Cannabis and Cannabis Use Disorders

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Answer Sheet/Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

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

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Division Planner/Director Disclosure

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

Audience

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

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About the Sponsor

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Course Objective

The purpose of this course is to allow dental professional to effectively identify, treat, and provide appropriate referrals for patients who use or abuse cannabis.

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 use disorder and withdrawal.
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 psychologic 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.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Cannabis products such as marijuana and hashish comprise the most widely used recreational drugs both in the United States and worldwide [1]. 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 psychologic 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 use disorders.

HISTORY OF CANNABIS USE

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, archeologic discovery indicates that it was used in China since around 4000 B.C.E. 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 [2; 3].

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 [2; 3].

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 B.C.E. Following this, cannabis was cultivated for its fiber, seeds, medicinal use, and recreational consumption, which then spread to India from China [2].

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, claiming 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 [3]. Cannabis was removed from the U.S. Pharmacopoeia in 1942 [2].

DEFINITION OF CANNABIS USE DISORDERS

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 use or dependence in 2019 of all illicit drugs [4]. (Please note that laws passed in 18 states and the District of Columbia have fully legalized (recreational and medicinal) use of cannabis [5].)

Cannabis use disorder 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 [6]. The single most defining aspect of cannabis use disorder 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. Individuals who use cannabis often believe it is necessary to get through daily activities, alleviate stress, and cope with problems. Physiologic adaptation, evidenced by tolerance and withdrawal, is often present but may not be sufficient for diagnosis. Cannabis use disorder 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, psychologic, social, or occupational consequences [6]. Cannabis use disorder may be further qualified as mild, moderate, or severe based on the number of diagnostic criteria fulfilled.

Cannabis withdrawal is a condition that occurs following cessation or substantial reduction in use in previously heavy and chronic users [6]. Withdrawal symptoms (e.g., depression/mood changes, anxiety, sleep difficulties, anorexia, physical symptoms) must result in significant distress and/or affect the patient's social, occupational, or other important areas of functioning.

Identifying patients with a cannabis-related disorder can be difficult, because use disorders 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 [7].

Psychoactive substances have been misnamed "synthetic marijuana" and "synthetic cannabis;" however, these drugs include no actual cannabis. Instead, they consist of molecules developed in illicit labs and sprayed onto inert non-cannabis plant material for smoking. These molecules interact with cannabinoid and other receptors, making their toxicity a very serious concern.

EPIDEMIOLOGY OF CANNABIS USE

The 2019 National Survey on Drug Use and Health (NSDUH) found that 46.2% of Americans 12 years of age and older had tried cannabis at least once in their lifetimes, and 11.5% had used cannabis in the past month [4; 8]. Adolescent boys in all age groups are more likely than girls to have used cannabis in the last 30 days [4; 8]. Among ethnic groups, those of two or more races (19.7%) and Black/African Americans (13.7%) 12 years of age and older are the most likely to have used cannabis within the last month, followed by White and American Indian/Alaska Native (12.0% each), non-Hispanic/Latino mixed race (10.6%), Hispanic/Latino (9.5%), and Asian (4.4%) [8].

Of the 50.2 million illicit drug users in the United States, 84.2% were current (past month) users of cannabis [4; 8]. Approximately 3.0% of adolescents and 7.5% of adults who have used cannabis in the past year meet the *Diagnostic and Statistical Manual of Mental Disorders* 4th edition (DSM-IV) criteria for cannabis use disorder [4; 6; 8]. Analysis of data from 2002 to 2012 by researchers at the National Institutes of Health revealed that dependence/abuse rates (using DSM-IV criteria) increased significantly (from 1.5% to 2.9%), with the most notable increases among those 45 to 64 years of age (0.4% vs 1.3%); Black individuals (1.8% vs 4.6%); Hispanic individuals (1.2% vs 2.8%); those with the lowest income (2.3% vs 5.4%); and those in the South (1.0% vs 2.6%) [9]. The researchers noted that the increase in use disorders was unrelated to a substantial overall increase in frequency or quantity of use and was possibly associated with higher cannabis potency, decreased cost, and various societal factors [9]. The 2019 NSDUH noted a rate of 1.8% [4].

A study published in 2015 compared data from the National Epidemiological Survey on Alcohol and Related Conditions in 2001–2002 to 2012–2013 and showed that past-year cannabis use among U.S. adults more than doubled from 2001 (4.1%) to 2013 (9.5%), and cannabis use disorder (using DSM-IV criteria) increased from 1.5% to 2.9% in the general population during the same time [9]. However, the prevalence of cannabis use disorder among current users in the surveys actually decreased from 35.6% in 2001 to 30.6% in 2013, possibly due to changing laws and attitudes from the time of the first survey [9]. Another study showed the prevalence of cannabis use disorder among adolescents decreased by nearly 24% between 2002 and 2013, along with a concurrent decrease in conduct problems (e.g., fighting, stealing) in this age group [10].

The DSM-5 was published in 2013 with updated criteria for cannabis use disorder. These new criteria combined dependence and abuse into a single disorder, removed the legal problems criterion, and added craving, withdrawal, and a severity metric [6; 11]. While prevalence data using the DSM-5 cannabis use disorder criteria are limited, one study showed a 2.54% past-year and 6.27% lifetime prevalence of cannabis use disorder in U.S. adults, an increase from the diagnostic criteria of the DSM-IV [11]. Using DSM-5 criteria of severity, 1.38% of cases of cannabis use disorder were considered mild, 0.59% were moderate, and 0.57% were classified as severe [11]. Regarding race and ethnicity, DSM-5 cannabis use disorder trends follow that of the cannabis-using population, with highest past-year rates seen in Native American (5.3%) and Black (4.5%) populations, followed by Hispanic (2.6%), White (2.2%), and Asian (1.3%) populations [11]. Higher rates are seen in adults 18 to 29 years of age (6.9%) than those 30 to 44 years of age (2.5%) and 45 years of age and older (0.8%) [11]. More studies are needed to accurately depict the impact of the DSM-5 changes on cannabis use disorder diagnoses.

According to the 2019 NSDUH, 3.7% of persons who use cannabis are daily or nearly daily users [8]. The population rate affected by cannabis use disorder (1.8%) is higher than any other illicit drug; however, this is because the population rate of cannabis use is substantially higher than any other illicit drug [4; 8; 12; 13]. In a study using DSM-IV criteria, dependence developed within 10 years of initial nicotine (15.6%), cocaine (14.8%), alcohol (11.0%), and cannabis (5.9%) use [14]. The lifetime rates are 67.5% for nicotine, 20.9% for cocaine, 22.7% for alcohol, and 8.9% for cannabis. Compared with use of nicotine, alcohol, or cocaine, cannabis dependence develops less frequently but more rapidly [14].

