Cannabis withdrawal: Epidemiology, clinical features, diagnosis, and treatment

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INTRODUCTION

Cannabis (also called marijuana) is the fourth most commonly used psychoactive substance worldwide, after alcohol, caffeine, and tobacco (nicotine) [1]. Its euphorigenic, sedative, and analgesic properties are primarily due to one cannabinoid: delta-9-tetrahydrocannabinol (THC). THC concentration is commonly used as a measure of cannabis potency [2].

Cannabis withdrawal is manifested by a constellation of signs and symptoms occurring within one week after abrupt reduction or cessation of heavy and prolonged cannabis use. The symptoms are nonspecific and may include sleeplessness, irritability, anxiety, and depressed mood. Symptoms can be disabling and can inhibit attempts to cut down or abstain from cannabis use.

The epidemiology, pathogenesis, clinical manifestations, course, assessment, diagnosis, and treatment of cannabis withdrawal are reviewed here. Other aspects of cannabis use are discussed separately.

- (See "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment".)
- (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)
- (See "Cannabis (marijuana): Acute intoxication".)
- (See "Synthetic cannabinoids: Acute intoxication".)

EPIDEMIOLOGY

There are limited data on the prevalence of cannabis withdrawal, in part because of the lack of large-scale studies that attempt to correlate participants' intensity of cannabis use with their withdrawal experience. Additionally, most published studies include data collected from recreational users a decade or more ago, when cannabis was consumed primarily by smoking and the potency (delta-9-tetrahydrocannabinol [THC] concentration) was approximately one-third that of currently available cannabis [2].

Prevalence — A meta-analysis of population-based and clinical (inpatient and outpatient) studies found a past-year prevalence of cannabis withdrawal syndrome (variously defined) of 31 percent (95% CI 27-36) among individuals with "regular" cannabis use or cannabis use disorder [3]. As expected, lifetime prevalence was found to be substantially higher (76 percent; 95% CI 70-82) [3] and also varied broadly due to heterogeneity across studies [3-7].

Low-quality, cross-sectional data from samples of medical cannabis users suggest that they experience cannabis withdrawal at roughly comparable rates as recreational users [8,9].

Risk factors — THC is the cannabinoid most strongly associated with cannabis withdrawal [10]. In contrast, abrupt cessation of oral cannabidiol (750 mg twice daily) is not associated with withdrawal symptoms [11].

The primary risk factors for cannabis withdrawal are intensity (usually measured as frequency) and recency of cannabis use [10]. For example, a meta-analysis found the past-year prevalence of cannabis withdrawal syndrome (variously defined in different studies) was significantly greater among daily cannabis users than among less-than-daily users (47 versus 23 percent) [3]. An observational study of 73 adults with moderate-severe cannabis use disorder who were admitted for 24 days of inpatient detoxification found a somewhat weak but statistically significant positive correlation between withdrawal severity (assessed with the Marijuana Withdrawal Checklist) and urine concentration of the major THC metabolite 11-nor-9-carboxy-THC (THC-COOH; r = 0.248, 95% CI 0.152-0.339) [12].

The prevalence of cannabis withdrawal syndrome does not vary significantly by age (adolescent to older adult), sex, or race/ethnicity [3,13]. In regard to gender, limited evidence from cross-sectional studies suggests that men and women may experience cannabis withdrawal differently, with women experiencing more mood and gastrointestinal symptoms and men experiencing more sleep disturbance [14,15].

Twin studies suggest that genetics also play a role in susceptibility to cannabis withdrawal [16]. There is inconsistent evidence as to whether individuals with mood, anxiety, or substance use disorders are at increased risk of cannabis withdrawal syndrome [3,13]. We are not aware of any studies evaluating the influence of cannabis route of administration on cannabis withdrawal syndrome in humans.

