# Cannabinoids

# 10

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**High-Yield Review Points**

- The psychoactive components and activity of cannabis and cannabinoid products vary widely, and most safety data are derived from studies conducted with products less potent than ones currently available.
- Cannabinoids have dose-dependent, often biphasic, and time-dependent effects. While medical use of cannabinoids may benefit a select group of patients, systematic scientific evidence supporting most claims remains limited.
- Because of tolerance, patients may gradually require more cannabinoids to achieve a desired effect, and abrupt discontinuation may precipitate a withdrawal syndrome.
- Cannabinoids may impair cognition, and the effect can be potentiated when combined with other psychoactive substances including opioids, benzodiazepines, and alcohol, or when used by those with neurocognitive disorders.
- Individuals with major psychiatric disorders and adolescents may be more prone to developing adverse effects of cannabinoids.
- New onset or worsening of anxiety, mood disturbance, cognitive impairment, or psychosis should prompt clinical evaluation of whether cannabinoids are a contributing factor.

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## Epidemiology and Recent Trends in Cannabinoid Use

Cannabis is one of the most widely used substances in the United States. According to the 2016 National Survey on Drug Use and Health (NSDUH), 127.5 million individuals – approximately 45% of Americans aged 12 years or older – used cannabis in their lifetime [1]. Approximately 41 million individuals used cannabis in the past year, and three million used for the first time, which amounts to approximately 8300 new users each day [1]. From 1992 until 2012, the proportion of Americans regularly using cannabis increased by roughly 60%. Several factors may account for this, such as increased perception of cannabis as "benign" and higher social acceptability, especially among adolescents. Of the three million individuals using cannabis for the first time in 2016, most were under the age of 18. Consistent with this, since the Monitoring the Future (MTF) survey of 12th graders began in 1975, the perceived risk of cannabis use has declined, and the prevalence has increased, with nearly 8% of all youth aged 12 to 17 currently smoking cannabis [2].

**Medical and Recreational Cannabinoid Use Policy** In recent years, there have been several changes to legislation surrounding the use of cannabinoids, with several US states and other jurisdictions in Europe, and South and Central America moving toward legalization.

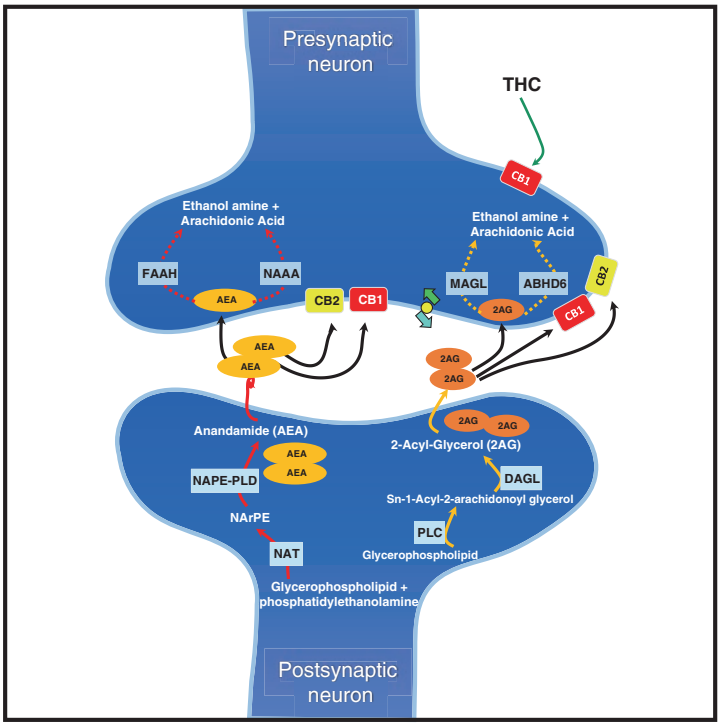
In the United States, medical cannabis programs were originally promoted as compassionate care initiatives for terminally ill patients. They were created to guarantee the rights of patients using cannabis to treat nausea, cachexia, or spasticity. Between 1979 and 1991, five states – Virginia (1979), New Hampshire (1981), Connecticut (1981), Wisconsin (1988), and Louisiana (1991) – approved medical cannabis legislation. Since 1996, as of the beginning of 2019, starting with California, 33 states and the District of Columbia have authorized the possession of cannabis for medical purposes, or have created state agencies to license the production and dispensation of medical cannabis**.** In these states, physicians can recommend medicinal use of cannabis to patients with qualifying conditions; though, since it is still considered a Schedule I substance under federal law, they do not have the authority to *prescribe* it. Notably, there is significant inconsistency between states regarding which are the qualifying conditions, and, more importantly, there is great discrepancy between what is allowed under state law and the scientific evidence base – which thus far supports cannabinoid-based therapeutics for nausea and vomiting, in addition to specific types of pain, such as neuropathic pain and spasticity related to multiple sclerosis. In many states, individuals may receive recommendations for cannabis from physicians whom they have seen for a single visit and with whom they do not regularly follow-up for standard care.