The rate of cannabis use by children and adolescents doubled during the 1990s [13]. After a slight decline and leveling off from 2000 to 2008, the rate peaked in 2010 and again began to decline, reaching the lowest levels since the mid-1990s in 2016 [4; 8; 10]. Occasional cannabis experimentation during adolescence, while illegal, is often considered normative behavior and is not strongly correlated with behavioral or emotional disorders in the general population [13]. Although the exact number is unclear, approximately one-half of "very young" individuals who use cannabis more than monthly exhibit behavioral or emotional difficulties. It is unclear if these difficulties exist before or are an effect of cannabis use or of overlapping factors. Genetic behavior disorders, parents who use cannabis, family disintegration, and "loss of trusting attachments to key adults" have been implicated as both causes of adversity leading to cannabis use and of anxiety, depression, and risk-taking behaviors in pre-adolescents [13]. The perceived impact that cannabis has on physical and psychologic health, along with other negative factors, strongly predicts use patterns. Although adolescents' perceived great risk of harm from smoking marijuana weekly declined from 40.6% in 2015 to 34.6% in 2019, perceived risk remains a strong protective factor for this population [4; 15].

EVIDENCE-BASED PRACTICE RECOMMENDATION

Researchers from the Institute for Mental Health Policy Research recommend avoiding early age initiation of cannabis use (i.e., definitively before the age of 16 years) in order to lower the risks associated with cannabis use.

(https://ajph.aphapublications.org/doi/full/10.2105/AJPH.2017.303818. Last accessed July 12, 2021.)

Level of Evidence: Substantial (Based on several supportive findings from good-quality studies with few opposing studies)

TREATMENT UTILIZATION

Increases in both the prevalence of cannabis use and the potency of cannabis contributed to a 381% increase in cannabis- and other cannabinoid-related emergency department episodes reported from 2002 to 2011. The number of cannabis-related emergency department visits for adolescents 15 to 17 years of age was 61% higher in 2011 than in 2005. Visits increased 65% among boys and 53% among girls[16]. Cannabis-related conditions that may be seen in an emergency department include chronic addiction to cannabis, acute cannabis psychosis, and cannabis-related schizophrenia [17].

Utilization of treatment services for cannabis dependence has also increased. Adults entering substance abuse treatment programs with cannabis-related problems doubled in the 1990s, and primary admissions for cannabis rose from 13% in 1999 to 19% in 2010 to 19.8% in 2019 [8]. With the ongoing opioid epidemic, cannabis-related treatment admissions fell from the second most common in 2012 to the third most common in 2019, at a rate of 19.8%. Alcohol admission rates were 54.1% and opioid treatment admission rates were 33.5%. Those for cocaine (14.4%) and stimulants (4.6%) are lower than those for cannabis [8].

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 [3]. In a sample of 311 cannabis-dependent users (according to the DSM-IV criteria), the leading reasons for failure to seek treatment included a desire for self-reliance (36.7%), perceived treatment ineffectiveness (16.7%), and avoiding stigma (13.3%) [18].

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 [3; 8]. 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.

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 [19]. Co-occurrence of these problems is a strong predictor of poor outcome following substance abuse treatment [19]. Factors associated with cannabis dependence include male gender, adolescent aggression/delinquency, childhood abuse (particularly sexual abuse), and evidence of adolescent risk-taking behaviors, such as cigarette smoking, conduct problems, and involvement in a delinquent peer group [20; 21]. One study found that externalizing disorders (e.g., antisocial personality disorder) from proximal developmental periods

were a significant risk factor for future cannabis use disorders in adolescents and young adults; internalizing disorders were not [22]. Exposure to multiple risk factors is associated with poorer prognosis.

Early subjective response to cannabis is associated with later risk of misuse [23; 24]. Participants in a survey reporting five positive reactions to the drug had 20 times greater risk of later use disorder than those who did not experience positive reactions, even after controlling for confounding factors. These findings suggest that early subjective and physiologic reactions to cannabis are predictive of later misuse and possibly reflect underlying genetic differences in vulnerability to use disorders. These possible genetic predispositions are likely mediated by individual differences in the responsiveness of the mesolimbic dopamine system to substance use [23].

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, exposure to formal treatment, higher socioeconomic status, high school completion, and non-using friends [25; 26; 27].

Genetic Vulnerability Theory

Analyses of several adoption, family, and twin studies that examined the relationship between cannabis use and heritable factors determined that the use of cannabis (and other licit and illicit substances) is due in part to genetic vulnerability and an overlap of environmental influences [28; 29]. There appear to be substantial genetic influences on measures of cannabis involvement that correlate with progression to greater levels of addiction, and an individual's vulnerability to cannabis abuse/dependence is shaped by a common susceptibility to multiple substance abuse and also by risk factors unique to cannabis. Researchers in one twin study clarified the basics of this theory in their conclusion, stating that genetic factors predispose individuals to substance use/abuse whereas environmental experiences determine which class of psychoactive substances a predisposed individual will prefer over another [30]. In a meta-analysis evaluating the relative magnitude of the influence of genetic and environmental factors on problematic cannabis use, researchers estimated that the proportion of the total variance attributable to genetics was 51% in men/boys and 59% in women/girls [29].

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 [31].

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 [28]. However, it should be noted that evidence of a causal relationship between cannabis use and progression to other drug use has not been clearly proven [28]. A report from the National Center on Addiction and Substance Abuse at Columbia University found that cannabis's "gateway" effect (if any) is far less important than that of cigarettes and alcohol, and teens who use alcohol and nicotine are 30 times more likely to try cannabis [32]. Analysis of data from the National Epidemiological Survey on Alcohol and Related Conditions found that 44.7% of individuals who try cannabis progress to another illicit drug in their lifetimes, although the researchers in this study did not control for lifetime alcohol or nicotine use [33]. One theory is that dopaminergic effects of alcohol, cannabis, and nicotine lead users to seek similar effects from other, more potent drugs.

PHARMACOLOGY

Cannabis contains more than 480 known chemicals, more than 100 of which are grouped under the category of cannabinoids [2; 34]. The primary psychoactive ingredient is delta-9-tetrahydrocannabinol (delta-9-THC), which accounts for up to 25% of the total dry weight of high-potency strains [35]. Other cannabinoids, including delta-8-THC, cannabinol, cannabicyclol, cannabichromene, and cannabigerol, are present in small quantities (typically less than 5% dry weight) 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 [2].

