette, and respiratory tract retention is greater than smoking a tobacco cigarette [21; 22]. As a result, cannabis use may result in impairment of lung function, leading to airflow obstruction and hyperinflation [59].

### Endocrine/Reproductive System Effects

Cannabinoids, including THC, bind to androgen receptors, and cannabis is considered antiandrogenic. However, the drug's effects, if any, on fertility are unclear. In women, regular cannabis smoking may be associated with suppression of ovulation. Chronic use may cause galactorrhea in women and gynecomastia in men. Endocrine changes resulting from cannabis use may be inconsequential in adults but significant in prepubertal users, in whom cannabis use may suppress sexual maturation as well as social and personal development and learning of coping skills. There is no evidence of teratogenicity during pregnancy, but some studies suggest low neonatal birth weight from chronic maternal cannabis smoking, possibly related to fetal hypoxia [21; 22].

### Developmental Effects

Adolescents who regularly use cannabis may have impairments of learning and personal development. However, the possible effects of cannabis consumption on educational performance are difficult to demonstrate [14]. As noted, social development and the acquisition of coping skills may also be stunted.

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## LONG-TERM CANNABIS EFFECTS

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### RESPIRATORY EFFECTS

Chronic cannabis smoking is associated with bronchitis, emphysema, and squamous metaplasia (a pre-cancerous change), which all occur more frequently in those who have only smoked cannabis than in those who have only smoked tobacco. Chronic cannabis and tobacco smokers are at an increased risk for respiratory symptoms and histopathological changes than those who only smoke tobacco or cannabis [21; 22].

### IMMUNOSUPPRESSANT EFFECTS

There is not sufficient evidence of significant immunological damage in humans from cannabis [22]. However, it is important to note that cannabis may be contaminated with microorganisms, such as *Aspergillus* and *Salmonella*, as well as fecal matter. Therefore, a potentially serious adverse effect of cannabis is the risk of infection. In addition, chronic cannabis use may lead to impaired pulmonary defense against infection. The risk of infection is of particular concern in patients with HIV/AIDS due to their increased susceptibility to infection from fungal and bacterial contaminants and epithelial damage from the smoke [4].

### NEUROPSYCHOLOGICAL IMPAIRMENT

Chronic cannabis use has been reported to adversely affect cognitive functioning, demonstrated by impaired cognitive performance on a wide range of tasks, including memory and executive functioning [13]. Impairment of short-term visual and verbal memory persisting for 6 weeks after cessation of cannabis use has been reported, and there is a potential for persisting memory deficits in academic performance in school-aged children and college students. Adolescents and those with borderline or low intelligence quotient (IQ) may be particularly susceptible to these effects [22]. A small drop in overall IQ among current but not previous heavy users has also been shown [9].

Computed tomography (CT) studies in cannabis users have failed to identify gross structural brain changes, such as cerebral atrophy. In one study, older long-term cannabis users (mean age: 36 years) and control subjects with no history of cannabis abuse or dependence were compared, with cannabis users displaying no significant adjusted differences in volumes of gray matter, white matter, cerebrospinal fluid, or left and right hippocampus. Moreover, hippocampal volume in the cannabis users was not associated with age of onset nor total lifetime use. This is in support of studies suggesting that cannabis use is not associated with structural changes in the brain as a whole or the hippocampus in particular [25].

In another study of possible neurotoxic effects of chronic cannabis use, neuropsychological tests were administered to 77 current heavy cannabis users who had smoked cannabis at least 5000 times in their lives and to 87 control subjects who had smoked no more than 50 times in their lives. During a supervised abstinence period, the heavy smokers showed memory deficits on days 0, 1, and 7. However, few significant differences were found between the two groups by day 28, and significant associations between total lifetime cannabis consumption and test performance were scarce. The authors conclude from these results that cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure rather than cumulative lifetime use [26].

Overall, claims that chronic cannabis use is permanently neurotoxic have produced little scientific validation. Modestly impaired attention and ability to filter out irrelevant information in former cannabis users has been found in some studies, but other studies have not revealed impairment in cognitive function [24].

Although a degree of controversy exists surrounding whether heavy long-term consumption results in cognitive impairment, irreversible impairment seems to be minimal, if it exists at all. Medical use of cannabis for more than 15 years is generally considered to be well-tolerated without significant physical or cognitive impairment [23].

## PSYCHIATRIC COMORBIDITY AND CANNABIS USE

Cannabis use disorders are associated with high rates of other psychiatric diagnoses. The most frequent psychiatric comorbidities are depressed mood, major depression, and dysthymia [14]. It is also possible that cannabis use is a risk factor for serious mental illness, such as schizophrenia [14]. Patients with dependence on cannabis are at an increased lifetime risk for a variety of other psychiatric disorders. Current cannabis dependence is strongly associated with alcohol use disorders, affective and anxiety disorders, and tobacco use in the past year [17].