PATHOGENESIS

Phytocannabinoids are partial agonists at cannabinoid CB1 and CB2 receptors, part of the body's endogenous cannabinoid (endocannabinoid system). Studies in humans and animals have shown that down regulation of CB1 receptors occurs as the receptors adjust to the increased activation from heavy exposure to both endogenous and exogenous agonist [10]. Cessation of cannabis use results in a loss of exogenous agonist activation, leaving CB1 receptors in a hypoactive state that presumably mediates withdrawal symptoms. Over time, the receptors return to their normal precannabis exposure state (up-regulation). (See "Cannabis (marijuana): Acute intoxication", section on 'Pharmacokinetics'.)

Positron emission tomography studies find that chronic daily or almost daily cannabis smokers have 10 to 15 percent CB1 receptor down-regulation (reduced receptor density or reduced receptor binding potential) in many brain regions, especially the cingulate and temporal cortex, during the first 24 hours after last cannabis use [17,18]. This down-regulation is normalized after four weeks of monitored abstinence. However, the temporal course of receptor normalization and its association with cannabis withdrawal symptoms remain unclear. Studies attempting to correlate receptor normalization with the time course of cannabis withdrawal symptoms have been heterogeneous and shown mixed results [17-19].

Synthetic cannabinoids have a variety of chemical structures that differ from those of plant-derived cannabinoids (phytocannabinoids). Additionally, they are more potent agonists at CB1 receptors than phytocannabinoids [20]. (See "Synthetic cannabinoids: Acute intoxication", section on 'Toxicity and pharmacology'.)

CLINICAL MANIFESTATIONS

Symptoms of withdrawal from cannabis or delta-9-tetrahydrocannabinol are generally less severe and shorter lasting than those of withdrawal from synthetic cannabinoids.

Cannabis — Cannabis withdrawal is manifested by a constellation of signs and symptoms occurring within one week after abrupt reduction or cessation of heavy and prolonged cannabis

use. The symptoms of cannabis withdrawal range from very mild to more severe. Cannabis withdrawal has clinical significance when the symptoms are severe enough to be distressing, interfere with activities of daily living, or serve as negative reinforcement for continued abstinence [4,21].

In a national survey of 1527 cannabis users who reported at least three times per week use, the most common symptoms of withdrawal were sleep difficulty (14 percent), irritability or anger (14 percent), anxiety (13 percent), headache (12 percent), and depressed mood (11 percent) [13]. Other symptoms such as restlessness, decreased appetite or weight loss, abdominal pain, shaking or tremors, sweating, and fever or chills have been described.

Disturbed sleep is one of the most common symptoms of cannabis withdrawal [22]. Most polysomnography studies during the first week of cannabis withdrawal find increased sleep onset latency and decreases in total sleep time, slow wave sleep, sleep efficiency, and rapid eye movement latency [22,23].

Withdrawal from cannabis, unlike withdrawal from synthetic cannabinoids, is not generally associated with clinically significant cardiovascular changes or symptoms such as sympathetic autonomic hyperactivity. Two small (13 and 39 participants) prospective longitudinal inpatient studies of adult daily cannabis users had inconsistent findings [24,25]. Both studies found no change in heart rate during early cannabis withdrawal, but one of the two studies found modest increases in blood pressure in 6 of the 13 participants [24].

Synthetic cannabinoids — Abrupt cessation of synthetic cannabinoid use can give rise to clinically significant physiological withdrawal symptoms, such as sympathetic autonomic hyperactivity resulting in tachycardia, hypertension, and diaphoresis, seizures, and altered mental status (eg, psychosis, delirium) [26,27].

While there are no systematic studies of synthetic cannabinoid withdrawal, a growing number of case series and case reports suggest that serious, often life-threatening, phenomena such as seizures, cardiac arrhythmias, kidney failure, delirium, and prolonged psychosis are not rare [26,28,29]. However, it is often difficult to distinguish which of these phenomena are due to the persisting effects of synthetic cannabis intoxication, in particular high-dose cannabis [30] and/or intravenous cannabis administration [31], or whether they arise as withdrawal symptoms with onset only after initiation of abstinence. (See "Synthetic cannabinoids: Acute intoxication".)