At the time of writing, Canada, 10 US states, and the District of Columbia have also allowed cannabis for recreational use by adults over 21 years old**.** Given rapid societal changes, elucidating what is known about the impact of cannabinoid use on mental health takes on urgent public health importance.

# Pharmacology

## Overview of the Endocannabinoid System

The endocannabinoid (eCB) system is one of the most widespread systems in the central nervous system (Fig. 10.1). It consists of receptors, endogenous transmitters or eCBs, and enzymes that synthesize and degrade eCBs, including fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). The two main receptors




CB1 Cannabinoid receptors located mainly centrally

AEA Anandamide

NAT N-acyltransferase

NAPE-PLD N-acylphosphatidylethanolamine-selective phospholipase D

FAAH Fatty acid amide hydrolase

NAAA N-Acylethanolamine-Hydrolyzing Acid AmidaseSolid

arrows: synthetic pathway

CB2 Cannabinoid receptors located mainly peripherally

2AG 2-arachidonoylglycerol

DAGL Diacylglycerol lipase

PLC Phospholipase C

MAGL Monoacylglycerol lipase

ABHD6 2-arachidonoylglycerol hydrolase

Dotted arrows: degradation pathway

Endocannabinoid cell membrane transporter?

**Fig. 10.1** The endocannabinoid system. *ABHD6* 2-arachidonoylglycerol hydrolase; *AEA* anandamide; *2AG* 2- arachidonoylglycerol; *CB1* cannabinoid receptors located mainly centrally; *CB2* cannabinoid receptors located mainly peripherally; *DAGL* diacylglycerol lipase; *FAAH* fatty acid amide hydrolase; *MAGL* monoacylglycerol lipase; *NAAAN* acylethanolamine-hydrolyzing acid amidase; *NAPE-PLD* N-acylphosphatidylethanolamine-selective phospholipase D; *NAT* N-acyltransferase; *PLC* phospholipase C; *Solid arrows* synthetic pathway; *dotted arrows* degradation pathway

are the G-protein-coupled receptors cannabinoid-1 receptor (CB1R) and cannabinoid-2 receptor (CB2R). In addition, some cannabinoids engage transient receptor potential (TRP) channels and peroxisome proliferator-activated receptors (PPARs). The two most well-studied eCBs include the lipid ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG). CB1Rs are densely expressed in the brain and critical in mediating the psychoactive effects of cannabis, as they are the targets of tetrahydrocannabinol (THC), a partial agonist at these receptors. CB2Rs, in contrast, are mostly expressed peripherally (immune, gastrointestinal, and peripheral nervous systems).

## Plant-Based Cannabinoids

Cannabis is a complex and highly variable mixture of approximately 400 or more chemical compounds, including plant-based cannabinoids (or phytocannabinoids), terpenoids, and flavonoids that produce individual and interactive effects. Delta-9-tetrahydrocannabinol (THC) is the principal psychoactive constituent of cannabis. Some of the other 70 currently known phytocannabinoids also have individual effects. For example, cannabidiol (CBD) may have anxiolytic and antipsychotic-like effects that offset THC-induced anxiety and psychotomimetic effects. Preclinical studies suggest the individual effects of phytocannabinoids are multi-phasic and dose-dependent, which is exemplified by the anxiolytic effects of THC at lower doses, and anxiogenic effects at higher doses. An interesting aspect of cannabinoids is that they exhibit a phenomenon known as the "entourage effect" – which means that their activity can be enhanced by structurally related – but otherwise biologically inactive – constituents [3].