### Depression

Although there is little evidence to support a correlation between depression and infrequent cannabis use, a modest association between early-onset regular cannabis use and later depression has been reported. Because there is little evidence of an increased risk of later cannabis use among patients diagnosed with depression, the self-medication hypothesis is not supported. However, research has shown that depression and chronic use of cannabis are associated, and evidence indicates that heavy cannabis use may increase depressive symptoms in some users. It is important to note that this correlation may be the result of common social, family, and contextual factors that increase the risk of both heavy cannabis use and depression. Overall, heavy cannabis use appears to play a minor role in explaining population rates of depression [27].

### Psychoses

Healthcare professionals have observed a possible association between cannabis use and psychotic symptoms for many years. However, there is considerable disagreement regarding the degree of causation attributable to cannabis use in the development of psychotic symptoms in users without an obvious vulnerability to this effect.

There is biological evidence that there may be a causal relationship between cannabis and psychosis [19; 20]. When administered intravenously, delta-9-THC has been found to induce dose-dependent positive and negative psychotic symptoms in individuals with schizophrenia, and an interaction between cannabis use and a polymorphism of the acetylcholinesterase gene that codes for dopamine has also been reported [19].

In theory, cannabis use may precipitate a psychosis in several ways [14]:

- Acute induction of a toxic or organic psychosis, with symptoms of confusion and hallucination, that remits on abstinence
- Induction of an acute functional psychosis, similar to an acute schizophreniform state, that lacks the organic features of a toxic psychosis

- Induction of a chronic psychosis that persists after abstinence
- An organic psychosis induced by long-term use that only partially remits after abstinence, leaving a residual deficit state (an amotivational syndrome)

It is also possible that cannabis use is a risk factor for serious mental illness, such as schizophrenia [14].

Based on the literature, it is likely that cannabis use induces psychotic disorders in vulnerable individuals, defined as those with a history of unusual experiences that may be in part genetically mediated [19]. The relationship between cannabis use and vulnerability may explain the small (2 to 3 times) increase in risk for psychosis among cannabis users. This interaction has also been used to elucidate the lack of large increases in the incidence of psychoses to correspond with the increase in cannabis use rates among young adults and the earlier age of onset of schizophrenia-form disorders in cannabis users [19].

Although there appears to be at least some evidence linking cannabis use to the development of psychotic disorders, some argue that the studies have been flawed. Criticisms of studies linking cannabis and psychosis include failure to separate organic and functional psychotic reactions to cannabis; insufficient discrimination between psychoses; and lack of weighing the evidence for and against the category of cannabis psychosis [14]. There is strong evidence to support the belief that cannabis use may contribute to psychosis in certain circumstances, but the possible causal mechanisms are complex [14].

Robust evidence associating regular cannabis use with the development of psychoses comes from a 2007 meta-analysis by Moore et al. [20]. The researchers found consistent increased risk for psychosis in individuals with any history of cannabis use, with a correlation between frequency of use and heightened risk that suggests a dose-dependent effect. Pooled analysis showed a 40% increase in the risk of any psychotic outcome in individuals who had ever used cannabis, with the most frequent users showing a 50% to 200% increase in risk for psychosis [20]. The elevated risk of the late development of psychotic symptoms remained consistent even after adjusting for confounding factors, including polysubstance use, personality disorders, family relationships, criminality, socioeconomic factors, intellectual functioning, and mental health problems. The results of this analysis indicated that cannabis use was associated with increased lifetime risk of developing psychosis [20].

There has also been criticism of the belief that chronic heavy cannabis use leads to an amotivational syndrome, described as personality deterioration with loss of energy and drive to work [14]. Some have argued that the supporting evidence for this theory largely originates from uncontrolled studies of long-term cannabis users in various cultures and may be

a reflection of ongoing intoxication in frequent users of the drug [14]. More research in this area is required.

### Panic Disorder

Cannabis use has also been linked to the development of panic disorder. A study involving 1000 people 18 to 25 years of age found that 22% reported panic attacks or anxiety symptoms during cannabis intoxication, with women twice as likely as men to report these symptoms [14].

An individual's experience of cannabis intoxication may be variable; the same person given the same dose at different times may report different subjective effects. Although many users report a calming, tranquilizing effect, cannabis use may provoke feelings of anxiety or panic in some cases. For patients for whom cannabis use induces panic, a history of previous panic attacks (while sober) may not be present. A study of 66 panic disorder patients found that 24 experienced their first panic attack within 48 hours of cannabis use [54]. Ingestion of high doses of delta-9-THC produces intense anxiety in nearly all users predisposed to anxiety. It has been suggested that cannabis may provoke anxiety reactions via gamma-aminobutyric acid (GABA) antagonism, which may provoke CNS excitatory neurotransmission and brain hyperexcitability [54].