COURSE

Most cannabis withdrawal symptoms appear 24 to 72 hours after cessation of use, reach peak intensity over the first week, and largely resolve after one to two weeks [32,33]. Sleep disturbances may last several weeks, although there appears to be substantial interindividual variation. Patients with moderate to severe withdrawal have a higher likelihood of relapse due to negative effects on sleep or daily functioning.

Withdrawal from synthetic cannabinoids may have a longer course, with severe psychiatric and medical disturbances persisting for weeks [26].

A prospective, 16-day longitudinal study of 39 adult, treatment-seeking, chronic, heavy cannabis users (daily use for six months to 30 years) admitted for inpatient detoxification found that all participants experienced cannabis withdrawal, assessed with a 12-item modified Marijuana Withdrawal Checklist [32]. Cannabis withdrawal was:

- Present on day 1
- Reached peak intensity on day 4 (range day 1 to 8)
- Declined substantially by day 16, resolving completely in many

Peak withdrawal intensity ranged from moderate (18 percent) to severe (41 percent).

A current or lifetime history of mood or anxiety disorder may affect the duration of cannabis withdrawal symptoms. In a prospective study of 50 young adults who achieved abstinence in outpatient treatment, a longer duration of severe cannabis withdrawal was experienced in those subjects with a current or lifetime mood or anxiety diagnosis than in those subjects without a current or lifetime diagnosis (significant reduction in symptom intensity over two weeks versus one week.) [34].

ASSESSMENT AND DIAGNOSIS

Observation/interview — Otherwise unexplained mood changes, restlessness, sleep disturbance, decreased appetite or weight loss, or physical symptoms such as abdominal pain, muscle twitching, aches, or tremors should arouse suspicion of possible cannabis withdrawal in an individual who was recently a heavy cannabis user.

The patient should be asked about past and recent cannabis intake, in particular whether they have recently decreased or stopped use and the time of their last use in relation to symptom onset.

Diagnostic criteria — The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, (DSM-5-TR) diagnostic criteria for cannabis

withdrawal are as follows [35]:

- A. Cessation of cannabis use that has been heavy and prolonged (ie, usually daily or almost daily use over a period of at least a few months).
- B. Three or more of the following signs and symptoms develop within approximately one week after cessation of heavy, prolonged use:
  - 1. Irritability, anger, or aggression.
  - 2. Nervousness or anxiety.
  - 3. Sleep difficulty (ie, insomnia, disturbing dreams).
  - 4. Decreased appetite or weight loss.
  - 5. Restlessness.
  - 6. Depressed mood.
  - 7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache.
- C. The signs or symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Differential diagnosis — Cannabis withdrawal symptoms are largely nonspecific, so they must be carefully distinguished from other withdrawal syndromes, especially tobacco [36], and from other psychiatric disorders (eg, generalized anxiety disorder, major depressive disorder) that may produce similar symptoms. In all cases, the major distinguishing feature is the temporal association with abrupt cessation of chronic or heavy cannabis use and the gradual resolution of symptoms with increasing duration of abstinence.

Tobacco withdrawal may be particularly difficult to distinguish from cannabis withdrawal, as the symptoms overlap, and many cannabis users also use tobacco [37]. Small, open-label retrospective and prospective outpatient studies in adult, nontreatment-seeking daily cannabis and daily tobacco smokers find that the two withdrawal syndromes have comparable symptom profiles, intensities, and time courses [36,38]. These findings are confirmed by an outpatient,

open-label study of 12 adult, nontreatment-seeking chronic daily or almost-daily users of cannabis and tobacco [39]. This study reported similar withdrawal severity between the two substances; concurrent withdrawal from both was more severe than from either alone. (See 'Cannabis and tobacco co-use' below.)

Among adolescent girls, the triad of poor appetite, weight loss, and gastrointestinal symptoms associated with cannabis withdrawal may be misdiagnosed as an eating disorder [40].

Withdrawal severity — We consider mild cannabis withdrawal as consisting of symptoms that minimally interfere with the patient's functioning and do not contribute to a high risk of relapse. In our experience, patients with mild cannabis withdrawal, absent comorbid psychiatric illness, do not typically present clinically for treatment of withdrawal.

