Cannabis use disorder: Clinical features, screening, diagnosis, and treatment

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INTRODUCTION

Cannabis (also called marijuana) is the third most commonly used psychoactive substance worldwide, after alcohol and tobacco (nicotine) [1]. Its psychoactive properties are primarily due to one cannabinoid: delta-9-tetrahydrocannabinol (THC); THC concentration is commonly used as a measure of cannabis potency. Cannabis can be used by smoking, vaping, dabbing, ingesting (edibles, beverages, and tinctures), and topical cream. The potency of cannabis has increased significantly around the world over the past two decades [2], which may have contributed to increased rates of cannabis-related adverse effects.

The legal status of cannabis use, for medical as well as recreational purposes, varies internationally as well as across the United States. Cannabis use disorder develops in approximately 10 percent of regular cannabis users and up to 50 percent of chronic daily users and may be associated with cognitive impairment, poor school or work performance, and psychiatric comorbidity such as mood disorders and psychosis.

The clinical manifestations, diagnosis, and treatment of cannabis use disorder are reviewed here. Other aspects of cannabis use, including epidemiology, risk factors, acute intoxication, and presentation and treatment of cannabis withdrawal, are reviewed separately:

- (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

- (See "Cannabis (marijuana): Acute intoxication".)
- (See "Synthetic cannabinoids: Acute intoxication".)
- (See "Cannabis withdrawal: Epidemiology, clinical features, diagnosis, and treatment".)

CLINICAL MANIFESTATIONS

Cannabis use disorder presents as a problematic pattern of cannabis use that results in clinically significant functional impairment or distress, with at least two manifestations occurring within a period of 12 months [3]. The defining feature of cannabis use disorder is loss of control over cannabis use, epitomized by persisting use despite knowledge of adverse consequences. The severity of cannabis use disorder is specified as mild, moderate, or severe by the number of symptoms present. (See 'Cannabis use disorder' below.)

Acute intoxication — The clinical manifestations of acute intoxication are delta-9-tetrahydrocannabinol-concentration dependent and include physiologic signs such as tachycardia, blood pressure changes, conjunctival injection (“red eye”), dry mouth, slowed or slurred speech, and ataxia [4]. Common psychological manifestations include euphoria (“high”) and relaxation. Sedation and increased appetite (“munchies”) are also common. Cannabis use acutely impairs neuropsychological functions, especially attention, concentration, episodic memory, and associative learning [5,6]. Additional undesired effects include depression, anxiety (eg, panic attacks), perceptual disturbances, and changes in thought content (including transient paranoia or frank psychosis).

Common emergency department presentations associated with acute cannabis use include psychiatric (acute anxiety, agitation, or psychosis), cardiovascular (chest pain, palpitations), or nausea and vomiting (often due to cannabinoid hyperemesis syndrome) [7].

Manifestations of acute cannabis intoxication are described in detail separately. (See "Cannabis (marijuana): Acute intoxication", section on 'Adolescents and adults' and "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects", section on 'Other effects'.)

Patterns of use — While patterns of cannabis use vary widely across individuals, most cannabis users who develop cannabis use disorder do so after several years of use [8,9] and with at least weekly use [10]. Increased frequency of cannabis use [11,12] and use of more potent cannabis products [13] are associated with greater risk of cannabis use disorder.

Persistent symptoms

Neurocognitive symptoms — Evidence of an association between regular cannabis use and long-term neurocognitive deficits is mixed. Most studies show a modest dose-dependent cognitive impairment associated with regular cannabis use [6,14,15]. Impairment resolves with abstinence, typically after three days to one month. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

Mood and anxiety symptoms — Cannabis use or cannabis use disorder can produce chronic mood changes such as those seen in persistent depressive disorder and major depressive disorder [16]. Additionally, studies support an association between cannabis use and new-onset mania as well as exacerbation of manic symptoms in patients diagnosed with bipolar disorder [17]. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

While acute intoxication with cannabis may cause transient acute anxiety (including panic attacks), the association between cannabis use disorder and development of anxiety or trauma-related disorders is unclear [18,19].

Psychosocial functioning — Typical manifestations of cannabis use disorder include impairment in school or work function, giving up of previously enjoyed social and recreational activities, and persistent or recurrent interpersonal problems.

Psychotic symptoms — There is substantial evidence that chronic cannabis use, especially during early adolescence, is associated with increased risk of psychosis and development of schizophrenia [20,21]. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

Clinical course — Prospective, longitudinal studies in nonclinical, community populations suggest that cannabis use and cannabis use disorder have highly variable courses [22-26]. As an example, a prospective, longitudinal study that followed 817 randomly selected western Oregon high school students from age 14 to 30 years old found them grouped in three trajectories of development of cannabis use disorder: stable cannabis use with negligible risk of developing cannabis use disorder (84 percent of cohort), increasing risk peaking around age 20 years (60 percent risk) then declining to negligible risk by age 30 years (9 percent of cohort), and steadily increasing risk through age 30 years (90 percent risk; 7 percent of cohort) [27].