## Synthetic Cannabinoids

Synthetic cannabinoids (SC) originated from basic research on cannabinoid agonists. They are full CB1R receptor agonists, and up to 800 times more potent than plant-based cannabinoids. The various products sold as "spice" or "K2" often contain diverse compounds. The effects of SC products are generally more pronounced than those of cannabis, including higher levels of anxiety, psychotomimetic effects, hypertension, and tachycardia. Also, because some of the products contain cathinones (or "bath salts") combined with SCs, there have been cases of life-threatening or fatal effects, including seizures, toxic hepatitis, cardiac ischemia, and stroke. The withdrawal symptoms are similar in time course to those of cannabis; however, they also tend to be more pronounced and to involve somatic symptoms such as nausea and vomiting.

SC use is more likely among individuals who use cannabis, users of other synthetic drugs, and individuals who may try to avoid detection by commonly administered drug urine screens that typically only screen for THC (e.g., those on probation, in the military, or in workplaces that utilize drug testing).

## Clinical Significance and What Psychiatrists Should Know About Cannabinoids

### Available Cannabis Products

Varieties of cannabis, cannabis-based products, and synthetic cannabinoids (SC) differ widely in their cannabinoid proportion and content (Table 10.1). It is increasingly recognized that THC content (potency) of cannabis in the United States has steadily increased over the past decades, from 4% in 1995 to 12% in 2014. Some potent strains of cannabis have a THC content of approximately 30%, and other cannabis-based products have a THC content of over 80% [4]. In comparison, the cannabis made available by the National Institute of Drug Abuse (NIDA) for

**Table 10.1** Currently available cannabinoid products

| Cannabinoid product | Description | Method of use |
|---|---|---|
| Smoked products | Dried cannabis leaves and flowers ("marijuana") | Smoked in hand-rolled cigarettes ("joints", "blunts"), pipes with filtration systems created to reduce the harshness and temperature of the smoke ("bong", "hookah"), or vaporizers |
| Hashish | Concentrated trichomes with a higher THC concentration than other parts of the plant | Smoked or mixed with food. |
| Kief | Powder extracted from THC-rich trichomes (resin glands) | Smoked or compressed into hashish "cakes" |
| Hash oil | A mixture of essential oils and resins extracted from the cannabis plants using solvents, such as ethanol or butane | The solvent is evaporated, leaving a THC-rich oil that can be smoked, vaporized, or mixed with food |
| Edibles | Food products infused with cannabis | Directly added cannabis, or cannabis butter or oil. Can be alcoholic beverages |
| Tincture | Cannabinoids extracted using alcohol | Liquid form, absorbed through the mucous membranes (oral mucosa or sublingually) |
| Topicals | Oils infused with cannabis | Salve or cream applied topically |
| Skunk | *Cannabis* strains that are strong-smelling and THC-rich | Smoked |
| Shatter | A cannabis concentrate with a transparent, amber appearance that looks glassy when cold, and like thick honey when warm | "Dabbing" (special pipe) or vaporizing |
| Wax | Opaque cannabis concentrate with a buttery appearance. Different wax consistencies are created using varying oil textures and different moisture and heat levels. | "Dabbing" (special pipe) or vaporizing |

*THC* Delta-9-tetrahydrocannabinol

research purposes has less than 4% THC, and so, the limited studies with cannabis do not reflect products being used. The THC/CBD ratio has also increased, such that many popular forms of cannabis have low CBD and high THC content.