Moderate and severe syndromes constitute the middle and high end of this spectrum.

Cannabis withdrawal severity is based upon clinical judgment. The DSM-5-TR does not define the categories by the number of withdrawal symptoms present (as they do in criteria for other substance use withdrawal syndromes).

Cannabis withdrawal intensity can be more formally assessed using the 15-item Marijuana Withdrawal Checklist (table 1) [33]. This checklist was originally devised as a 22-item questionnaire for research purposes [41].

TREATMENT

Indications for treatment — The majority of acute cannabis withdrawal episodes are mild and resolve without the need for formal treatment. However, patients with moderate to severe withdrawal have a higher likelihood of relapse due to negative effects of sleep or daily functioning. These individuals may benefit from treatment of withdrawal. (See 'Withdrawal severity' above.)

Treatment options — A number of medication options are available. Dronabinol (synthetic delta-9-tetrahydrocannabinol [THC]), nabiximols (a plant-derived 1:1 ratio of THC:cannabidiol [CBD]), and gabapentin have shown efficacy for reducing cannabis withdrawal in at least one randomized clinical trial [42-44]. Several other medications have shown efficacy in small trials or case series.

Individuals with mild cannabis withdrawal often self-treat with physical exercise [45], meditation or prayer, relaxation techniques, herbal preparations, over-the-counter analgesics, sedatives, hypnotics, and alcohol use [5].

There are no head-to-head clinical trials comparing the effectiveness of medication treatments or with other treatments such as cognitive-behavioral therapy (CBT). No medication is approved for the treatment of cannabis withdrawal by any national regulatory authority, including the US Food and Drug Administration (FDA). Thus, treatment choices may reasonably be informed by treatment availability and patient preference. For example, some patients may prefer CBT rather than medications because of concern about medication side effects or because of CBT's effectiveness in other substance use disorders. The efficacy of CBT in the treatment of cannabis withdrawal is not well studied [5,45]. (See 'Cognitive-behavioral therapy' below.)

Initial treatment

Patients with prominent sleep disturbance — In patients with a prominent sleep disturbance that affects daily functioning, we suggest initial treatment with zolpidem [46], a nonbenzodiazepine gamma aminobutyric acid (GABA)-A agonist. In these cases, sleep disturbance may lead to severe anxiety and irritability that impairs personal relationships and may prompt the individual to resume cannabis use as a means of self-medicating.

Nitrazepam, a benzodiazepine, is a reasonable alternative; its use is supported by limited data [47]. However, it has greater abuse liability and is not available in the United States. Other treatments are also reasonable for such patients, including dronabinol for patients who also have other severe withdrawal symptoms, as well as gabapentin and CBT, as described below.

Support for the use of zolpidem or nitrazepam includes the following:

- **Zolpidem** – Zolpidem improved most measures of sleep disturbance in two randomized clinical trials. A total of 31 patients with daily or near daily cannabis use were treated with zolpidem 12.5 mg extended release or placebo for withdrawal-related sleep disturbance [48,49]. Subjects receiving zolpidem showed improved sleep quality and duration compared to placebo. Sleep parameters were assessed by polysomnography [48] or wrist-worn activity meters [49]. Zolpidem side effects were not reported in these trials, but the FDA labeling lists major side effects as ataxia, confusion, and depression. (See "Pharmacotherapy for insomnia in adults", section on 'Nonbenzodiazepine BZRAs'.)

- **Nitrazepam** – Nitrazepam improved sleep in an open-label observational study of 38 adult inpatients participating in a randomized trial of lithium for cannabis withdrawal [47]. Patients were prescribed as needed nitrazepam 10 mg/nightly for up to three nights. On nights in which nitrazepam was used, sleep duration and efficiency improved compared to nights in which the medication was not used. Nitrazepam side effects were not reported in this trial, but the FDA labeling lists major side effects as daytime drowsiness, ataxia,

confusion, amnesia, dizziness, lightheadedness, headache, and muscle weakness. (See "Pharmacotherapy for insomnia in adults", section on 'Benzodiazepine hypnotics'.)