One notable exception is cannabidiol (CBD), which in some cannabis strains can account for up to 5% dry weight and has demonstrated therapeutic efficacy for psychosis, anxiety, and other disorders in small-scale studies [35; 36; 37]. The psychotomimetic and anxiogenic effects of THC itself are thought to be attenuated by CBD [38]. In a 2011 study, cannabis users who ingested high-CBD-content cannabis experienced significantly lower degrees of psychotic symptoms compared to those who ingested high-THC-content cannabis [36]. Cannabinoid receptor type 2 (CB2) activity accounts for some anti-inflammatory and antinociceptive effects, while the anxiolytic effects of CBD probably result from 5HT1-A (serotonin) receptor agonist activity [38; 39]. CBD also exhibits significant anti-inflammatory and analgesic effects [40].

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 (e.g., "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 [41; 42]. Vaporizing cannabis (heating below its flash point), either with a purpose-built vaporizer unit or with a heating wand and a conventional pipe or water pipe, is becoming increasingly popular, especially among medicinal and/or "health conscious" users. This method of use offers slightly elevated THC availability (allowing the user to "smoke" less) and greatly reduced combustion byproduct toxicity compared to smoking [42; 43].

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 over time [44].

During the 1960s and 1970s, an average joint contained about 10 mg of THC. Today, a similar-size 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 or resin. 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 early 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 [41; 45].

PHARMACOKINETICS OF CANNABINOIDS

Approximately 50% of the THC and other cannabinoids present in a cannabis cigarette enter the mainstream smoke and are inhaled [45]. 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 [45].

The onset of action of inhaled cannabis is within seconds, and full effect is achieved within 30 minutes; vaporized cannabis results in higher serum THC levels after 30 to 60 minutes, but this can vary based on self-administration preferences. The bioavailability after oral ingestion is lower than that seen with inhalation; blood concentrations are as

low as 25% to 30% of those obtained by smoking the same dose, partly due to hepatic first-pass metabolism [41]. The onset of effect is delayed (up to four hours) after oral ingestion, but the duration is prolonged because of continued slow absorption from the gut [41].

As little as 2.5 mg of THC is enough to produce measurable psychologic and physical effects in the occasional cannabis user. Upon transferring to the bloodstream, cannabinoids are distributed rapidly systemically, first reaching the fatty tissues and organs with the highest blood flow, such as the brain, lungs, and liver [46]. 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 [45]. Whether THC accumulates in the brain with long-term use is unknown, due to limits in THC access and accumulation imposed by the blood-brain barrier.

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 [45].

Cannabinoids are mainly 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. The major metabolite is 11-hydroxy-THC, which may be more potent than the parent compound and be responsible for some of the effects of cannabis. Relative to inhalation, first-pass hepatic metabolism with oral ingestion yields a greater proportion of 11-hydroxy-THC [46].

Elimination occurs over several days due to the slow rediffusion of THC from body fat and other tissues. Roughly 20% to 35% of THC is eliminated in urine and 65% to 80% in feces. By five days, 80% to 90% of THC is eliminated, although THC from a single dose can be detected in plasma up to 13 days later in chronic smokers as a result of extensive storage and release from body fat [46].

PHARMACODYNAMICS

Cannabinoids act primarily by binding to the CB1 and CB2 receptors. 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 [2; 3].

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. The first substance, discovered in 1992, was eventually isolated and named anandamide after the Sanskrit word for bliss, *ananda*; 2-arachidonoylglycerol was discovered soon after. Anandamides are derivatives of arachidonic acid, a polyunsaturated omega-6 fatty acid, and are related to prostaglandins [45; 47].

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 [41]. The endogenous cannabinoid system is a signaling system that includes cannabinoid receptors, endogenous receptor ligands (termed endocannabinoids), and their synthesizing and degrading enzymes [48]. Core functions of the endogenous cannabinoid system (ECS) have been described as "relax, eat, sleep, forget, and protect," shorthand for the diversity of processes involving the ECS [49]. The ECS regulates neuronal excitability and inflammation in pain circuits and cascades and also helps regulate movement, appetite,

aversive memory extinction, hypothalamic-pituitary-adrenal axis modulation, immunomodulation, mood, wake/sleep cycles, blood pressure, bone density, tumor surveillance, neuroprotection, and reproduction. A number of the cannabinoids' pharmacologic effects can be explained on the basis of these interactions, examples being tachycardia and xerostomia, which are caused by the effects of THC on acetylcholine [50].

CB2 receptors are primarily found in immune cells, suggesting that cannabinoids may play a role in the immune response [47]. CB1 receptors are found throughout the body but are concentrated in the brain, with the highest density in the substantia nigra, cerebellum, globus pallidus, and caudate nucleus. Other brain regions with high CB1 receptor density include the cerebellum, hippocampus, cerebral cortex, and nucleus accumbens. The distribution of CB receptors indicates that the endocannabinoid system has effects on a broad range of behaviors [3].

TOXICITY

There are no cases in the literature of death due to toxicity following the maximum oral THC dose in dogs (up to 3,000 mg/kg THC) and monkeys (up to 9,000 mg/kg THC). In animals and humans, it is virtually impossible to induce fatal toxicity, and no human fatalities resulting from cannabis ingestion have been documented to date [39]. The greatest risk for toxicity and potential overdose is among children who may consume cannabis edibles, beverages, or candies inadvertently [51; 52; 53; 54]. In adults, most toxic reactions are mild, but in children, overdose can result in significant respiratory depression [51]. Findings compiled by the National Academies of Sciences indicate an increase in pediatric cannabis exposures in states where cannabis has been decriminalized [55].

TOLERANCE

Tolerance to most of the THC effects eventually develops in regular users. Cannabis tolerance primarily results from pharmacodynamic mechanisms, including changes in CB1 signaling ability due to receptor desensitization and down-regulation. THC tolerance varies across different brain regions, possibly explaining why tolerance develops to some cannabis effects but not to others [56]. Tolerance to most THC effects develops after a few doses and then disappears rapidly following cessation.

DRUG-DRUG INTERACTIONS

As with many drugs, cannabis 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 [57]. 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 [50].

THERAPEUTIC USE OF CANNABIS

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 pain [58]. 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 [58].

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 [2]. Cannabis was reintroduced into medical use in 1996 by popular vote and legislative acts in California. By 2021, 35 states and the District of Columbia had followed suit [59]. (For information on laws pertaining to the medical use of cannabis in your state, visit https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc.) In addition, cannabis is used by millions of patients for medicinal purposes in jurisdictions where it remains illegal for medical use [60].