## Associated Effects

### Acute Intoxication

The onset of cannabinoid effects depends on the route of administration, with effects emerging within minutes after inhalation, but taking hours (60–90 minutes) following oral consumption [5]. The duration of effects is highly variable but usually lasts for 2 (inhaled) to 4 hours (oral). The acute effects of cannabinoids are likely to be more pronounced with higher doses, higher THC/CBD ratio, and with full agonists, such as SCs. It is not fully understood why some healthy individuals are more vulnerable than others to the acute effects of cannabinoids. Individuals who use cannabinoids regularly may show blunted responses due to tolerance.

## Behavioral Effects

**Mood/Anxiety** Cannabis may produce acute transient effects on mood. The "high" produced by cannabis includes a combination of effects reported as relaxation, euphoria, relaxed inhibitions, and an overall sense of well-being. Although cannabis is generally anxiolytic, especially at lower doses, the higher concentration of THC found in cannabis in recent years has probably led to an increase in reports of panic-like effects. THC has been reported to increase anxiety when administered alone, especially at high doses, and under conditions of stress, while co-administration with CBD can counter THC-induced anxiety.

There are observational reports of elevated mood and reduced depressive symptoms following short-term consumption of cannabis, which are blocked by CB1R antagonists. However, it is challenging to differentiate this from the euphoria induced by cannabis intoxication. Further, the administration of a CB1R inverse agonist (rimonabant) to healthy individuals increased anxiety, depression, and suicidal ideation. The evidence for the antidepressant effects of herbal cannabis remains contradictory, as brief dysphoric reactions are also well-recognized consequences of acute cannabis use, especially to those who are cannabis naïve.

**Psychosis** Cannabis intoxication is associated with transient psychosis-like effects that include depersonalization, derealization, ideas of reference, grandiose and paranoid delusions, flight of ideas, disorganized thinking, and auditory and visual hallucinations. These effects have been increasingly reported with high-THC strains of cannabis and SCs, and individuals with psychosis liability or a family history of psychosis are more prone to experiencing psychotomimetic effects.

**Cognitive Effects** Cannabis can acutely impair various cognitive domains. Daily heavy users of cannabis may have blunted responses to the cognitive deficits induced by cannabis, and in these populations abstinence from cannabis may in fact be associated with cognitive impairment [6]. The acute effects of cannabis on cognition may depend on the THC/CBD ratio, with higher concentrations of CBD reducing cognitive deficits.

**Attention** Deficits in selective, focused, and divided attention tasks can be induced by cannabis. In addition, allocation of attention and signal detection have been demonstrated after acute administration of both cannabis and THC to healthy individuals. Impaired performance on a divided attention task following administration of THC was shown in only occasional, but not heavy, users, indicating tolerance.

**Memory** Cannabis may affect spatial working memory, procedural memory, verbal learning and recall, and associative learning [6]. Deficits in verbal learning and memory are recognized as the most robust impairments associated with acute cannabis use. THC was shown to interfere with encoding, but not retrieval of verbal memory, suggesting that learning information prior to using cannabinoids is not likely to disrupt recall of that information. Whether THC impairs encoding of nonverbal information and memory consolidation remains to be elucidated [7]. The activation of CB1Rs, especially in the hippocampus, which contains a high density of these receptors, may interfere with short-term memory, and may impair memory consolidation.

**Inhibitory Control** Impairment of inhibitory control has been shown following acute cannabis intoxication, and THC and CBD may have opposite effects on response inhibition following "Go/NoGo" tasks. It has been proposed that the eCB system may modulate dopaminergic tone in the prefrontal cortex and nucleus accumbens, contributing to incentive salience to specific stimuli and impulsivity, and that THC disrupts these physiological mechanisms underlying inhibitory and decision-making processes [8].

## Motoric Effects and Relevance for Driving Ability

Consistent with the known distribution of CB1Rs in areas involved in cognitive and motor processes (i.e., brain cortex, basal ganglia, and cerebellum), driving simulation studies collectively suggest that cannabinoids produce acute impairments in driving ability, exemplified by an increase in lateral position errors and lane deviation, steering instability, braking distance, and collisions. Impairment can be further pronounced while under the influence of other substances such as alcohol or prescribed drugs (i.e., benzodiazepines or opioids).