Patients with other withdrawal symptoms

Delta-9-tetrahydrocannabinol: Dronabinol, nabiximols — For patients with moderate to severe cannabis withdrawal symptoms (eg, irritability, restlessness, anger, or depression) that affect daily functioning, we suggest pharmacologic management with THC. THC, a CB1 receptor partial agonist found in the cannabis plant, activates CB1 receptors, thereby ameliorating their hypoactive state resulting from down-regulation during chronic cannabis (THC) exposure. The use of THC to reduce symptoms of cannabis withdrawal is analogous to the use of the mu-opioid receptor agonists methadone or buprenorphine in treating opiate withdrawal [43]. (See "Opioid use disorder: Pharmacologic management".)

Two types of THC have been tested in the treatment of cannabis withdrawal, dronabinol and nabiximols (marketed under the name Sativex, not available in the United States). Although there have been no head-to-head trials comparing dronabinol and nabiximols, they have been found to reduce withdrawal symptoms by similar amounts (eg, mean of 25 to 50 percent) [50]. Clinical trials, with one exception, have found that THC reduced cannabis withdrawal symptoms following cessation of cannabis use but did not necessarily lead to sustained abstinence.

We suggest the use of nabiximols for initial treatment of cannabis withdrawal, where it is available, because the evidence supporting its use is somewhat more robust. Also, because it is combined with CBD, there is less likelihood of abuse. Dronabinol is a reasonable alternative in the United States, where nabiximols is not available.

A potential disadvantage for the use of these drugs is that patients taking dronabinol and nabiximols will likely test positive for cannabinoids on drug testing.

- **Nabiximols (Sativex)** – Nabiximols is a cannabis plant extract that is approved in Canada and several European countries for indications other than cannabis withdrawal. (See "Cancer pain management: Role of adjuvant analgesics (coanalgesics)", section on 'Cannabis and cannabinoids'.)

  Nabiximols is delivered via an oromucosal (sublingual) spray. In clinical trials, the medication was delivered via multiple sprays several times per day, resulting in a total daily dose between 86.4 mg THC/80 mg cannabidiol and 108 mg THC/100 mg cannabidiol. Adverse effects include nausea, diarrhea, and disturbed sleep [51,52].

In clinical trials, nabiximols has been found to attenuate cannabis withdrawal symptoms as compared to placebo [51,52]. In one clinical trial of 51 treatment-seeking patients with cannabis dependence and a history of cannabis withdrawal, treatment with nabiximols reduced overall severity of cannabis withdrawal versus placebo for the duration of the treatment (mean 66 percent decrease versus mean 52 percent increase). Subjects treated with nabiximols showed less irritability, depression, and cannabis craving than those treated with placebo. Additionally, subjects assigned to nabiximols were more likely to remain in the treatment until the end of the medication phase than those in placebo (hazard ratio 3.66, 95% CI 1.18-11.37) [51].

- **Dronabinol** – Dronabinol is a synthetic THC that is approved in the United States for indications other than the treatment of cannabis withdrawal [53,54].

  Oral dronabinol suppresses cannabis withdrawal at doses of 30 to 90 mg/day (in divided doses); suppression is dose dependent [53]. A liquid solution of dronabinol is also available but has not been tested in the treatment of cannabis withdrawal. Side effects include drowsiness, increased blood pressure, and light-headedness [54]. (See "Characteristics of antiemetic drugs", section on 'Cannabinoids' and "Management of poorly controlled or breakthrough chemotherapy-induced nausea and vomiting in adults", section on 'Cannabinoids and medical marijuana'.)