For some clinical conditions, most of the published research involves oral cannabinoids, and there are questions over the extent this efficacy can be extrapolated to cannabis. Some reports indicate that patients benefiting from oral cannabinoids are likely to benefit from smoked cannabis, but the reverse is not always true [61]. For example, inhaled cannabis trials for the management of nausea and vomiting are sparse. Although randomized controlled trials of dronabinol or nabilone predominate and have consistently shown efficacy, patients tend to prefer smoked over oral delivery due to the rapid alleviation of nausea and vomiting, ease of titration, and greater tolerability. Thus, for indications for which cannabis randomized controlled trials are few or absent, it seems reasonable to extrapolate non-cannabis cannabinoid efficacy to smoked cannabis.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Dronabinol, a synthetic THC derivative, 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) [50]. Dronabinol and nabilone, another synthetic derivative, are generally considered safe, effective antiemetics and are recommended by the National Comprehensive Cancer Network for this use [40]. A vast body of anecdotal evidence from the past 150 years as well as preclinical and clinical trial results strongly indicate a valuable role for cannabis in controlling nausea and vomiting caused by cytotoxic drug administration or secondary to another primary medical condition [62]. A meta-analysis of cannabinoid efficacy in chemotherapy-induced nausea and vomiting found superior antiemetic efficacy of dronabinol, nabilone, levonantradol (not approved for use in the United States), and smoked cannabis compared with conventional drugs and placebo [63].

CHRONIC PAIN

Cannabis has been safely co-administered with a wide range of other drug agents (as discussed) and acts synergistically with opioids to enhance analgesia and allow opioid dose reduction. Chronic pain treatment often requires multiple drug agents that target different pain mechanisms, and the novel mechanism and superior safety profile of cannabis versus opioids suggests that it can be a valuable addition to therapeutic options for chronic pain [64; 65].

In one study, 10-mg and 20-mg doses of THC were found to be roughly equivalent to 60 mg and 120 mg codeine doses, respectively, and a strong sedative effect was observed [66]. A 2010 British study found that improved analgesia was realized with a THC/CBD extract oromucosal spray in patients whose pain was not alleviated with strong opioids [67]. Twice as many patients given the THC/CBD extract had a 30% reduction in pain (the measure of

success) than those administered placebo or a pure THC extract. A 2012 study concluded that patients with cancer being treated with opioids but who had poorly controlled chronic pain achieved significantly better control of the pain and sleep disruption with THC/CBD oromucosal spray (lower doses of 1–4 and 6–10 sprays/day) compared with placebo [68].

A comprehensive review of randomized controlled studies found that higher doses or strengths of cannabis are not necessarily the best therapeutic strategy for managing chronic pain. Higher doses and strengths may actually increase pain and or the incidence of adverse effects [69]. These findings highlight the need for clinical studies to assess dose-dependent effects, particularly in light of the high-strength cannabis and cannabis-derived products available at medical dispensaries.

SPASTICITY

Spasticity is a core symptom of multiple sclerosis, is common after stroke and with other neurologic conditions, and greatly limits movement, activities of daily living, and participation in life by those afflicted. Oral antispasmodic agents are of limited effectiveness, and beneficial treatment options for spasticity have not significantly expanded since the late 1990s [70]. Consequently, many patients with multiple sclerosis have sought relief through cannabis use. The oromucosal cannabinoid spray nabiximols appears efficacious in multiple sclerosis but is not yet approved for clinical use in the United States [71; 72]. Several clinical trials of cannabis in multiple sclerosis have been performed, and these studies have demonstrated cannabis efficacy in reducing spasticity and pain [73; 74; 75].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Academy of Neurology asserts that clinicians might offer oral cannabis extract to patients with multiple sclerosis to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain).

(https://www.aan.com/Guidelines/home/GetGuidelineContent/651. Last accessed July 12, 2021.)

Level of Evidence: A (Established as effective for the given condition in the specified population.)

CANCER- AND HIV-ASSOCIATED ANOREXIA AND WEIGHT LOSS

The effectiveness of cannabis and THC derivatives 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 [58]. A double-blind clinical trial of HIV-positive patients found smoked cannabis increased daily caloric intake and body weight, with few adverse effects [76]. Benefits from smoked cannabis reported by 252 patients with HIV/AIDS included relief of anxiety and/or depression (57%), improved appetite (53%), increased pleasure (33%), and pain relief (28%). However, recent use of cannabis was strongly associated with severe nausea [77].

A review of cannabinoid use in cancer patients found a beneficial effect in stimulating appetite in patients who were receiving chemotherapy or experiencing pain [78]. However, because pain can be a persistent symptom in patients with cancer, intermittent use among respondents may indicate limits to the benefits of cannabis use for pain control. Future studies evaluating cannabis in cancer-related pain control are needed to assess its role as a potential adjunct to currently approved pain-control strategies [79]. Interestingly, the results of several

preclinical and preliminary clinical testing studies have suggested that cannabinoids inhibit tumor and/or malignant cell growth in pancreatic, lung, leukemic, melanoma, oral, and lymphoma cancers and other malignant tumors [80]. Despite nearly all respondents in a survey-based study of patients with cancer desiring more information and education about cannabis use, they reported that they were more likely to get information from sources outside the healthcare system than from their oncology or hematology providers [79].

SEIZURES

An oral solution of cannabidiol (a cannabis derivative) was approved in 2018 for the treatment of Lennox-Gastaut syndrome and Dravet syndrome. When taken in conjunction with other medications, this drug has been found to reduce the frequency of seizures (compared with placebo) [81; 82]. It may be used in patients 2 years of age or older, and common side effects include sleepiness, elevated liver enzymes, and decreased appetite. One systematic review and meta-analysis evaluated the efficacy and safety of CBD as an adjunct to treatment in patients with epilepsy [83]. The study included four trials of oral CBD (10 mg and 20 mg) involving 550 patients with uncontrolled Lennox-Gastaut syndrome or Dravet syndrome. Adjunctive CBD in these patients resulted in greater reduction in seizure frequency, but a higher rate of adverse events. A reduction in all-types seizure frequency by at least 50% occurred in 37.2% of the patients in the CBD 20 mg group and 21.2% of the placebo-treated participants. Adverse events associated with use of CBD included somnolence, decreased appetite, diarrhea, and increased serum aminotransferases [83]. Despite these promising results, some researchers report finding inconsistent results in systematic reviews of the therapeutic benefits of cannabis-based medicines compared with placebo [84; 85].

ACUTE CANNABIS EFFECTS

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 [13; 86]. Transmission of dopamine is increased in the nucleus accumbens following acute administration of cannabinoid agonists.

BEHAVIORAL AND PSYCHOLOGIC EFFECTS

The pharmacologic actions of cannabinoids are 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 [45; 87]. The experience of intoxication is highly variable and is influenced by the dose, the environment, and the experience and expectations of the user [86]. Tolerance to cannabinoids occurs by variations in pharmacodynamics. Tolerance can affect mood, memory, psychomotor performance, sleeping heart rate, arterial pressure, and body temperature, among other symptoms [88].