### Psychosocial Impairment

Antisocial behavior commonly occurs among cannabis users, and this is particularly evident among adolescent users. Adolescents who use cannabis regularly are at risk of experiencing delinquency, school failure, physical and psychological problems, and selling illegal drugs [12].

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## CANNABIS WITHDRAWAL SYNDROME

A cannabis withdrawal syndrome has been clearly demonstrated and is characterized by a variety of symptoms, including restlessness, anxiety, dysphoria, irritability, insomnia, anorexia, muscle tremor, increased reflexes, autonomic effects (e.g., changes in heart rate and blood pressure), sweating, diarrhea, and in some cases aggressive behavior [14; 28; 29]. The most frequent symptoms of cannabis withdrawal are emotional and behavioral in nature and do not typically cause significant physical, medical, or psychiatric disorders [30]. Regular daily use of cannabis can lead to withdrawal symptoms or a full-blown withdrawal syndrome upon cessation of use. A 1976 research project in India found that 98% of chronic cannabis users felt uncomfortable if they were unable to obtain their daily supply, with 86% experiencing strong drug cravings and 74% experiencing mental irritability and anxiety upon cessation [31].

The cannabis withdrawal syndrome requires near daily use to develop and is more likely to occur in adolescents and persons with other behavior difficulties. In a sample of adolescent cannabis users, the majority reported cannabis withdrawal, with an associated inability to perform school work and increased arguing, that began within 24 hours and worsened during the first several days of the abstinence period, especially in heavy users [32]. The majority of adults seeking treatment for a cannabis use disorder report a history of cannabis withdrawal, with most reporting a co-occurrence of 4 or more symptoms of substantial severity [30].

Neurochemical causes of cannabinoid withdrawal include reduced dopaminergic activity along the ventral tegmental area-nucleus accumbens pathway, and upregulated expression and release of corticotropin-releasing hormone (CRH) in the central nucleus of the amygdala [13].

### COURSE

The onset of abstinence symptoms consistently occurs during the first 1 to 2 days following cessation of cannabis or oral THC administration. Most symptoms return to baseline or to comparison-group levels within 1 to 2 weeks, although irritability, muscle tension, and sleep problems, particularly unusual dreams, may not return to baseline for an extended period. Because most transient symptoms return to baseline and because persons with psychiatric disorders are excluded from studies examining cannabis withdrawal, it is believed that the withdrawal symptoms are not rebound effects indicative of the participants' condition before initiation of cannabis smoking [30].

The administration of cannabis during the first 24 to 96 hours of abstinence results in an abrupt reduction and return to baseline of multiple abstinence symptoms, suggesting that cannabis withdrawal syndrome is specific to THC in humans [30].

### CLINICAL SIGNIFICANCE

Cannabis withdrawal has important treatment implications. Multiple symptoms of cannabis withdrawal syndrome are experienced among non-treatment-seeking daily cannabis users as well as inpatients and outpatients with cannabis dependence. In most cases, withdrawal symptoms are clearly observable to persons living with the user, who are able to document the disruption to daily living caused by the symptoms. The majority of persons enrolled in treatment for cannabis dependence acknowledge cannabis withdrawal symptoms, label at least some as moderate-to-severe, and complain that they make cessation of cannabis use more difficult [13; 30]. The significance of cannabis withdrawal and its potentially negative impact on treatment retention and relapse to cannabis use has not escaped the attention of researchers; several pharmacotherapy trials investigating medications of possible utility in cannabis withdrawal have been undertaken.

## TREATMENT OF CANNABIS ABUSE AND DEPENDENCE

Until fairly recently, cannabis was not considered a drug with a liability of dependence and addiction. Withdrawal did not lead to any obvious physical symptoms, and animals failed to self-administer the drug, a behavior usually associated with drugs of addiction [24]. Little research had focused on the treatment of cannabis abuse or dependence. However, research suggests that individuals can develop a chronic use pattern associated with dependence symptoms and recurrent psychosocial problems [6]. Two factors have contributed to the lack of research: the common beliefs that cannabis abuse rarely occurred as a primary problem and that cannabis use did not produce a true dependence syndrome. Data contrary to these assumptions first appeared in the late 1980s, and treatment development and efficacy studies specific to cannabis dependence first began to appear in the scientific literature during the 1990s [11].

### CHARACTERISTICS OF PATIENTS SEEKING TREATMENT FOR CANNABIS USE DISORDERS

Although an increasing number of individuals are seeking treatment specifically for a primary problem of cannabis dependence, most do not do so until they are older than 30 years of age. Young adults and adolescents generally seek treatment only when it is mandated by school officials, parents, or the criminal justice system [15].