Trials have been inconsistent in demonstrating efficacy. In one trial, 156 adults seeking treatment for moderate-severe cannabis use disorder were treated with dronabinol versus placebo [53]. All participants received CBT focused on relapse prevention and contingency management to reward study adherence. Patients treated with dronabinol had lower withdrawal discomfort scores overall, with approximately 25 percent lower scores than placebo over weeks 2 to 8. The dronabinol group also had higher retention (77 versus 61 percent). Dronabinol was well tolerated; there was no difference between the two treatment groups in proportion of participants experiencing any adverse effect (67 versus 58 percent). In contrast, one trial of 122 patients with intensive cannabis use compared treatment with THC (dronabinol) plus lofexidine (an alpha-2 adrenergic receptor agonist) or placebo [52,54]. Intensity of cannabis withdrawal symptoms was similar in both treatment and placebo groups.

Other treatment options

Gabapentin — The GABAergic drug gabapentin was found to reduce cannabis withdrawal in a clinical trial which randomly assigned 50 adult treatment-seeking daily users of cannabis to receive gabapentin 1200 mg/day or placebo for 12 weeks [44]. All participants received weekly individual CBT focused on relapse prevention. Patients treated with gabapentin had reduced

withdrawal intensity overall, with group differences becoming apparent at week 3 (time of peak withdrawal intensity). Gabapentin was well tolerated. The most common side effects were headache, insomnia, nausea, and muscle or joint pain, though none were significantly more common than with placebo.

Gabapentin is a reasonable choice for patients who may be subject to drug testing.

Cognitive-behavioral therapy — There are no randomized clinical trials examining the efficacy of CBT for cannabis withdrawal either as monotherapy or in combination with medication. There are no clinical trials directly evaluating whether CBT or medication is more effective as the initial treatment for cannabis withdrawal.

Small case series involving a few dozen patients suggest that CBT, administered individually or in groups, may alleviate some withdrawal symptoms [55]. Approximately one-third of patients achieved short-term abstinence, but these groups typically have high drop-out rates (50 percent or more).

CBT is usually provided weekly for 8 to 16 weeks for treatment of substance use disorders, although there are no data to indicate the optimum duration of treatment for cannabis withdrawal. As cannabis withdrawal syndrome is typically resolved within three weeks in medication trials, absence of clinically significant improvement within this time period suggests consideration of a switch to, or addition of, medication treatment.

CBT seeks to help patients with substance use disorder to modify biased cognitions and attributions related to substance use and alter behaviors that increase vulnerability to substance use. The use of CBT in the treatment of substance use disorders generally is reviewed in greater detail separately. (See "Substance use disorders: Psychosocial management", section on 'Cognitive-behavioral therapy'.)

Patients with inadequate response — For patients with moderate to severe withdrawal who do not respond or respond only partially to a medication or CBT, we suggest the substitution or addition, respectively, of another intervention. As examples:

- For most patients with moderate to severe withdrawal who do not respond to either dronabinol or nabiximols after several weeks, we suggest a trial of gabapentin on the theoretical grounds that a different mechanism of action may lead to a different response. (See 'Gabapentin' above.)

- For patients whose inadequate response to dronabinol is largely due to persisting cannabis craving, we suggest a trial of nabiximols, on the grounds that the cannabidiol in

nabiximols may moderate persistent craving. (See 'Delta-9-tetrahydrocannabinol: Dronabinol, nabiximols' above.)

- CBT can be tried following any failed medication trial or after all medication options have been exhausted. There are no clinical trials that have compared the combination of CBT and medication with either modality as monotherapy in cannabis withdrawal.

Cannabis and tobacco co-use — Many cannabis users also use tobacco (chiefly as cigarettes), with rates above 50 percent in some studies [37,56]. Some of this co-use is simultaneous (eg, smoking cannabis within a hollowed-out cigar [a so-called “blunt”]).

Reducing or stopping both cannabis and tobacco use at the same time will trigger both withdrawal syndromes, which may be more severe than either syndrome alone [39].

The nicotine skin patch should be used cautiously in patients trying to abstain from both cannabis and tobacco use, as it may exacerbate cannabis withdrawal. Such patients may be advised to first achieve stable tobacco abstinence (with use of the nicotine skin patch, if appropriate) before attempting cannabis abstinence. A controlled clinical trial involving 127 adults with moderate-severe cannabis use disorder and no or light tobacco use found that wearing a nicotine (7 mg) skin patch for 15 days significantly worsened cannabis withdrawal symptoms compared with a placebo patch (one to two point increase in Marijuana Withdrawal Checklist scores), while significantly reducing negative affect [57].