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 psychologic 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 psychologic reaction similar to that of post-traumatic stress disorder [45].

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 [45].

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 [45].

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 [45].

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 [45].

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 [45]. Psychomotor performance further deteriorates at higher doses, and impairment can persist several hours following a single dose [45].

Aggression and Violence

Cannabis typically decreases aggression and increases sociability. However, some individuals, particularly those under stress and predisposed to violence, become aggressive after taking cannabis. Research has shown that cannabis users with a history of aggression have a 60% greater likelihood of perpetrating partner violence than nonusers [89]. Violent behavior may be more common among those with acute paranoid or manic psychosis induced by cannabis and polydrug use [45].

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 [90]. After taking a large dose of THC, vulnerable or heavy users may temporarily experience a form of drug-induced psychosis [91]. This is classified in the DSM-5 as cannabis intoxication with perceptual disturbances or as a substance-induced psychotic disorder and is diagnosed if the hallucinations are not better explained by another medical or mental disorder and if the symptoms appear during or within two hours of substance use or withdrawal [6]. The frequent use and rising potency of cannabis suggest that young people may have their first-episode of psychosis earlier than historically usual [91].

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 [86].

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 [45]. Reddening of the conjunctivae, a characteristic sign of cannabis use, is the result of widespread vasodilation [41].

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 benzopyrenes 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 [41; 45]. As a result, cannabis use may result in impairment of lung function, leading to airflow obstruction and hyperinflation [92].

Although many carcinogens and tumor promoters are common to tobacco and cannabis smoke, differences in the active constituents result in different biologic outcomes. Molecules in tobacco smoke enhance carcinogenic pathways through several mechanisms. In contrast, molecules in cannabis smoke inhibit carcinogenic pathways through down-regulation of immunologically generated free radical production (the innate response to inhaled smoke and particulate); THC blockade of enzymatic conversion of smoke constituents into carcinogens; the absence of cannabinoid receptors in respiratory epithelial cells (which maintains DNA damage checkpoint mechanism integrity with prolonged cannabis smoke exposure); and the anti-angiogenic, tumor-retardant, and anti-inflammatory activity of many cannabinoid smoke constituents [93]. Large studies assessing the potential risk of lung cancer with chronic cannabis use have reached different conclusions, with one finding no increased risk and another reporting a twofold increase in the risk of lung cancer among long-term heavy users [94; 95]. Additional research is necessary to parse these findings.

A University of California, San Francisco, study found that vaporizing cannabis eliminates many of the harmful combustion byproducts (e.g., benzene, naphthalene, toluene, other aromatic hydrocarbon toxins) and greatly reduces tar and carbon monoxide from the inhaled charge [43]. Therapeutic plasma THC levels are slightly increased with this administration, and it was determined that vaporizing cannabis is safer than smoking.

Endocrine/Reproductive System Effects

Cannabinoids, including THC, bind to androgen receptors, and cannabis is considered antiandrogenic. However, the drug's effects on fertility are unclear. Chronic cannabis ingestion appears to have negative effects on sperm quality (e.g., a reduction in the volume and number of spermatozoa, changes in morphology and motility) [96]. 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 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 and placental complications [41; 45]. In a large study, prenatal cannabis use was associated with significantly greater odds of low birth weight and small for gestational age, but not preterm birth [174]. This effect was particularly marked among heavy users (weekly or more frequent).

Developmental Effects

There is some evidence that offspring of mothers who consumed cannabis during pregnancy may be at increased risk for behavioral and conduct problems, impaired executive functioning, and poor school achievement [97]. In addition, 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 [90]. As noted, social development and the acquisition of coping skills may also be stunted. In one study, onset of cannabis use before 17 years of age was associated with a significantly increased risk of cannabis dependence, use of other illicit drugs, suicide attempt, depression, and welfare dependence by 30 years of age [98].

LONG-TERM CANNABIS EFFECTS

RESPIRATORY EFFECTS

Chronic cannabis smoking is associated with bronchitis, cough, shortness of breath, and asthma [41; 45]. Cannabis smoke contains many of the same chemicals as tobacco smoke, several of which are known carcinogens. Evidence for a link between cannabis smoking and serious conditions such as lung cancer is mixed. Further research is needed to clarify whether cannabis smoke is a causal factor for lung cancer [99].

IMMUNOSUPPRESSANT EFFECTS

There is not sufficient evidence of significant immunologic damage in humans from cannabis [45]. However, it is important to note that cannabis may be contaminated with micro-organisms, 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 [7].

NEUROPSYCHOLOGIC 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 [3]. Impairment of short-term visual and verbal memory persisting for six 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 [45; 100]. Studies regarding effect of long-term cannabis use on IQ have been mixed [13]. In a New Zealand longitudinal study, heavy users were found to have a decline in IQ from childhood to midlife (mean:-5.5 IQ points), poorer learning and processing speed relative to their childhood IQ, and informant-reported memory and attention problems [175].

Imaging studies in cannabis users have identified structural brain changes [101]. In studies using magnetic resonance imaging, heavy cannabis use was correlated with larger cerebellum grey matter volume and reduced amygdala and hippocampus grey matter volume as well as changes in higher functional connectivity in the orbitofrontal cortex network and higher structural connectivity in the forceps minor [101; 102].

A prospective study of 1,037 individuals who regularly use cannabis were followed from birth to 38 years of age [100]. The researchers conducted neuropsychologic testing at 13 years of age (prior to initiation of cannabis use) and again at 38 years of age and found that persistent cannabis use was associated with neuropsychologic decline broadly across domains of functioning, even after controlling for years of education. In addition, in users who began using cannabis in adolescence, these deficits remained even after cessation of use [100]. This study did not take into account potential confounding variables, such as personality, family situation, or socioeconomic status.

In 2018, a systematic review and meta-analysis on the cognitive function of heavy cannabis use in adolescents and young adults showed relatively small reductions in cognitive functioning. When abstinence was maintained for 72 hours or longer, cognitive functions were regained and the deficits were diminished significantly [103].

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 [86; 100].

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 [50].

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 [90]. It is also possible that cannabis use is a risk factor for serious mental illness, such as schizophrenia [90]. Patients with a history of cannabis dependence are at an increased lifetime risk for a variety of other psychiatric disorders, and current cannabis dependence is strongly associated with alcohol misuse, affective and anxiety disorders, and tobacco use in the past year [25]. However, the pathogenesis of most psychoses is not well understood. Based on postmortem and other studies, abnormalities and dysfunction of the endocannabinoid system may play a significant role in psychologic disorders (e.g., depression, suicide, schizophrenia), making the use/misuse of exogenous cannabinoids an ongoing area of research for both therapeutic potential and causation [104].