The constellation of concerns that bring cannabis users to treatment may not be major socioeconomic or psychosocial problems. Rather, patients tend to express more subtle dissatisfaction with multiple areas of functioning and concerns about future health problems, which motivates the desire to quit or reduce use [6]. Individuals seeking treatment for cannabis use tend to exhibit social impairment and psychiatric distress, report multiple adverse consequences associated with cannabis use, and have a history of repeated unsuccessful attempts to stop using. Most patients perceive themselves as unable to quit [10].

Contrary to the popular belief that dependent individuals have to want treatment before it can be effective, most enter treatment in a relatively involuntary state, often to avoid or to undo the consequences of the drug use [34]. A significant opportunity to intervene is often the point at which drug abusers confront the legal consequences of their substance, especially taking into consideration the fact that more drug users are involved with the legal system than with the drug abuse treatment system [15].

## PHARMACOTHERAPY

The majority of treatment studies to date involving cannabis use disorders have investigated behavioral and psychosocial therapies. However, given the high rate of relapse and overwhelming numbers of cannabis-dependent individuals, the importance of pharmacotherapy for the treatment of cannabis-dependent individuals, particularly those who have been unresponsive to other treatment modalities, is important [13].

### Treatment of Cannabis Withdrawal Symptoms

As cannabis withdrawal symptoms may be a factor contributing to continuing cannabis use, medications alleviating these symptoms could be useful. Unfortunately, there is little research completed that evaluates the effectiveness of potential treatment medications on cannabis withdrawal in humans. According to completed studies, no medication has been shown to definitively decrease cannabis use by humans [13].

A study evaluating bupropion for cannabis withdrawal was performed by Haney et al. [35]. This study was based on the observation that bupropion facilitates abstinence from cigarette smoking, in part through its ability to decrease negative mood symptoms. Because similar mood symptoms have also been associated with cannabis withdrawal, it was suggested that this medication may have a place in the treatment of cannabis withdrawal. However, the authors found that bupropion worsened several ratings of mood, possibly caused by bupropion-associated enhanced norepinephrine activity [13; 35].

The efficacy of nefazodone (450 mg/day) was used in another study by the same research group [13; 36]. Nefazodone was chosen because of its demonstrated effectiveness in clinical populations with conditions also associated with cannabis withdrawal, including depression, agitation, and anxiety. Nefazodone decreased some symptoms associated with cannabis withdrawal (i.e., ratings of anxiety and myalgia) but in general had no effect on most symptoms (e.g., ratings of irritability and disordered sleep).

A third study evaluated the effectiveness of divalproex, which was chosen for testing based on evidence of successful treatment of some symptoms associated with cannabis withdrawal, such as irritability and mood lability [13; 37]. Divalproex was not found to positively affect cannabis withdrawal symptoms; in fact, many withdrawal symptoms (e.g., anxiety and irritability) increased compared to placebo. Divalproex also resulted in psychomotor performance disruptions.

Another agent evaluated for its effect on attenuating cannabis withdrawal was oral delta-9-THC [37]. Use of oral THC in the treatment of withdrawal symptoms was based on the concept of substituting a longer-acting, pharmacologically equivalent drug for the abused substance to stabilize the patient, with the intent to gradually withdraw the substituted

drug. Oral delta-9-THC markedly reduced withdrawal symptoms, including self reports of drug craving, anxiety, misery, and sleep disturbance. Withdrawal-associated psychomotor performance deficits, anorexia, and weight loss were also ameliorated. The authors conclude that moderate doses of oral delta-9-THC might be beneficial in the treatment of cannabis dependence [13; 37].

An issue of potential concern related to treating cannabis-dependent patients with delta-9-THC is the abuse potential. Abuse liability is influenced by the neurochemical effects as determined by the route of administration, drug concentrations, and the maximum drug concentrations. Thus, oral administration of delta-9-THC would be expected to produce much less reinforcement than smoked cannabis. Another advantage is that, unlike smoked cannabis, oral delta-9-THC is not associated with adverse pulmonary effects. Considering all of these factors, the benefits of oral delta-9-THC in the treatment of cannabis withdrawal appear to outweigh potential risks [13].

#### Pharmacotherapy for Relapse Prevention

A 12-week, open-label trial investigated the usefulness of a flexible dose of buspirone (mean daily dose: 39.1 mg) with 11 cannabis-dependent patients. Reductions in frequency and duration of craving and degree of irritability were produced, and participants had a 76.9% reduction in cannabis use during the study. Participants reported using cannabis on nearly three-quarters of the days in the three months prior to study entry and on 38.9% of the days during the study. A significant reduction was also seen on an anxiety rating scale during the study. However, although 44% of urine drug screens collected during treatment were cannabis-negative, only 2 subjects completed treatment [38].

