When and How to Treat Possible Cannabis Use Disorder

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KEYWORDS

• Cannabis use disorder • Treatment • Psychosocial • Pharmacologic
• Synthetic cannabinoid

KEY POINTS

- Psychosocial interventions are the first-line for the treatment of cannabis use disorder.
- The most effective available treatments are cognitive–behavioral therapy and motivational enhancement therapy, with greater benefits found when combining approaches.
- Adding contingency management to these interventions can provide further benefit.
- There is no pharmacotherapy approved for the treatment of cannabis use disorder.
- Cannabinoid analogues and gabapentin have been tested with preliminarily positive results. Further research is warranted to clarify the potential role of these medications.

INTRODUCTION

Cannabis is the most frequently used illicit drug worldwide.[1] The lifetime probability of developing cannabis use disorder after a first exposure to the substance is approximately 9%.[2,3] Moreover, the likelihood of developing cannabis use disorder increases significantly if an individual starts using cannabis during adolescence.[4] In the United States, 4 million individuals were estimated to fulfill criteria for cannabis use disorder in the past year, representing approximately 1.5% of the American population aged 12 or older in 2015.[5]

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The plant *Cannabis sativa* contains approximately 60 identified cannabinoid compounds, some of which exert an effect in the human body via interaction with the CB_1 and CB_2 receptors, located predominantly in the central nervous system and in the immune system, respectively.[6,7] The main psychoactive properties of cannabis are attributed to the cannabinoid compound delta-9-tetrahydrocannabinol (THC), a partial agonist of the CB_1 and CB_2 receptors, that has been associated with the high produced by cannabis use and with its effects that lead to the development of addiction.[6,8,9] Recently, there has been a growing interest in cannabidiol, a nonpsychotropic component also present in different strains of cannabis. Cannabidiol has been shown to have antiepileptic properties in well-conducted clinical trials, and preclinical studies suggest it may have possible therapeutic properties, including its ability to decrease THC induced paranoia and euphoria, in addition to exerting a positive impact on anxiety and depression.[6,10–15] It should be noted that, so far, only the antiepileptic effect of cannabidiol has been tested properly in human subjects, and the other properties of cannabidiol remain to be evaluated in rigorous large-scale clinical trials.[15]

Cannabis is often used recreationally for its euphoria-producing effects. Other symptoms and signs of acute cannabis intoxication include increased appetite, tachycardia, tachypnea, high blood pressure, ocular erythema, dry mouth, and altered judgment. Cannabis use has been associated with a number of deleterious health outcomes, including worsening of respiratory problems, worsening of bipolar disorder-associated symptoms, short-term impairment of learning and memory, and higher risks of death from motor vehicle accidents.[16] There is also substantial evidence regarding the association between frequent cannabis use and psychosis, including schizophrenia, although the exact interplay remains controversial.[16] It is possible that exposure to cannabis may precipitate an earlier occurrence of psychotic symptoms in predisposed subjects, as suggested by the transient occurrence of symptoms that resemble those of a psychosis after THC administration in human laboratory studies.[17] However, the fact that the prevalence of schizophrenia has been stable over time while the use of cannabis and the potency of cannabis used has increased does not support a causal relationship between cannabis use and schizophrenia.

A diagnosis of cannabis use disorder as defined by the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) is made when there is a problematic pattern of use leading to significant impairment or distress, as manifested by at least 2 of the symptoms listed in the DSM-5, occurring within a 12-month period.[18] Discontinuation of cannabis use after regular, prolonged use is associated with a withdrawal syndrome that is recognized by the DSM-5, characterized by the emergence of symptoms such as anxiety, dysphoria, sleep disturbance, irritability, and anorexia.[18,19] Although cannabis withdrawal can be distressing, it is not life threatening. Nonetheless, the experience of withdrawal symptoms makes cannabis cessation more challenging and individuals experiencing a higher number of withdrawal symptoms have greater risks of rapid relapse to cannabis use compared with those experiencing fewer symptoms.[20]