Depression

Although there is little evidence to support a correlation between depression and infrequent cannabis use, a modest association between early-onset or heavy, habitual cannabis use and later depression has been reported [105]. 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 [106].

Psychoses

Healthcare professionals have observed a possible association between habitual cannabis use and psychosis for many years. However, there is considerable disagreement regarding the degree of causation attributable to cannabis use in the development of psychosis among users without an obvious vulnerability to this effect (e.g., genetic factors).

There is biologic evidence of a possible causal relationship between cannabis use and psychosis, particularly in relation to non-affective schizophrenia-spectrum disorders [107; 108]. When administered intravenously, delta-9-THC has been found to induce dose-dependent positive and negative psychotic symptoms in individuals with schizophrenia; an interaction between cannabis use and a polymorphism of the catechol-o-methyltransferase gene that codes for dopamine has also been reported [107].

In theory, cannabis use may precipitate a psychosis in several ways [90]:

- 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)

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 [107]. The relationship between cannabis use and vulnerability may explain the small (two to three 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 rates 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 [107].

There appears to be at least some evidence linking cannabis use to the development of psychotic disorders, but 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 [90]. Although there is evidence to support the belief that cannabis use may contribute to psychosis in certain circumstances, the possible causal mechanisms are complex [90].

A review of evidence from multiple trials demonstrated a likely causal relationship between cannabis use (particularly frequent, chronic use) and psychotic illness, particularly schizophrenia-spectrum disorders [108]. Furthermore, onset of psychotic symptoms in persons with schizophrenia is earlier (by 2.7 years) in those who use cannabis than in nonusers [108]. The first psychotic episode in cannabis users is more likely to present with positive symptoms (e.g., hallucinations, delusions) than negative symptoms (e.g., apathy, social withdrawal) than first episodes in individuals who do not use cannabis.

One study recruited 97 volunteers with psychosis (i.e., schizophrenia, schizoaffective, or bipolar psychosis) and 64 controls. Participants were categorized using history of cannabis use into nonusers, adolescent-onset users, and late-onset users. The researchers were testing the hypothesis that individuals with psychosis and a history of adolescent cannabis use would have better global neuropsychological performance compared with those with psychosis and no cannabis use history. Neuropsychological

performance was measured using the Brief Assessment of Cognition in Schizophrenia (BACS) battery. Scores were significantly higher in individuals with psychosis and adolescent cannabis use compared with those with psychosis and no prior cannabis use. Adolescent cannabis use was associated with better cognitive function in schizophrenia but not bipolar psychosis [109].

Researchers have linked new high-potency cannabis strains with increased emergency admissions for psychosis, implicating not only higher levels of THC but also the absence of CBD, which ordinarily tempers the psychotomimetic effects of THC [110; 111]. A British study noted that the typical cannabis product available in the United Kingdom before 2000 was hashish resin, containing essentially equal parts THC and CBD (each up to 4% by weight), and that the typical high-potency herbal cannabis that now dominates the market contains 12% to 18% THC and less than 1.5% CBD. (This is also typical of cannabis available in the United States, particularly strains grown in California [112].) Researchers suspect that the rise in admissions for psychosis is related to this shift. The study concluded that individuals with a longer duration of use and with a preference for high-potency cannabis are at a much greater risk for enduring psychosis than individuals who occasionally smoke hashish [110]. This is supported by research showing that cannabis psychosis is THC dose dependent and that CBD can reverse indicators of THC-induced psychosis in test subjects [111; 113].

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 [90]. 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 [90]. More research in this area is required.

One study used a two-round design to rule out concomitant risk factors responsible for the connection from marijuana intake to lower general self-efficacy. A total of 505 college students completed measures of marijuana use, demographics, personality, other substance use, and general self-efficacy in two assessments one month apart. Marijuana use forecast lower initiative and persistence, even after ruling out baseline covariates (e.g., demographics, personality traits, alcohol or tobacco use, self-efficacy) and taking into account the precedence of the processes (e.g., initiative, effort, persistence, alcohol, cigarette and marijuana use). Results showed that only marijuana intake significantly and longitudinally prompted lower initiative and persistence, providing partial support for the marijuana amotivational syndrome, underscoring marijuana as a risk factor for decreased general self-efficacy and offering insights into future research [114].

Panic Disorder

Cannabis use has also been linked to the development of panic disorder [115]. A study involving 1,000 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 [90]. Conversely, in a study of nearly 7,000 adults, the presence of social phobia and panic disorder predicted progression from casual use to cannabis use disorder [116].

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 [117]. 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.

Ingestion of high doses of delta-9-THC produces intense anxiety in nearly all users predisposed to anxiety, and the high THC:CBD ratio of cannabis available today may lead to a rise in anxiety/panic disorders among cannabis users in general [112]. In fact, studies indicate that CBD alone has promise in the treatment of social anxiety [118].

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 psychologic problems, and selling illegal drugs [19].

Cannabinoid Hyperemesis Syndrome

Cannabinoid hyperemesis syndrome (CHS) is characterized by severe cyclic nausea and vomiting in chronic (usually heavy) cannabis users [119]. It is a relatively rare adverse effect, but increasing case reports have been noted with the liberalization of cannabis in several states [120]. Individuals with CHS experience temporary relief of symptoms with hot baths or showers, and compulsive bathing is often an identifying feature (differentiating the condition from other causes of cyclic vomiting) [121]. Typically, patients begin with recurrent nausea and progress to intense, persistent vomiting with continued use of cannabis.

The underlying pathogenesis of CHS is unclear, although several theories have been presented. One theory is that the enteric emetic effects of cannabis (e.g., decreased gastrointestinal motility) may promote emesis by over-riding the antiemetic effects mediated by the CNS [121]. Symptoms resolve with cessation of cannabis use; relapse to use often results in a recurrence of the syndrome.

CANNABIS WITHDRAWAL SYNDROME

A cannabis withdrawal syndrome has been clearly demonstrated and is characterized by a variety of symptoms, including restlessness, nervousness, 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 [90; 122; 123; 124]. The most frequent symptoms of cannabis withdrawal are emotional and behavioral in nature and do not typically cause significant physical, medical, or psychiatric disorders [125]. Regular daily use of cannabis can lead to withdrawal symptoms or a full-blown withdrawal syndrome upon cessation of use. With abrupt cessation, withdrawal symptoms emerge within one to two days, reach peak intensity after two to six days, and generally resolve within one to two weeks, though sleep difficulties may persist for more than one month.