In another study, 25 adult outpatients were randomized to either 6 weeks of placebo or divalproex, then switched to the alternate treatment for an additional 6 weeks. No significant between-groups differences were found in regards to treatment retention, with 38% of divalproex subjects and 33% of control subjects completing the entire study. Persons started on divalproex did not display better outcomes in terms of improvement in cannabis use or psychological symptoms than those started on placebo. All 25 patients had low blood levels of the study medications, suggesting poor compliance. However, retention during the first 8 study weeks was high (>75%), suggesting the medication was discontinued because it was poorly tolerated in this population [31].

#### Pharmacotherapy of Cannabis Dependence in Patients with Comorbid Mental Illness

In a pilot study, Potvin treated 8 cannabis-dependent patients with schizophrenia or affective bipolar disorder with quetiapine 100–1200 mg daily for a mean of 5.8 months [39]. Cannabis use declined from a mean of 35.6 g/week at baseline to 1.1 g/week, a 97.3% reduction. The mean daily dose of quetiapine during the study period was 388 mg.

## PSYCHOSOCIAL THERAPY

Several psychosocial therapy modalities have been evaluated in the treatment of patients with cannabis use disorders.

### Individual Drug Counseling

Cannabis users seeking therapy to quit may participate in standard counseling that is typically offered in community-based substance abuse clinics. Individual drug counseling emphasizes abstinence from cannabis and other drugs through use of self-help groups and a 12-step approach [15].

### Contingency Management (CM)

Contingency management approaches to adult substance abuse are effective behavioral interventions to increase drug abstinence and other treatment goals when integrated with other effective psychosocial treatments [40]. Essentially, CM interventions use reinforcement or punishment contingencies to increase or decrease the frequency of predetermined therapeutic and behavioral objectives [12].

### Relapse Prevention

Relapse prevention assists patients with decreasing their vulnerability to relapse by addressing topics such as lifestyle balance and managing high-risk situations [11].

### Social Support

Social support is based on the necessity of group support for change. Topics discussed in the group setting include getting and giving support, dealing with denial and mood swings, and interacting with peers who continue to use cannabis [11].

### Brief Motivational Interviewing

In brief motivational interviewing, a therapist provides feedback from a comprehensive assessment using motivational interviewing techniques. The therapist also instructs subjects on cognitive-behavioral therapy (CBT) techniques that could be used to abstain from cannabis use [11; 41].

### Psychosocial Treatment of Adults

In the first study published in which interventions specifically targeting cannabis dependence were evaluated, a 10-week social support group treatment was compared with a 10-week cognitive-behavioral relapse prevention group treatment using a sample of 212 adults [11; 42]. Results of the study indicated no significant differences between treatment conditions; both groups experienced a reduction in cannabis use throughout the follow-up period. After 1 year, about 17% of participants reported abstinence from cannabis use and an additional 19% of participants were considered “improved,” defined as cannabis use 50% or less of pretreatment levels.

The authors conducted a follow-up study comparing a cognitive-behavioral relapse-prevention treatment; a brief, 2-session motivational intervention; and a delayed-treatment control group [41]. The active treatment interventions resulted in greater reductions in cannabis use than delayed

treatment. Four months post-intake, participants in the two active groups reported reduced cannabis use compared to the delayed treatment group, reductions in frequency of use per day, lower number of dependence symptoms, and fewer problems related to cannabis use. At 16-month assessment, cannabis use increased in both active treatment groups but was lower than pretreatment levels. Urine drug screens were not obtained, and all drug use data was based on self-report and collateral verification.

In another study, 136 cannabis-dependent adults, 18 to 25 years of age, referred by the criminal justice system, were randomized to one of four treatment conditions. CM consistently produced positive effects in terms of treatment retention and cannabis use, both of which were specifically targeted. There were few significant main effects for motivational enhancement therapy/cognitive-behavioral therapy (MET/CBT) over drug counseling. However, additional analysis suggested that a combination of CM and MET/CBT resulted in better outcomes than MET/CBT without CM and drug counseling plus CM. All three treatments were found to be significantly more effective than drug counseling without CM. Participants assigned to MET/CBT continued to reduce the frequency of their cannabis use through a 6-month follow-up. The study population was noteworthy in that the participants were primarily young African American men with an average of five arrests by 21 years of age, 43% of whom met diagnostic criteria for antisocial personality disorder. Most had not completed high school and were unemployed [15].