## Effects of Chronic Use

### Cognitive Effects

The chronic cognitive effects of cannabinoids are more complex and controversial than their acute effects, appearing to be related to the dose of exposure and age of onset of use [7]. The evidence is stronger for impairments in verbal learning and memory, as well as working memory and attention, with mixed evidence for effects on decision-making. Whether these impairments are permanent is not fully understood.

In one of the largest and longest prospective studies controlling for premorbid function, Meier et al. reported that cannabis use before the age of 18 resulted in greater decline in intelligence by age 38, persisting even after cessation or reduction of use in the past year. A recent meta-analysis, conversely, found that only small magnitude effects are apparent in the first few weeks of abstinence (of the order of $d = 0.25$ to 0.35), and these become non-significant with extended abstinence (to around $d = 0.15$) [9].

## Cannabis Use Disorder

Cannabis use disorder (CUD) is the most prevalent substance use disorder (SUD) in the general US population after alcohol and nicotine use disorders. Approximately 1 in 10 individuals who use cannabis progress to compulsive use at the CUD level. In the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), the lifetime prevalence of CUD was 6.3%. The lifetime rates of CUD in those who begin use in adolescence have been reported to be close to 17% [10]. Importantly, participants in the NESARC-III with CUD experienced considerable disability across a variety of domains. Their level of disability correlated with the frequency of cannabis use and was greater than the corresponding levels of disability associated with alcohol use disorder [11].

It is unclear whether medical cannabis is associated with lower or higher levels of CUD, although some evidence suggests the latter, as states where medical cannabis is legal had higher rates of CUD diagnoses among veterans in 2002, 2008, and 2009 [12].

Some evidence suggests that regular cannabinoid use might be implicated in the development of SUDs other than CUD (i.e., the "gateway hypothesis" of cannabis). Approximately 1 in 10 cannabis users develop a SUD other than CUD, and this number is higher among adolescents [12]. In a large nationally representative sample, cannabis use was prospectively associated with increased prevalence and incidence of alcohol and other SUDs, after adjusting for several covariates that predicted cannabis use. It has also been proposed that the neurocircuitry involved in mediating the effects of cannabis overlaps with that involved in other substances. It is not fully clear whether overlap may contribute cross-sensitization to other substance use, rather than a common underlying vulnerability across distinct substances [12].

## Cannabis Withdrawal Syndrome

Recognized in DSM-5 as a distinct entity, cannabis withdrawal syndrome (CWS) is characterized by anger, aggression, appetite change, weight loss, irritability, anxiety, restlessness, sleep disturbance, cannabis craving, and physical discomfort. Other, less common symptoms include chills, depressed mood, stomach pain, and diaphoresis. Most symptoms appear within one day of abstinence, peak within 2–3 days, and resolve within 1–3 weeks. However, some studies suggest that withdrawal symptoms may persist longer than 4 weeks, especially sleep disturbances.

## Adolescent Psychiatric Disorders

In general, the adolescent brain differs from the adult brain in that the adolescent brain is more susceptible to external influences. As a result, adolescents are more likely to develop psychiatric consequences of prolonged cannabis use. The mesolimbic dopaminergic system and the hypothalamic pituitary-adrenal-axis (HPA) both develop earlier than the prefrontal cortex (PFC), and such differences result largely from the incomplete structural and functional maturity of the PFC. The eCB system regulates developmental processes through the brain, including pyramidal cell specification, interneuron migration and morphogenesis, neuronal connectivity, and synaptic plasticity, which all contribute to the maturation of the PFC. The influence of exogenous cannabinoids may interfere with these processes, increasing the risk of psychiatric disorders.

**Psychotic Disorders** Transient, cannabis-induced psychosis is often clinically indistinguishable from a primary psychotic disorder, and can outlast the period of acute intoxication and persist for as long as 30 days. Although most people who consume cannabis do not experience psychosis, the cannabis-psychosis link may occur in those with predisposing genetic and environmental factors. As with other negative effects of cannabis, the risk of psychosis appears to be heightened by heavy and early use.