Cannabis withdrawal syndrome is included in the DSM-5, and it is new to this edition [6]. Three of the following seven symptom clusters must be identified for a diagnosis according to the DSM-5 definition [6]:

- Irritability, anger, or aggression
- Nervousness or anxiety
- Sleep difficulty (e.g., insomnia, disturbing dreams)
- Decreased appetite or weight loss
- Restlessness
- Depressed mood
- At least one of the following physical symptoms causing significant discomfort:
  - Stomach pain
  - Shakiness/tremors
  - Sweating
  - Fever
  - Chills
  - Headache

Using the proposed DSM-5 criteria, researchers asked 384 lifetime, non-treatment-seeking cannabis addicts about their worst abstinence experience and found that 40% would be diagnosed with cannabis withdrawal syndrome [124]. According to the DSM-5, 50% to 95% of adults and adolescents who are enrolled in treatment or who are heavy cannabis users report cannabis withdrawal symptoms [6].

Cannabis withdrawal syndrome typically requires heavy, prolonged use to develop and may significantly impact social, educational, and occupational functioning [6]. 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 [126]. The majority of adults seeking treatment for a cannabis use disorder report a history of cannabis withdrawal, with most reporting a co-occurrence of four or more symptoms of substantial severity [125].

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 [3].

COURSE

The onset of abstinence symptoms consistently occurs during the first one to two days following cessation of cannabis or oral THC administration. Most symptoms return to baseline or to comparison-group levels within one to two 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 [125; 127].

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 [125].

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 [3; 125]. The symptoms of cannabis withdrawal may overlap with other conditions, including disordered eating, sleep disturbances, and depressive disorders, and therefore heavy cannabis use should be considered in the evaluation of patients with weight loss, sleep problems, and other similar presentations [128].

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. To date, CBD and nabiximols have both been shown to improve withdrawal symptoms, though additional research is necessary to establish efficacy and safety [129; 130; 131; 132; 133].

TREATMENT OF CANNABIS USE DISORDERS

Until fairly recently, cannabis was not considered a drug with a liability of dependence and addiction. In the limited research, withdrawal did not appear to lead to any obvious physical symptoms, and animals failed to self-administer the drug, a behavior usually associated with drugs of addiction [86]. Few studies had focused on the treatment of cannabis abuse or dependence. However, it is now known that individuals can develop a chronic use pattern associated with dependence symptoms and recurrent psychosocial problems [124; 134]. Two factors have contributed to the historical 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 [135]. As medicinal use of the drug has accelerated into the mainstream, and bolstered by the discovery of the human endocannabinoid system, a large amount of research into many facets of cannabis and cannabis use has emerged.

CHARACTERISTICS OF PATIENTS SEEKING TREATMENT FOR CANNABIS USE DISORDERS

Before current laws legalizing cannabis in many states, individuals who received treatment tended to do so as the result of legal consequences, and those seeking treatment voluntarily for primary problem of cannabis dependence usually waited until they were older than 30 years of age. In addition, young adults and adolescents would generally seek treatment only when mandated by school officials, parents, or the criminal justice system [31]. However, 2019 NSDUH data indicate that trends have shifted. Individuals 18 to 25 years of age now comprise 45.8% of past-year cannabis treatment. Individuals 26 years of age and older comprise 19.6% [8].

Among adults, 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 motivate the desire to quit or reduce use [134]. 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.

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 [136]. According to 2019 NSDUH data, common reasons for not receiving treatment among people 12 years of age and older include not being ready to stop using (39.9%), not knowing where to go for treatment (23.8%), and having no healthcare coverage and not being able to afford the cost of treatment (20.9%) [4]. 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 [31].

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 [3].

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, including selective serotonin reuptake inhibitors, mixed-action antidepressants, atypical antidepressants, anxiolytics, and norepinephrine reuptake inhibitors, has been shown to definitively decrease cannabis use by humans [3; 137; 138; 139].

There is some evidence that bupropion may be effective in lessening the symptoms of cannabis withdrawal [140]. Bupropion facilitates abstinence from cigarette smoking, in part through its ability to decrease negative mood symptoms, and 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. The authors of one study found that bupropion resulted in less craving for the drug, but other studies have reported worsened mood and continued sleep difficulties, possibly caused by bupropion-associated enhanced norepinephrine activity [3; 140; 141]. A 2019 systematic review found that bupropion was likely of little value in the treatment of cannabis dependence [137].

Other researchers have evaluated the role of nefazodone because of its demonstrated effectiveness in clinical populations with conditions also associated with cannabis withdrawal, including depression, agitation, and anxiety. In a 2009 study, nefazodone decreased irritability and the severity of cannabis dependence, but it is unclear if these effects would ultimately result in improved long-term abstinence [141].

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 [3; 142]. 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. Most small studies to date find little relevant effect of divalproex for cannabis withdrawal symptoms [143].

Treatment of cannabis withdrawal with gabapentin has shown some promise in a pilot clinical trial [139]. Although the dropout rate was very high (72%), 1,200 mg per day significantly reduced withdrawal symptoms compared to placebo and resulted in decreased cannabis use among those participants that remained [144].

Another agent evaluated for its effect on attenuating cannabis withdrawal is dronabinol (oral delta-9-THC) [142]. Use of dronabinol in the treatment of withdrawal symptoms is 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 is successful in markedly reducing withdrawal symptoms, including self-reports of drug craving, anxiety, misery, anorexia, and sleep disturbance [145]. Although use of dronabinol is associated with improved withdrawal symptoms and treatment retention, it has not been shown to reduce cannabis self-administration [145]. Another 11-week trial examining the effects of dronabinol on cannabis use disorder showed no statistical difference between the placebo group and those receiving dronabinol combined with motivational enhancement and relapse-prevention therapy [146]. However, there was a reduction in both groups, likely due to the addition of behavior therapy.

An issue of potential concern related to treating cannabis-dependent patients with dronabinol 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, administration of dronabinol would be expected to produce much less reinforcement than smoked cannabis.

Another advantage is that, unlike smoked cannabis, dronabinol is not associated with adverse pulmonary effects. Considering all of these factors, the benefits of dronabinol in the treatment of cannabis withdrawal appear to outweigh potential risks [3].

One study compared the treatment efficacy of oral dronabinol and the synthetic THC analogue nabilone [147]. The results showed that nabilone has a longer time to peak effect, is more sustained, has fewer negative cognitive effects, and results in greater mood enhancement characteristics compared to dronabinol. Also, the effects are more dose-related, perhaps making it the better option for cannabinoid-replacement withdrawal treatment. Although dronabinol also decreases symptoms of cannabis withdrawal, the drug is ineffective in preventing relapse [147]. Researchers hope nabilone can prove effective for both purposes in clinical trials.