Demand for cannabis-related health care services has been increasing in most regions of the world, including North America.[1] This finding may partly be explained by a significant increase over the past decades in the concentration of THC in cannabis as well as by the emergence of synthetic cannabinoid, a group of chemically synthesized highly potent cannabinoid analogues that are often associated with more severe use-related outcomes.[21] Moreover, the recent legalization of marijuana use in numerous US states has contributed to easier access to the substance. Hence,

data from the states that have legalized marijuana for recreational use indicate an increase in cannabis use and in cannabis-related emergency room visits and hospitalizations.[22–24]

Despite the high prevalence of cannabis use disorder, awareness regarding effective treatment options remain limited within the medical community. Better knowledge by clinicians regarding the management of cannabis use disorder could likely improve patient outcomes. This article offers an overview of the different effective approaches for the treatment of cannabis use disorder.

GENERAL TREATMENT PRINCIPLES

The intensity of the treatment recommended for a patient using cannabis largely depends on the clinical presentation. Therefore, a proper assessment and screening needs to be performed before establishing an appropriate treatment plan. Although no consensus screening recommendations have been published, authors have suggested the following recommendations. Physicians should question every patient at least once regarding cannabis use. Adolescents, young adults, and patients at high risk for cannabis-related harm (eg, patients with comorbid psychiatric or substance use disorders) should be asked about cannabis use more frequently, for example, at every routine medical visit.[25] When a patient reports using cannabis, the physician should inquire about clinical indicators of problematic cannabis use, including daily or near daily use, poor social functioning, poor functioning at work or school, unsuccessful attempts to reduce use, and concerns from family or friends.[25] When problematic use is suspected, the DSM-5 criteria should be reviewed to establish a diagnosis of cannabis use disorder.

Differentiating between recreational cannabis use and cannabis use disorder is an important step to determine what type of treatment is appropriate. The type of treatment offered also depends on a patient's motivation and desire to quit, and is often related to the level of distress experienced in relation to substance use. For patients using cannabis without fulfilling the criteria for cannabis use disorder, and for patients with cannabis use disorder who have no desire to diminish or discontinue their use, offering counseling as a part of medical visits is appropriate. Counseling can be based on the Lower Risk Cannabis Use Guidelines, a guideline based on a systematic literature review conducted by a group of international experts to identify behaviors that could be modified to decrease adverse health consequences from cannabis use.[26] The main recommendations issued by the group are summarized in **Box 1**.

For patients with a diagnosis of cannabis use disorder who are interested in receiving treatment, it is generally recommended to provide a referral to an addiction physician or to an addiction treatment program. If these options are not available, psychiatrists, psychologists, or counselors with expertise in addiction can also provide valuable specialized care. The treatment of cannabis use disorder is generally performed in an outpatient setting. Inpatient or residential treatments are generally limited to patients with comorbid psychiatric or substance use disorder justifying a higher level of care. It is recommended to establish treatment goals early in the episode of care to inform the appropriate treatment approach. Treatment goals are based on a patient's individual objectives, and may vary greatly, ranging from total abstinence, reducing the amount of cannabis used, to avoiding hazardous use. The use of urine drug screening may be useful in the course of treatment to monitor abstinence in patients aiming to fully discontinue cannabis use, but is of little usefulness in patients aiming to decrease their use, because routine drug screening only provides qualitative results. In patients with regular, heavy cannabis use, the interpretation of cannabis

Box 1
Main recommendations from the lower risk cannabis use guidelines

1. Abstaining from using cannabis to fully prevent cannabis-related health problems.
2. Avoiding initiation of cannabis use before the age of 16 years.
3. Choosing cannabis products with low THC potency or balanced THC-cannabidiol ratio.
4. Abstaining from using synthetic cannabinoid.
5. Favoring nonsmoking methods of consumption.
6. Avoiding deep inhalation practices, which may increase risks of respiratory problems.
7. Avoiding daily or near-daily cannabis use.
8. Abstaining from driving while impaired from cannabis to prevent motor vehicle accidents.
9. Populations at higher risk of cannabis-related adverse effects should refrain from using cannabis, including pregnant women and individuals with a predisposition for, or with a first-degree family history of psychosis or substance use disorder.
10. Avoiding to combine the aforementioned risk behaviors (eg, combining early initiation and high-frequency use could magnify the likelihood of experiencing cannabis-related adverse outcomes).