Cannabis use has also been shown to exacerbate the course of illness in individuals with established psychotic disorders [13]. With the rising potency of cannabis strains and more frequent use, there is some evidence that the age of onset of first-episode psychosis is decreasing. Consistent with this, SC users are generally more frequently diagnosed with psychotic disorders.

**Anxiety Disorders** Long-term cannabis use can exacerbate anxiety, cause panic attacks, and exacerbate the neuroendocrine response to stress. While individuals with anxiety disorders report a high incidence of cannabis use, whether cannabis is used to try to decrease anxiety, or whether it contributes to anxiety disorders may be difficult to discern clinically. Cannabis use has also been associated with social anxiety disorder.

**Mood Disorders** Cannabis use is associated with a worse clinical course of mood disorders, including more frequent hospitalizations, more frequent and longer manic episodes, and greater prevalence of psychotic symptoms in individuals with bipolar disorder [12]. There is also preliminary evidence of cannabis use conferring a higher risk for bipolar and depressive disorders. Conversely, both unipolar and bipolar mood disorders appear to increase rates of cannabis use and CUD in prospective studies.

**Attention-Deficit/Hyperactivity Disorder (ADHD)** Preliminary data indicate that ADHD is a risk factor for developing cannabis misuse in adulthood. However, the impact of cannabis use on the course of ADHD is not fully clear. Some evidence indicates that specific phenotypes of ADHD may be more closely associated with distinct patterns of cannabis use (i.e., the inattention type is associated with more severe cannabis use, and the hyperactivity-impulsivity phenotype is associated with earlier onset of cannabis use). Though data are sparse, it appears that chronic, and especially early cannabis use, is associated with negative outcomes in ADHD, including further attention deficits, and refractoriness of hyperactivity and impulsivity to pharmacological treatment [12].

**Sleep Disorders** The relationship between cannabis use and sleep is complex, in that time-dependent effects, as well as intoxication and withdrawal must be considered. Overall, cannabis use is associated with reduced rapid eye movement (REM) sleep, shortening of sleep-onset latency, and increased stage 4 sleep. Sedation after cannabis exposure may continue into the following day [14]. Further, insomnia and vivid dreams are common during CWS [15], especially among heavy users. Preliminary evidence also indicates childhood-onset sleep disorders may predict cannabis and alcohol use in adolescence and early adulthood [16].

**Posttraumatic Stress Disorder** Individuals with posttraumatic stress disorder (PTSD) have higher rates of cannabis use – as well as SUDs in general – than the general population. Thus far, there is no evidence, however, that cannabis use is a risk factor for the development of PTSD. Although cannabis is increasingly being offered as a treatment for PTSD, systematic reviews indicate that the evidence examining its benefits and harms in patients with this disorder is still conflicting and incomplete.

## Treatment of Cannabis Use Disorder

### Assessment of Cannabis Use

Individuals who use cannabis and seek treatment typically have used nearly every day for more than 10 years, and have tried to quit approximately 7 times. A small minority presents to addiction specialty treatment with specific concerns about cannabis misuse. More frequently, individuals present to general psychiatric treatment

or primary care settings, with symptoms of depression, anxiety, fatigue, impaired concentration, irritability, or relationship stress. Individuals with high-intensity use may present to emergency departments with acute anxiety, psychotomimetic effects, or altered mental status. Adolescents present with declining school performance, whereas adults may experience impaired performance at work.

Several screening tools may assist the clinician in assessing cannabis use, including the Cannabis Use Problems Identification Test (CUPIT) [16], the Severity of Dependence Scale (SDS), and the Cannabis Problems Questionnaire. Terminology relating to cannabis is highly regional, as are the names of distinct cannabis strains. Clinicians should have some working knowledge about the ways cannabis is consumed and common cannabis products and forms to adequately assess use.

## Pharmacological Interventions

Currently, there are no FDA-approved medications for treating CUD, although there is increased interest in drug development, given the recognition of a cannabis withdrawal syndrome, and greater understanding of the physical and societal burden of cannabis misuse.