Pharmacotherapy for Relapse Prevention

A small study (11 participants) of daily cannabis users found that nabilone decreased reversed withdrawal-related irritability, sleep disturbances, and anorexia, though psychomotor skills were impaired [148]. Nabilone (8 mg per day) also decreased the rate of relapse, indicating the need for further research [148]. Another small study of 11 non-treatment-seeking participants examined the effects of zolpidem (a sedative hypnotic) versus a zolpidem/nabilone combination on three factors, each tested in a different phase of the study. Withdrawal-related symptoms were decreased in both groups, and the combination drug (zolpidem/nabilone) showed decreases in self-administration of cannabis but small increases in certain abuse-related subjective capsule ratings [149]. More research is needed to determine the effectiveness of nabilone alone or in combination with other drugs.

In another study, 25 adult outpatients were randomized to either six weeks of placebo or divalproex, then switched to the alternate treatment for an additional six 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 psychologic 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 eight study weeks was high (>75%), suggesting the medication was discontinued because it was poorly tolerated in this population [150]. Other medications studied for alcohol relapse prevention, including buspirone, baclofen, and mirtazapine, have proven ineffective for cannabis relapse prevention [137; 151; 152].

N-acetylcysteine (NAC), an over-the-counter supplement, has been studied in adolescents with cannabis use disorder [139]. NAC is thought to reinstate normal glutamate activity that is disrupted by chronic cannabis use. The participants who received NAC (1,200 mg twice daily) and contingency management were more than twice as likely to have a negative drug screen compared to those receiving only contingency management [153]. However, a 12-week trial of NAC in more than 300 adults with cannabis use disorder did not show the same results. When compared to placebo, the NAC group had no statistically significant reduction in the results of urine cannabinoid tests [154]. Further research into the efficacy of NAC with regard to adolescents versus adults is warranted.

Pharmacotherapy of Cannabis Dependence in Patients with Comorbid Mental Illness

Although clozapine is known to be effective in the treatment of patients with schizophrenia and substance use disorders, its side effect profile limits its clinical utility. A small pilot study comparing clozapine and the second-generation antipsychotic ziprasidone, both agents were found to decrease cannabis use [155]. Ziprasidone was associated with fewer side effects and better compliance with treatment than clozapine. The American Psychiatric Association recommends that patients diagnosed with schizophrenia and cannabis use disorder should be offered pharmacotherapies effective for the treatment of cannabis withdrawal and relapse prevention in addition to psychotherapy [156].

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 [31].

Contingency Management

Contingency management (CM) approaches to adult substance abuse are effective behavioral interventions to increase drug abstinence and other treatment goals when integrated with other effective psychosocial treatments [157]. Essentially, CM interventions use reinforcement or punishment contingencies to increase or decrease the frequency of predetermined therapeutic and behavioral objectives [19]. Contingency management programs have been found effective to decrease rates of relapse among patients in treatment for cannabis use disorders [157].

Relapse Prevention

Relapse prevention assists patients with decreasing their vulnerability to relapse by addressing topics such as lifestyle balance and managing high-risk situations [135].

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 [135].

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 [135; 158].

Psychosocial Treatment of Adults

One study compared a cognitive-behavioral relapse-prevention treatment; a brief, two-session motivational intervention; and a delayed-treatment control group [158]. 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 six-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 [31].

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 treat-

ment 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 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 [134].

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 CBT for cannabis dependence [159].

The American Psychiatric Association notes that treatment of cannabis use disorder with CBT and MET may be improved with the concurrent use of CM strategies [156]. Combined treatment results in improved initial and long-term abstinence.

Psychosocial Treatment of Adolescents

Approximately 3.9 million high school students (15.8%) used cannabis at least once in 2019 [4; 8]. Among the 1.1 million adolescents who did not receive substance use treatment in the past year, 98.5% did not feel that they needed treatment, 0.9% felt that they needed treatment but did not make an effort to obtain it, 0.6% felt that they needed treatment and made an effort to obtain it, and only 1.5% felt that their use was problematic and sought help/treatment [8]. These findings suggest the need for interventions to increase motivation for change and encourage treatment entry for this population.

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 three-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 three-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 three-month follow-up, with an overall reduction in cannabis use by 16% (6 fewer 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 [160].

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 [19]. 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 weekly 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 [19].

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 [161]. Among adults 19 years of age or older in 2019, those with a past-year serious or any mental illness were more likely than those without mental illness to be users of marijuana (39.8% and 32.5% vs. 14.2%) [8]. Unfortunately, the amount and quality of research regarding the psychosocial treatment of these patients is limited. In one study, researchers conducted a randomized, single-blind controlled comparison of routine care with a program of routine care integrated with motivational interviewing, cognitive behavior therapy, and family or caregiver intervention in patients with comorbid schizophrenia and substance use disorder (including cannabis misuse) [161]. They found that the integrated treatment approach resulted in significantly greater improvement in patients' general functioning than routine care alone at the end of treatment and at one year follow-up [161]. Longer and more intensive treatment may be necessary for dually diagnosed patients, particularly those with chronic mental illness [162]. Randomised controlled trials of interventions within "real world" mental health systems among adults with severe mental disorders suggest that cannabis use is amenable to treatment in these settings among people with psychotic disorders. Additionally, trials of guided interventions among cannabis users indicate that while brief interventions are associated with reductions in cannabis use, longer interventions may be more effective. These trials suggest that treatment with antipsychotic medication is not associated with a worsening of cannabis cravings or use and may be beneficial [163]. 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 [164].

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 [164; 165].

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 [166].

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 psychologic functioning as a result of NA involvement has been observed [167]. 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 three years exhibit levels of anxiety and self-esteem similar to the general population [167].

Being active as an NA sponsor over a one-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 [168].

One study sought to explore the factors related to treatment retention in NA members [169]. The authors interviewed 12 NA members who had been recovered for more than two years. After gathering (and analyzing) data through purposeful sampling and recording and transcribing participants' interviews, two main areas related to treatment retention were revealed: personal-psychological factors (e.g., self-knowledge, change of attitude, self-confidence) and social factors (e.g., interaction with others, reforming social/familial relationships, receiving support). The authors concluded that providing the necessary special care and support following the user's elimination of physical attachment would lead to elimination of psychological dependence as well [169].

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 36 states in the United States and in many countries [170].

In a study of 1,288 male patients, participation in a 12-step program predicted maintenance of cannabis abstinence and the re-initiation of abstinence after a relapse [171]. Participation in 12-step groups during and after treatment has been associated with positive outcomes among substance users, including cannabis-dependent patients [172]. 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 [172]. 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 [172].

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.

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 [173]. The authors found that 71% of those who were abstinent went on to exhibit full relapse, defined as four 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 [134]. As noted, motivational enhancement therapy combined with CBT may enhance outcomes [17]. 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 [159].

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 [25].

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 symptoms associated with chemotherapy/cancer, AIDS, and other conditions.

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