Abbreviation: THC, delta-9-tetrahydrocannabinol.
Adapted from Fischer B, Russell C, Sabioni P, et al. Lower-risk cannabis use guidelines: a comprehensive update of evidence and recommendations. Am J Public Health 2017;107(8):e4; with permission.

toxicology results can be challenging because qualitative results may remain positive up to 4 weeks after cessation of use. Furthermore, urine drug screening is of little usefulness in patients using synthetic cannabinoid because many of these compounds are not captured by urine drug testing.

Currently, psychosocial interventions are the first line for the treatment of cannabis use disorder, with some specific forms of such interventions having shown effectiveness in reducing cannabis use. A number of pharmacologic approaches have been tested in regard to their impact on cannabis use and on the severity of withdrawal symptoms yielding limited positive outcomes. Although a few medications have shown some promising results warranting further research, no medication is currently approved by the US Food and Drug Administration for the treatment of cannabis use disorder.

PSYCHOSOCIAL INTERVENTIONS

Different psychosocial interventions have been shown to be effective in reducing the frequency of cannabis use and the severity of cannabis use disorder.[27] The most effective approaches are cognitive–behavioral therapy (CBT), motivational enhancement therapy (MET), and a combination of both. Contingency management (CM) is also efficacious when combined with either of these interventions.[27] As a general principle, greater effectiveness is achieved when psychosocial treatments are implemented with higher intensity over longer periods of time (>4 treatment sessions over a period of >1 month).[27] This section presents an overview of the different psychosocial interventions available for the treatment of cannabis use disorder (**Table 1**).

Cognitive–Behavioral Therapy

CBT is a psychotherapeutic approach that focuses on the identification and modification of problematic thoughts and behaviors. It can be delivered in a group or individual

Table 1
Main psychosocial interventions recommended for the treatment of cannabis use and cannabis use disorder

Condition	Intervention	Setting	Outcomes
Cannabis use	Brief counseling Education on safer cannabis use practices based on the LRCUG	Individual; can be delivered by any physician during a regular medical visit	Decrease adverse health consequences from cannabis use
Cannabis use disorder	CBT Identification and modification of problematic thoughts and behaviors	Individual or group setting; generally delivered by a trained addiction professional	Decrease cannabis use[a] Decrease cannabis related-problems
	MET Enhancement of intrinsic motivation to change by exploring and resolving ambivalence	Individual or group setting; generally delivered by a trained addiction professional	Decrease cannabis use[b] Decrease cannabis-related problems Decrease the severity of cannabis use disorder
	CM Providing incentives (vouchers) contingent upon positive treatment outcomes	Used as an augmentation treatment combined with CBT or MET	Enhances the effectiveness of CBT and MET to decrease cannabis use

Abbreviations: CBT, cognitive–behavioral therapy; CM, contingency management; LRCUG, lower risk cannabis use guidelines; MET, motivation enhancement therapy.

[a] The intervention is effective to decrease the number of days of use, to decrease the number of joints per day and to increase past month abstinence.

[b] The intervention is effective to decrease the number of days of use and the number of joints per day.

setting. In the context of substance use disorder, this approach emphasizes coping strategies learning, problem solving, and promoting the substitution of cannabis use by alternative, better adapted behaviors.[28] CBT effectively reduced the frequency of cannabis use among patients with cannabis use disorder.[27,29,30] A 2016 metaanalysis evaluating the effectiveness of different psychosocial interventions for the treatment of cannabis use disorder found that individuals receiving CBT used cannabis on fewer days in the month before assessment compared with those assigned to the inactive control group (mean difference, 10.94; 95% confidence interval [CI], 7.44–14.44; n = 134).[27] Compared with inactive control, CBT was also found effective in increasing abstinence in the month before assessment (risk ratio; 4.81; 95% CI, 1.17–19.70; n = 171), in reducing the number of joints used per day (standardized mean difference [SMD], 4.60; 95% CI, 2.21–7.00; 2 studies [n = 306]) and in decreasing cannabis-related problems (SMD, 7.88; 95% CI, 6.86–8.90; n = 135).[27]