A large 12-week RCT did not find that dronabinol (20 mg twice daily) improved abstinence during a two-week maintenance phase (dronabinol 17.7% vs. placebo 15.6%), though treatment retention and relief of withdrawal symptoms were better in the dronabinol group. Similarly, a two-site RCT investigating the effectiveness of nabiximol, a 1:1 ratio of THC and CBD in a spray formulation, for the treatment of CUD found that after 28 days the treatment and placebo groups showed no difference in self-reported cannabis use.

Antidepressants, buspirone, divalproex sodium, and lithium do not appear to be particularly useful for treating CUD, and little research informs a rational pharmacological approach to co-occurring psychiatric disorders. There are preliminary data for gabapentin, cannabinoid degradative enzyme inhibitors (FAAH inhibitors) [17], and glutamate modulators (N-acetylcysteine) for reducing cannabis use. N-acetylcysteine was found to reduce cannabis use in non-treatment seeking adolescents [16], but not adults. Lofexidine, recently FDA-approved to treat opioid withdrawal, has been shown to decrease symptoms of cannabis withdrawal.

Despite the limitations of the current literature, findings from basic science and human laboratory studies provide reasons for optimism that further clinical studies will lead to clinically meaningful pharmacotherapeutic interventions CUD and cannabis withdrawal.

## Psychosocial Interventions

Research on psychosocial treatments for CUD demonstrates moderately successful strategies. These interventions enhance skills than can be used to prevent return to use or decrease use [such as cognitive behavioral therapy (CBT)], foster internal

motivation [such as motivational enhancement therapy (MET)], or provide external incentives for interest in treatment plans to stop or decrease use [such as contingency management (CM)]. A meta-analysis of psychosocial intervention studies (CBT, CM, and MET) indicates that cannabis users who receive these treatments fare better than 66% of those in the control conditions for outcomes such as frequency and severity of use, and psychosocial functioning.

In recent times, there has been interest in software-based interventions, aiming to increase dissemination and reduce the cost of evidence-based treatments outside of traditional clinical settings. Various placebo-controlled studies indicate web-based interventions hold promise for treatment of CUD.

## Medical Use of Cannabinoids: Indications, Formulations, and Adverse Effects

Qualifying indications for medical cannabis use vary by state; however, evidence for most indications remains scant or preliminary. The most consistent evidence pertains to neuropathic pain, spasticity related to multiple sclerosis, and nausea and vomiting. Several pharmaceutical formulations of cannabinoids are available or under development in the United States. Dronabinol and nabilone are FDA-approved for the treatment of chemotherapy-induced nausea and vomiting. Dronabinol is also approved for the treatment of AIDS-associated anorexia. Nabiximols, administered in a spray form and containing THC and CBD in a 1:1 ratio, has been approved in Canada to treat cancer-related pain and multiple sclerosis-related spasticity, and a US phase 3 trial is planned to test this drug for the latter indication. The FDA has also recently approved CBD for a rare form of seizure disorder in the pediatric population.

## Interactions of Cannabinoids with Other Drugs

Pharmaceuticals that may interact with cannabis in a clinically significant manner include antiplatelet and anticoagulant agents, chemotherapy agents, antivirals, barbiturates, and some antibiotics. Cannabis can also induce mood changes when used with antidepressants, and can have synergistic effects with alcohol and other central nervous system depressants (Table 10.2).

## Genetic Factors

Genetic variation accounts for part of the variance of the risk of initiation and maintenance of cannabis use. A meta-analysis of twin studies reported heritability estimates of approximately 40%, with estimates ranging from 17–70% for lifetime use and 33–76% for CUD. A recent meta-analysis of genome-wide association studies, however, found that no genetic variant reached genome-wide significance, and that only about 6% of cannabis use initiation was due to common genetic variants.