In another study, efficacy of two brief interventions for cannabis-dependent adults across three study conditions was compared: two sessions of MET; nine sessions of multicomponent therapy (MET, CBT, and case management); and a delayed treatment control. The study followed 450 adult cannabis smokers with a diagnosis of cannabis dependence at baseline who were evaluated at 4, 9, and 15 months following treatment assignment. The nine-session intervention produced superior outcomes compared with the two-session treatment in terms of reductions in cannabis use and its consequences up to 12 months following treatment termination. The two-session treatment was more effective in use reduction than the control. Overall, the findings suggest that treatment for cannabis dependence could have a significant impact on chronic cannabis use, and both substance abuse treatment programs and behavioral healthcare providers should consider making cannabis-specific treatment more available and accessible. The authors also conclude that cannabis-focused treatments may be necessary for this population to achieve abstinence or to significantly reduce cannabis use; complete abstinence is not the only clinically meaningful outcome of treatment, and when given the opportunity, many cannabis abusers respond to treatment primarily by cutting back rather than quitting entirely [6].

A study of 90 cannabis-dependent adults seeking treatment randomly assigned participants to receive CBT, abstinence-based voucher incentives, or a combination of CBT and vouchers for 14 weeks. The authors found that, during treatment, abstinence-based vouchers were effective for facilitating prolonged periods of cannabis abstinence. CBT did not contribute to during-treatment abstinence, but it did enhance the post-treatment maintenance of the initial positive effect of vouchers. These results indicate that abstinence-based vouchers are a valuable treatment option, the use of which leads to greater rates of cannabis abstinence during treatment in comparison with a commonly used with CBT for cannabis dependence [43].

### Psychosocial Treatment of Adolescents

Approximately one-third of high school seniors (31.7%) used cannabis at least once in 2007 [56]. Less than 10% of adolescents who reported substance use disorder symptoms in the past year have ever received treatment, and when adolescents do enter treatment for cannabis use, only 20% believe their use is problematic. These findings suggest the need for interventions to increase motivation for change and encourage treatment entry for this population [44].

One study of the efficacy of psychosocial treatments in this patient population included 97 adolescents who had used cannabis at least nine times in the previous month. Participants were randomized to either an immediate two-session motivational enhancement intervention or a 3-month delayed treatment control. The majority (two-thirds) of the sample described themselves as in the pre-contemplation or contemplation stages of change regarding cannabis use. Cannabis use and negative consequences were assessed at baseline and at 3-month follow-up, and the assessment battery was carefully constructed to not appear biased toward demanding change. Both groups significantly reduced cannabis use at the 3-month follow-up, with an overall reduction in cannabis use by 16% (6 less days) over a 60-day period. Although reductions were modest and no differences between treatments were observed, the study succeeded in recruiting non-treatment-seeking adolescent cannabis smokers who were predominantly in the early stages of readiness for change, overcoming barriers in reaching adolescents who were frequent cannabis users [44].

Kamon et al. reported the results of a 14-week feasibility study of family-based CM with 19 adolescents 15 to 18 years of age [12]. The intervention consisted of a clinic-administered, abstinence-based incentive program; parent-directed CM targeting substance use and conduct problems; a clinic-administered incentive program targeting parental participation; and individual CBT for the adolescent patients. Twice-weekly urine and breath testing was conducted to monitor substance use. The adolescents attended an average of 10.3 of 14 sessions; parents attended an average of 10.6 sessions. By the end of treatment, substance use, externalizing behaviors,

and negative parenting behaviors had decreased. Based on results of the urine testing, abstinence increased from 37% at intake to 74% by the end of the study period; 53% of adolescents were abstinent 30 days post-treatment. The efficacy of a family-based CM model to treat adolescent substance use and conduct problems was demonstrated [12].

### Psychosocial Treatment of Patients with Comorbid Mental Illness

Cannabis is the most commonly used illicit drug among persons with mental illness and is associated with increased rates of recurrent psychiatric symptomatology and relapse. To study the impact of voucher-based contingent reinforcement in cannabis-dependent patients with serious mental illness, Sigmon and Higgins assigned 7 adults with schizophrenia and other serious mental illness to three conditions: a 4-week baseline, then a 12-week voucher intervention followed by another 4-week baseline [45]. During baseline, subjects received \$10 vouchers per urine specimen regardless of the results. During the intervention period, vouchers were given only to patients with specimens testing negative for cannabis, with total possible earnings of \$930. The participants were not required to seek treatment for cannabis abuse or be interested in quitting but to simply be willing to participate in a study in which they could receive incentives for cannabis abstinence. The percentage of cannabis-negative specimens was significantly greater during the intervention than during either baseline. The authors state that this study supports the use of voucher-based incentives to decrease problem cannabis use among individuals with serious mental illness. More research with this population is necessary in order to draw definitive conclusions.