There are no studies that directly address treatment of co-occurring cannabis and tobacco withdrawal.

Synthetic cannabinoid withdrawal — Because of the severity of withdrawal from synthetic cannabinoids, treatment is usually directed at stabilizing the patient and reversing psychiatric and physiological abnormalities [26,27]. This may involve sedation with benzodiazepines for agitation, second-generation antipsychotics for psychosis, anticonvulsants for seizures, and/or renal dialysis for kidney failure. There are no studies of treatment for mild synthetic cannabinoid withdrawal.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cannabis use disorder and withdrawal".)

SUMMARY AND RECOMMENDATIONS

- **Prevalence** – There are limited data on the prevalence of cannabis withdrawal, in part because of the lack of large-scale studies that attempt to correlate participants' intensity of cannabis use with their withdrawal experience. The primary risk factor for cannabis withdrawal are intensity or frequency of use and recency of cannabis use. (See 'Epidemiology' above and 'Risk factors' above.)

- **Clinical manifestations** – Cannabis withdrawal symptoms typically appear 24 to 72 hours after abrupt reduction of heavy and prolonged cannabis use, reach peak intensity over the first week, and largely resolve after one to two weeks without treatment. Withdrawal symptoms include irritability, anger, anxiety, depression, and disturbed sleep. Withdrawal symptoms can interfere with attempts to cut down or abstain from cannabis use. There appears to be substantial interindividual variation. (See 'Clinical manifestations' above.)

- **Synthetic cannabinoids** – Symptoms of withdrawal from synthetic cannabinoid use can give rise to clinically significant physiological withdrawal symptoms, such as sympathetic autonomic hyperactivity resulting in tachycardia, hypertension, and diaphoresis, seizures, and altered mental status (eg, psychosis, delirium). (See 'Synthetic cannabinoids' above.)

- **Treatment –** The majority of acute cannabis withdrawal episodes are mild and resolve without a need for formal treatment. Individuals in mild withdrawal do not typically present seeking treatment. In our experience, improved sleep hygiene, meditation and relaxation techniques, and physical exercise can be helpful for mild symptoms. (See 'Treatment' above.)

  Patients with moderate to severe withdrawal have a higher likelihood of relapse due to negative effects on sleep or daily functioning. These patients may benefit from treatment of withdrawal. (See 'Indications for treatment' above.)

- **Treatment options** – The choice of treatment for cannabis withdrawal depends on the treatment availability, the nature of the symptoms that are most bothersome to the patient, and the patient's preferences. (See 'Treatment' above.)

  - **Sleep disturbance** – For patients whose primary withdrawal symptom is sleep disturbance impairing functioning or increasing risk of relapse, we suggest zolpidem rather than other medications (**Grade 2C**). Nitrazepam is a reasonable alternative if zolpidem is ineffective; both have limited evidence of efficacy in this situation. (See 'Patients with prominent sleep disturbance' above.)

- **Other withdrawal symptoms** – For most patients with bothersome withdrawal symptoms other than or in addition to sleep disturbance, we suggest treatment with nabiximols, where available, rather than other medications (**Grade 2C**). Dronabinol is a reasonable alternative in the United States and other countries where nabiximols is not available. (See 'Patients with other withdrawal symptoms' above.)

- **Alternative approaches –** Alternative approaches include gabapentin (in individuals who face urine drug screening) or cognitive-behavioral therapy. These are chosen based on patient preference and availability.

- **Cannabis and tobacco co-use** – Tobacco withdrawal may be particularly difficult to distinguish from cannabis withdrawal as the symptoms may overlap. Reducing or stopping both cannabis and tobacco use at the same time may trigger both withdrawal syndromes, which may be more severe than either syndrome alone. (See 'Differential diagnosis' above and 'Cannabis and tobacco co-use' above.)

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