Motivational Enhancement Therapy

MET is a psychotherapeutic approach that promotes the importance of self-efficacy and positive changes. It can be delivered in an individual or group setting. The objective of MET intervention is to enhance intrinsic motivation to change by exploring and

resolving ambivalence in a nonjudgmental and empathic environment.[31] The aforementioned 2016 metaanalysis found a significant impact of MET on most of the primary outcomes examined (with the exception of past month abstinence), overall supporting the effectiveness of this psychotherapeutic approach for the treatment of cannabis use disorder.[27] MET was found effective in reducing the number of days of cannabis use in the month before assessment among participants treated with MET compared with inactive control (mean difference, 4.45; 95% CI, 1.90–7.00; 4 studies [n = 612]).[27] MET was also found superior to inactive control in reducing cannabis-related problems (SMD, 3.29; 95% CI, 1.85–4.72; 4 studies [n = 612]) and in decreasing the number of joints smoked per day (SMD, 3.14; 95% CI, 2.66–3.61; 4 studies [n = 611]) and the severity of cannabis use disorder (SMD, 4.07; 95% CI, 1.97–6.17; 2 studies [n = 316]).[27] The impact of MET on abstinence from cannabis in the month before assessment was not statistically significant (risk ratio, 1.19; 95% CI, 0.43–3.28; n = 197).[27]

Contingency Management

CM is often combined with other interventions as an augmentation approach for the treatment of substance use disorder. In CM, incentives are provided, often in the form of vouchers contingent upon positive treatment outcomes such as attendance at treatment appointments and abstinence from substance use verified with urine toxicology. A number of studies conducted in different populations of individuals with substance use disorders support the effectiveness of CM in improving retention to treatment and in promoting abstinence.[32,33] Although studies exploring the effectiveness of CM as a standalone treatment for cannabis use disorder are lacking, a number of clinical trials found that augmenting MET, CBT, or the combination of MET and CBT with abstinence-based CM improves the number of abstinent days compared with each of these psychotherapeutic approaches without CM.[27,34]

Alternative Approaches

Although the majority of studies on psychosocial interventions for the treatment of cannabis use disorder examined MET, CBT, or CM, alternative psychosocial approaches have also been tested, yielding weak or negative results. More specifically, evidence on mindfulness-based meditation, drug counseling, social support, and relapse prevention remain insufficient to recommend any of these approaches.[27] Marijuana Anonymous, a mutual help group based on the 12-step principle of Alcohol Anonymous, is widely available; however, its effectiveness has not been rigorously studied.

Combination Therapy

Although CBT and MET approaches were found equally effective for reducing cannabis use when compared with each other, a recent metaanalysis found maximal effectiveness of these interventions when delivered in combination compared with each treatment alone being delivered alone.[27] Furthermore, adding CM to either MET, CBT, or their combination likely further improves effectiveness.[27]

PHARMACOTHERAPY

There is currently no US Food and Drug Administration–approved medication for the treatment of cannabis use disorder, although a few trials have shown promising results. Cannabinoid agonists may be of potential value to decrease symptoms of withdrawal and improve retention to treatment. Some evidence also suggests gabapentin

may improve abstinence from cannabis. *N*-Acetylcysteine (NCA) was thought to be a promising approach based on data from an adolescent trial, but the initial positive findings have not been replicated in a recent clinical trial conducted in an adult population.[35,36] Further research is needed to confirm the effectiveness of these treatments. This section reviews the main pharmacotherapies that have shown preliminarily positive results for the treatment of cannabis use disorder.

Cannabinoid Agonists

Delta-9-tetrahydrocannabinol analogues

Dronabinol Dronabinol (Marinol) is a synthetic form of THC that is bioavailable orally. It is currently approved by the US Food and Drug Administration for the treatment of chemotherapy-related nausea and vomiting and for appetite stimulation in patients with advanced human immunodeficiency virus infection.