**Table 10.2** Cannabis-pharmaceutical interactions

| Mechanism | Drugs |
|---|---|
| Antiestrogenic effect | Contraceptive medications<br>Hormone replacement therapy |
| Competition with metabolism, leading to increased drug levels | Barbiturates (phenobarbital, pentobarbital, secobarbital) |
| Inhibition of platelet aggregation | Nonsteroidal anti-inflammatory drugs<br>Anticoagulants (warfarin)<br>Antiplatelet agents (clopidogrel) |
| Induction of cytochrome P450 2E1, leading to decreased levels of substrate drugs | Acetaminophen, ethanol, theophylline, anesthetics (enflurane, halothane, isoflurane) |
| Inhibition of cytochrome P450 3A4, leading to increased levels of substrate drugs | Lovastatin, cyclosporine, diltiazem, indinavir, triazolam, clarithromycin |
| Inhibition of P-glycoproteins, leading to increased levels of substrate drugs | Chemotherapy agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine)<br>Antifungals (ketoconazole, itraconazole)<br>Protease inhibitors (amprenavir, nelfinavir, saquinavir, indinavir)<br>Histamine H2 antagonists (cimetidine, ranitidine)<br>Calcium channel blockers (diltiazem, verapamil)<br>Corticosteroids<br>Others (quinidine, cyclosporine, loperamide, quinidine, erythromycin, fexofenadine) |
| Additive/synergistic effects | Ethanol<br>Other central nervous system depressants |

*Adapted from:* Compton [18]

## Review Questions

1. A 21-year-old man started using cannabis at age 15 and found himself escalating his daily use at age 17 to achieve the same desired effect. He feels "jittery" and "depressed," and cannot sleep when he stops using cannabis. He was an above-average student in junior high school, but his performance and grades subsequently fell and he often felt unmotivated. Despite wanting to pursue a college education, he missed several application deadlines. He took a job at a local coffee shop, because the short work shifts allowed more time to use cannabis alone at home. Which of the following diagnoses best describes this presentation?
   A. Cannabis hyperemesis syndrome
   B. Cannabis withdrawal syndrome
   C. Chronic cannabis syndrome
   D. Cannabis use disorder

   Answer D.

Explanation: This individual has symptoms of tolerance, withdrawal, difficulty with major role obligations in school and work, which are diagnostic criteria for cannabis use disorder. He does not present with the persistent nausea or vomiting of hyperemesis syndrome, or with the irritability after cannabis cessation of withdrawal. Chronic cannabis syndrome is not a DSM-5 diagnosis.

2. A 20-year-old woman has smoked hashish daily for the past 12 months. She was stopped by the police for driving while intoxicated and held in custody over the weekend until her court hearing on Monday. While unable to use hashish, which of the following sets of symptoms is she most likely to experience?
   A. Muscle twitches, lacrimation, rhinorrhea, and diarrhea
   B. Nausea, headache, irritability, vomiting, and insomnia
   C. Hallucinations, tachycardia, and hypertension
   D. Slurred speech, vomiting, ataxia, and hypotension

   Answer: B.

   Explanation: This person is likely to experience cannabis withdrawal syndrome. Muscle twitches, lacrimation, rhinorrhea, and diarrhea tend to occur with opioid withdrawal. Hallucinations, tachycardia, and hypertension are common with severe alcohol withdrawal. Slurred speech, ataxia, vomiting, and hypotension occur during opioid intoxication.

3. A 22-year-old man develops paranoid delusions and dissociative symptoms over seven months, until he is hospitalized for an episode of behavioral dysregulation. He reports smoking five joints of cannabis daily since the age of 13. He is diagnosed with unspecified psychotic disorder and started on an antipsychotic medication. Which of the following best describes the current scientific consensus regarding the relationship between cannabis use and psychotic disorders?
   A. Schizophrenia is caused by early cannabis use
   B. Prodromal psychotic symptoms are temporarily relieved by cannabis
   C. The development of a psychotic disorder is independent of cannabis use
   D. Though the relationship between psychosis and cannabis use is complex, cannabis does appear to be a risk factor for the development of psychosis

   Answer: D.

   Explanation: Cannabis use is a risk factor for psychosis; however, it is neither sufficient to cause it, as answer A suggests it, nor necessary. In this clinical scenario, it is likely that prolonged and heavy cannabis use contributed to the onset of the psychotic disorder. There is no evidence to suggest prodromal symptoms of psychosis are relieved by cannabis.

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