### 12-STEP/SELF-HELP THERAPY

Many persons addicted to cannabis lack the resources for inpatient or outpatient treatment for their substance abuse problem or may be in need of ongoing support following treatment. To meet these needs, self-help groups provide a vital resource for those seeking support for abstinence. Self-help groups are non-professional organizations operated by peers who share the same addictive disorder. Self-help group attendance is free [46].

The most successful self-help groups employ the 12-step program and are modeled after Alcoholics Anonymous (AA). These groups include Narcotics Anonymous (NA) and Marijuana Anonymous (MA). The 12-step model emphasizes acceptance of addiction as a chronic progressive disease that can be arrested through abstinence but not cured. Additional elements of the 12-step model include spiritual growth, personal responsibility, and helping other addicted persons. By inducing a shift in the consciousness of the addict, 12-step programs offer a holistic solution. Groups such as NA and MA are also a resource for emotional support and are perhaps more accurately classified as "mutual help" organizations [46; 47].

Spiritual beliefs and endorsement of the disease concept are not prerequisites for NA or MA attendance, and spiritual beliefs have not been found to cause external attribution for previous drug use or possible future lapse events [48].

### Narcotics Anonymous (NA)

Relative to the more established AA, there are few studies published on NA. However, the studies that have been conducted reveal important information about how NA functions to help the new member abstain from drug use.

Improvement in psychological functioning as a result of NA involvement has been observed [49]. Studies have shown that individuals who have been off drugs and involved with NA for longer periods tend to have lower trait anxiety and higher self-esteem scores. Those who are abstinent for more than 3 years exhibit levels of anxiety and self-esteem similar to the general population [49].

Being active as an NA sponsor over a 1-year period has been found to be strongly associated with substantial improvements in sustained abstinence rates, which suggests that providing direction and support to other newer addicts is a way to enhance the likelihood of one's own abstinence [50].

### Marijuana Anonymous (MA)

Marijuana Anonymous (MA), a self-help program specific to persons with a desire to stop using cannabis, was formed in California in 1989 by cannabis addicts who felt their addiction to cannabis was not taken seriously in other 12-step meetings. MA is modeled after AA and NA, and members use the same 12-step model. MA meetings can be found in 32 states in the U.S. and in many countries [51].

As of 2009, there are no reports in the published research on outcome related to MA participation. However, participation in 12-step groups during and after treatment has been associated with positive outcomes among substance users, including cannabis-dependent patients [52]. Clinicians should encourage 12-step group participation as an aspect of treatment. A study conducted by Laudet identified two major obstacles to 12-step program participation: motivation and readiness for change and the perceived need for help [52]. Other obstacles to participation include perceived convenience and scheduling issues. This underscores the importance of promoting motivation for change and the need to assess patient beliefs regarding experiences with 12-step programs on a case-by-case basis in order to find a good fit between patient needs and 12-step resources [52].

### INTERVENTIONS FOR NON-ENGLISH PROFICIENT PATIENTS

For those who are not proficient in English, it is important that information regarding the use and potential abuse of cannabis and available resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner

and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

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## PROGNOSIS

Lapse and relapse are common among cannabis-dependent outpatients, with relapse rates similar to those found in studies of alcohol, opiate, and smoking cessation. The relationship between lapse and relapse among 82 patients who achieved at least two weeks of abstinence during outpatient treatment for cannabis dependence was examined by Moore and Budney [53]. The authors found that 71% of those who were abstinent went on to exhibit full relapse, defined as 4 or more days of cannabis use per week.

Studies of treatment efficacy show that cannabis-dependent adults tend to respond well to a variety of interventions. Although continuous abstinence is a less common outcome, all psychosocial therapies tested demonstrate utility in reducing cannabis use when delivered in both individual and group sessions [6]. Furthermore, CM combined with CBT or motivational enhancement may enhance outcomes [10].

However, low abstinence rates are an indicator of the difficulty in treating cannabis dependence by psychotherapies in outpatient settings. These suboptimal drug use outcomes suggest that continued development and testing of more effective treatments for cannabis dependence should remain a priority [43].

Comorbid mental disorders are also a risk factor for poorer outcomes. In particular, the presence of antisocial personality disorder is associated with increased rates of addictive and externalizing disorders, use of illicit substances in early adolescence, and rates of hyperactivity. These patients have a relatively poor prognosis for treatment outcome [17].

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## CONCLUSION

Cannabis is a significant drug of recreation and abuse. It is nearly inevitable that healthcare professionals in a variety of settings will have contact with a patient who uses or has used cannabis. Therefore, an understanding of the acute and sustained effects associated with the drug will facilitate better patient care. Knowledge of possible therapeutic uses of the drug is also necessary, as cannabis has become a part of the treatment of some chronic diseases. The information provided in this course should allow clinicians to better address the use of cannabis in their patients as well as to discuss the role and effectiveness of cannabis in ameliorating some symptoms associated with chemotherapy/cancer and AIDS.