A few studies support the effectiveness of dronabinol alone or in combination with lofexidine to improve symptoms of cannabis withdrawal.[37–41] A 12-week trial of 156 adults with cannabis use disorder found that dronabinol 20 mg 2 times per day was effective in reducing symptoms of withdrawal and in improving retention to treatment but had no effect on marijuana use and on abstinence at the end of treatment.[39] Two studies also suggested a dose-dependent effect of dronabinol in suppressing withdrawal symptoms with tested doses up to 120 mg/d.[37,40]

Each study reported that the medication was well-tolerated with minimal side effects and an absence of adverse cognitive effects. Possible side effects from dronabinol include palpitations, tachycardia, flushing, vasodilation, euphoria, abnormality in thinking, dizziness, anxiety, and gastrointestinal symptoms.

Nabilone Nabilone (Cesamet) is a synthetic form of delta THC that acts as an agonist of the CB_1 and CB_2 receptors. It is approved for the treatment of nausea and vomiting induced by chemotherapy.

One small study of 11 non–treatment-seeking individuals who smoked cannabis daily found that nabilone significantly decreased relapse and improved withdrawal symptoms of irritability, insomnia, and disrupted food intake.[42] A dose of 8 mg/d was associated with a modest impact on psychomotor task performance. This adverse effect was not found at a dose of 6 mg/d. Adverse effects most frequently reported from nabilone include drowsiness, dizziness, vertigo, euphoria, ataxia, depression, lack of concentration, sleep disorder, xerostomia, and visual disturbance.

Combined delta-9-tetrahydrocannabinol/cannabidiol product

Nabiximols (Sativex) is a medication delivered as a buccal spray that contains THC and cannabidiol in approximately equal proportions. It acts as an agonist at the CB_1 and CB_2 receptors. Although it is not currently available in the United States, it is approved in different countries for the treatment of cancer pain as well as for spasticity and neuropathic pain associated with multiple sclerosis.

One Australian 28-day inpatient study of 51 adults with cannabis use disorder demonstrated the effectiveness of nabiximols administered at a dose up to 86.4 mg of THC and 80 mg of cannabidiol daily to reduce symptoms of withdrawal (including withdrawal- induced irritability, depression, and cravings) and to improve retention to treatment compared with placebo.[43] No symptoms of intoxication were experienced. A Canadian study of 9 patients with cannabis use disorder found that high doses of nabiximols ($\leq$108 mg of THC and $\leq$100 mg of cannabidiol daily) were effective in reducing symptoms of withdrawal during cannabis abstinence, but had no impact on cravings.[44] In both studies, there was no impact of the treatment on cannabis use outcome. More research studies are required to validate its use for

cannabis use disorder treatment. It should be noted that, in those trials, the rate of adverse effects did not differ between the medication and placebo. Importantly, symptoms of intoxication were not noted in the groups treated with nabiximols. Side effects most frequently reported with nabiximols include dizziness, drowsiness, fatigue, and nausea.

Gabapentin

Gabapentin is approved for the treatment of seizures and neuralgia. It acts by blocking voltage-dependent calcium channels, which indirectly modulates the inhibitory central nervous system neurotransmitter GABA. A 12-week randomized controlled trial of 50 adults with cannabis use disorder found that 1200 mg of gabapentin daily was effective in reducing cannabis use assessed both via urine drug testing and self-report, as well as in decreasing withdrawal symptoms including craving and improving executive function compared with the placebo group.[45] In this trial, gabapentin was administered 300 mg twice per day and 600 mg at bedtime. Both groups received weekly individual drug counseling. Although these results are promising, more research is needed to support the effectiveness of this medication for the treatment of cannabis use disorder.

The medication was well-tolerated and there was no difference in the proportion of adverse reactions between groups. The most frequent adverse effects reported with gabapentin are dizziness, drowsiness, ataxia, and fatigue.

N-Acetylcysteine

NAC is a derivative of the amino acid cysteine that modulates glutamate transmission. The presumed mechanism underlying NAC's possible efficacy is through the modulation of glutamate in the nucleus acumbens, a part of the brain reward circuitry that plays a significant role in the development of substance use disorders.

A study of 116 adolescents with cannabis use disorder aged between 15 and 21 years old showed that 8 weeks of treatment with NAC at a dose of 2400 mg/d doubled the odds of negative urine drug testing compared with placebo.[35] However, this finding was not replicated in a subsequent study by the same group, where 12 weeks of treatment with NAC at a dose of 2400 mg/d showed no difference in cannabis abstinence compared with placebo amongst 302 adults with cannabis use disorder aged 18 to 50 years old.[36]

Other

Numerous other tested pharmacologic approaches are likely of little value for the treatment of cannabis use disorder. These medications include escitalopram, fluoxetine, bupropion, nefazodone, venlafaxine, valproate, baclofen, modafinil, atomoxetine, buspirone, and naltrexone, all of which failed to demonstrate a significant positive impact on withdrawal or cannabis use outcomes.[38,46–57] In a human laboratory study, mirtazapine was found to improve sleep and food intake during abstinence, but did not impact withdrawal symptoms and relapse.[55] Similarly, a human laboratory study showed that the antipsychotic quetiapine improved sleep quality and food intake, but also increased marijuana craving and self-administration.[58]

Recently, data have emerged on the potential role of cannabidiol as a treatment option for cannabis use disorder given its ability to decrease THC-induced euphoria.[13,14] Although cannabidiol in combination with THC was found to improve symptoms of cannabis withdrawal, one laboratory study of cannabidiol administered alone did not show effectiveness in decreasing cannabis use or the subjective reinforcing effect of cannabis use.[43,44,59] It is unclear whether the impact of combination THC and

cannabidiol treatment on reducing withdrawal symptoms can be partly attributed to the cannabidiol component or is instead owing to the effect of THC alone.

Rimonabant, an inverse agonist/antagonist of the CB_1 receptor was found to decrease drug taking behavior and cue-induced reinstatement of drug-seeking behavior in abstinent monkeys and to attenuate the physiologic effect of cannabis intoxication in humans.[60,61] However, it was found to cause adverse psychiatric outcomes such as anxiety and depression and was removed from the market in 2008.[62,63]

AM4113, a CB_1 receptor neutral antagonist has been studied in animal models, showing positive impact on reducing the use of cannabis without the negative psychiatric side effects of rimonabant.[61,64] This may be a promising treatment and further studies would be of interest.

Finally, a number of clinical trials are currently exploring the impact of different medications for the treatment of cannabis use disorder, including clonazepam, quetiapine, lorcaserin, FAAH-inhibitor, nabilone, NAC, cannabidiol, dronabinol in combination with clonidine, dextroamphetamine/amphetamine, and varenicline.

SYNTHETIC CANNABINOIDS

Synthetic cannabinoids are chemically synthesized compounds that are analogues to naturally occurring cannabinoids. They were first developed in laboratories for medical research in the 1960s and started being sold for recreational use around 2008 in the United States, most frequently under the names of "spice" or "K2."[65] Over the past decade, they have gained popularity owing to their accessibility, the unclear legal status regarding their use, and the lack of detection in routine drug screening. An important feature of synthetic cannabinoid is the variability of their composition, with frequent occurrence of new derivative compounds, presumably with the objective of avoiding regulations.[66] The heterogeneity of the synthetic cannabinoid group of compounds makes intoxication symptoms variable and less predictable.

Synthetic cannabinoids and cannabis bind to the same receptors and, therefore, both substances share common features in terms of signs and symptoms of intoxication and withdrawal. However, a number of synthetic cannabinoid compounds can have greater potency and binding affinity to the receptors compared with cannabis.[67,68] Moreover, certain synthetic cannabinoids produce active metabolites that act as full receptor agonists as opposed to the partial agonist activity of THC.[67,68] These pharmacologic properties contribute to the greater severity of synthetic cannabinoids intoxication and withdrawal symptoms compared with regular cannabis.