Customer Information/Answer Sheet on pages 107–108.

TEST QUESTIONS

#9183 CANNABIS USE, ABUSE, AND DEPENDENCE

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*This 5 hour activity must be completed by July 31, 2012.*

1. Who is believed to be the first to describe the properties and therapeutic uses of cannabis?
  - A) Shen Nung
  - B) Walter O'Connor
  - C) The U.S. Government
  - D) William O'Shaughnessy
2. In what year was cannabis removed from the United States Pharmacopoeia?
  - A) 1839
  - B) 1915
  - C) 1942
  - D) 1967
3. The single most defining aspect of cannabis dependence is the
  - A) frequent use of the drug.
  - B) presence of a withdrawal syndrome.
  - C) salience of the relationship with the drug.
  - D) manifestation of physiological adaptation.
4. In comparison to the dependence syndrome, cannabis abuse is characterized by
  - A) less severity of symptoms.
  - B) more overt symptoms of use.
  - C) a shorter duration of drug use.
  - D) a greater number of behavioral symptoms.
5. Identifying patients with a cannabis-related disorder can be difficult because
  - A) associated problems are typically slow to develop.
  - B) patients may be attempting to conceal their drug use.
  - C) patients frequently do not recognize they have a problem.
  - D) All of the above
6. Approximately how many Americans 12 years of age and older have tried cannabis at least once in their lifetimes?
  - A) 18.6 million
  - B) 29 million
  - C) 76 million
  - D) 100 million

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7. Approximately what percentage of those who have used cannabis in the past year meet the DSM-IV criteria for cannabis dependence?
  - A) 1%
  - B) 6%
  - C) 10%
  - D) 19%
8. The majority of all patients admitted to adolescent substance abuse treatment programs report which drug as their primary substance?
  - A) Heroin
  - B) Cocaine
  - C) Cannabis
  - D) Methamphetamine
9. Which of the following is NOT a factor associated with cessation of cannabis use?
  - A) Male gender
  - B) Married marital status
  - C) High school completion
  - D) Infrequent cannabis use
10. The primary psychoactive ingredient in cannabis is
  - A) cannabinol.
  - B) delta-9-THC.
  - C) delta-8-THC.
  - D) cannabicyclol.
11. Cannabinoids are particularly abundant in the
  - A) seeds of the plant.
  - B) stalks of the plant.
  - C) leaves and flowers of the plant.
  - D) resin secreted by the female plant.
12. Cannabinoids are
  - A) highly water soluble.
  - B) metabolized in the liver.
  - C) distributed slowly throughout the body.
  - D) distributed to all parts of the brain at the same concentration.
13. THC can enhance the effects of
  - A) phenothiazines.
  - B) antidepressants.
  - C) non-steroidal anti-inflammatory drugs (NSAIDs).
  - D) None of the above
14. The therapeutic usefulness of cannabis has been well established in the treatment of
  - A) dependency to opiates and alcohol.
  - B) hypoxia and ischemia due to traumatic head injury.
  - C) refractory nausea and vomiting caused by antineoplastic drugs.
  - D) spasticity due to spinal cord injury, chronic pain, and Tourette's syndrome.
15. The assumed single most important characteristic in sustaining cannabis's widespread and often chronic recreational use is its
  - A) euphoriant potential.
  - B) dysphoric flashbacks.
  - C) antiemetic properties.
  - D) CNS depressant effect.
16. Which of the following has NOT been reported as a cannabis-induced change in perception?
  - A) Persistent visual changes
  - B) Distorted spatial perception
  - C) Heightened color perception
  - D) Decreased sound perception
17. Compared to tobacco smoke, the tar from cannabis smoke
  - A) contains almost no carcinogens.
  - B) is present in much lower amounts.
  - C) contains higher concentrations of the carcinogen benzpyrene.
  - D) contains lower concentrations of the carcinogen benzanthrancene.
18. Cannabis may be contaminated with
  - A) Aspergillus.
  - B) Salmonella.
  - C) fecal matter.
  - D) All of the above
19. One neurochemical cause of cannabinoid withdrawal is
  - A) catecholamine depletion.
  - B) upregulation of dopamine in the central nucleus of the amygdale.
  - C) decreased dopaminergic activity along the ventral tegmental area-nucleus accumbens pathway.
  - D) decreased expression and release of corticotropin-releasing hormone (CRH) in the central nucleus of the amygdale.

Test questions continue on next page →

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20. Which of the following medications has been shown to definitively decrease cannabis use?
- A) Nefazadone
  - B) Divalproex sodium
  - C) Oral delta-9-THC
  - D) None of the above

Be sure to transfer your answers to the Answer Sheet.

DO NOT send these test pages to CME Resource. Retain them for your records.

**PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.**