The majority of cases of intoxication are not life threatening and may present with tachycardia, nausea, vomiting, behavioral perturbation, and anxiety, although some severe symptoms of intoxication have been reported, including new-onset psychosis, kidney injury, rhabdomyolysis, respiratory depression, and seizures.[69–71] A few cases of death have been attributed to direct toxicity from synthetic cannabinoids causing cardiac arrhythmia, seizure, and kidney failure, whereas other cases of death were indirectly due to synthetic cannabinoids, such as hypothermia owing to individuals remaining unconscious outdoor in the winter or suicide.[69]

Management of Acute Intoxication

Mild to moderate symptoms of intoxication are managed in the emergency department until resolution of symptoms (which typically last 4–6 hours), although more severe symptoms may warrant inpatient admission. In the majority of cases, acute intoxication is managed with supportive care and with intravenous fluid repletion.[72]

Benzodiazepines are used as a first line to treat agitation, irritability, psychosis, and seizure.[72] Antipsychotics may also be used to treat agitation and psychotic symptoms.[72] Antiemetic medications can be used to treat hyperemesis, although they are not always effective.[73,74] Poison control centers are available at all times and should be consulted for patients who are critically ill or for whom presentation symptoms are unclear.

Management of Withdrawal

Abrupt discontinuation of synthetic cannabinoid after daily use has been associated with withdrawal symptoms ranging from mild symptoms such as headaches, anxiety, insomnia, nausea, vomiting, loss of appetite, diaphoresis, and craving to severe symptoms including seizure, chest pain, palpitations, and dyspnea.[72] In the absence of instruments designed to assess withdrawal symptoms from synthetic cannabinoids specifically, we suggest that clinicians use the DSM-5 diagnostic criteria for cannabis withdrawal. Similar to the management of acute intoxication, mild to moderate withdrawal symptoms can be managed in an outpatient setting, although severe cases may require inpatient care and continuous monitoring.

Benzodiazepines are used as a first-line treatment for the management of withdrawal symptoms including agitation, anxiety, and seizure.[75,76] Quetiapine has been used with effectiveness to treat withdrawal induced agitation and anxiety after failure of a benzodiazepine trial.[75,76]

Given the recent emergence of synthetic cannabinoids, knowledge regarding best treatment options remain limited and further research is needed to better guide clinical interventions.

FUTURE CONSIDERATIONS AND SUMMARY

Despite the high prevalence of cannabis use disorder, there are few effective treatment options available. MET and CBT are the most effective psychosocial interventions to reduce cannabis use in individuals with cannabis use disorder, with maximal results achieved when combining both approaches.[27] Adding CM in the form of vouchers for negative urine drug test results can provide further benefit in the short term, although little evidence is available regarding long-term benefits.[27] Treatment of greater intensity (>4 sessions over >1 month) is more effective than lower intensity interventions.[27]

Although no pharmacotherapy is approved for the treatment of cannabis use disorder, data suggest that some medications may be of potential value. In line with the concept of using agonist medications to treat other substance use disorders, such as buprenorphine and methadone for opioid use disorder and nicotine replacement and varenicline for nicotine use disorder, there has been a growing interest in the potential role of cannabinoid analogues for the treatment of cannabis use disorder. It has been hypothesized that cannabinoid analogues could improve abstinence by attenuating withdrawal symptoms and by decreasing the pleasurable effect of cannabis. Although studies have consistently demonstrated the ability of cannabinoid analogues to decrease acute cannabis withdrawal symptoms, no impact was found on cannabis use outcomes.[37–44] Hence, the role of cannabinoid medications in the long-term treatment of cannabis use disorder remains to be investigated.

Gabapentin may provide some benefit in decreasing cannabis use and cannabis withdrawal symptoms.[45] There are mixed results regarding the effect of NAC.[35,36] Further research is warranted to clarify the potential role of the aforementioned medications. A number of pharmacotherapies are currently under investigation for the

treatment of cannabis use disorder and may lead to the emergence of novel therapeutic options in the future.

Finally, data suggest gender differences in cannabis use and cannabis use disorder. Although men are more likely to initiate cannabis use and to have a lifetime diagnosis of cannabis use disorder, women demonstrate a faster progression from cannabis use to cannabis use disorder.[77,78] Women with cannabis use disorder are also more likely than men to experience withdrawal symptoms, to have low scores on quality of life assessment scales, and to have comorbid mood or anxiety disorders.[2,78–80] These gender differences could potentially lead to the development of gender-specific treatment approaches, such as placing a greater emphasis on withdrawal symptoms and on the treatment of comorbid psychiatric disorders for women. Future studies exploring the impact of gender on response to treatments for cannabis use disorder would be of great interest.

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