Factors associated with transitions from first use to heavy use or to cannabis use disorder include earlier age of first use [22], early and rapid progression to frequent use [23], concurrent use of other psychoactive substances (especially alcohol and tobacco) [22,24-26], comorbid psychiatric disorders (eg, depression, anxiety), stressful life events (eg, childhood abuse) [25,28,29], peer use of drugs [30,31], and social isolation [29].

Adoption of stable roles at school or work is associated with reduction in or cessation of cannabis use [32].

SCREENING AND ASSESSMENT

Screening

Indicators for screening — The United States Preventive Services Task Force recommends screening all adults for harmful use of psychoactive drugs, including cannabis, as long as "services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred" [33].

Screening for cannabis use disorder is often prompted by signs or symptoms from the patient's history or physical examination [3,26]. As examples, impairment in social, academic, or vocational functioning that is otherwise unexplained, exacerbation of conditions known to be worsened by cannabis (ie, depression, anxiety), chronic conjunctival injection, yellowing of fingertips, cannabis odor on clothing, or increase in appetite may be noted. Screening should occur at yearly preventive visits.

Screening methods — Screening should employ brief questions, rather than testing of biological specimens such as urine.

Brief (one to four items) questionnaires are an economical and efficient means of cannabis screening, either stand-alone or embedded within larger health questionnaires. These methods are typically used in high-volume clinical settings such as primary care practices or emergency departments. Several studies suggest that self-reports of cannabis and other psychoactive substance use can be fairly accurate, as long as there are no adverse consequences (such as criminal charges) for acknowledging use [34]. In one review involving 1997 study participants, screening with brief instruments in adults, with structured clinical interviews as the gold standard, had sensitivity of 0.79 to 0.82 and specificity of 0.95 for identifying unhealthy cannabis use and sensitivity of 0.71 to 0.83 and specificity of 0.75 to 0.95 for identifying cannabis use disorder [35]. Unhealthy cannabis use was variously defined as either having cannabis-related problems (not necessarily cannabis use disorder) or heavy cannabis use.

Based on simplicity of use and favorable test performance characteristics, we favor the use of the single question: "In the past year, how often have you used cannabis (or marijuana)?"

> In a study of 442 adolescents admitted to an emergency department with nonsubstance-related injuries, an answer of "more than once" to this question had a sensitivity of 0.96

(positive predictive value 0.55) and specificity of 0.86 (negative predictive value 0.99) for detecting cannabis use disorder as defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; based on a structured diagnostic interview) [36,37]. (See 'Patients identified by screening: Brief intervention' below.)

Drug testing — Because drug testing is more intrusive and expensive, it is typically reserved for screening in safety-sensitive workplaces or for high-risk populations. Examples include employees in transportation (where it is mandated by federal law) or law enforcement or patients seen in a specialty care setting for psychiatric disorders such as substance use disorder. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

Drug testing for recent cannabis use has the advantage of objectivity and, when properly administered (eg, observed sample collection), essentially 100 percent sensitivity [38,39]. Because of the complex pharmacokinetics of delta-9-tetrahydrocannabinol (THC) and other cannabinoids, an individual who last used cannabis weeks ago and is functioning normally may still test positive for cannabis use. This is especially true in persons who use cannabis chronically. THC or its metabolites may be detectable in urine of chronic heavy users of cannabis for up to six weeks.

Urine is most commonly used for testing, but oral fluid (saliva), blood, and hair are alternatives. Although screening tests (typically employing immunoassays) are highly sensitive, they are less specific. A positive screening result should be confirmed by a more specific assay (eg, liquid or gas chromatography, sometimes combined with mass spectrometry) when a positive result has legal or employment implications or major treatment implications such as a change in treatment status (eg, transfer to a different level of treatment or discharge).

Drug testing for cannabis almost always measures THC, the primary psychoactive compound in cannabis, and/or its major metabolite carboxy-THC [38]. Other clinically relevant pharmacologically active cannabinoids, such as cannabidiol, are detected with less sensitivity or not at all.

Drug tests identify cannabis use, not cannabis use disorder. Cannabinoid levels, especially in urine, are poorly correlated with impairment [40].

Assessment — A positive screen should be followed by evaluation of risk level, then brief intervention for individuals considered at low risk or referral for treatment for those at higher risk (moderate-severe cannabis use disorder) or who do not respond to brief intervention. This

is the Screening, Brief Intervention, and Referral to Treatment approach widely used in the addiction field [41].

We recommend thorough assessment for all patients screening positive for cannabis use. This is often done by a clinician trained to diagnose and treat substance use disorders. The assessment should be conducted in a private setting and in nonjudgmental fashion. In order to establish a level of comfort for the patient, it is often helpful to first ask about socially acceptable substances and then progress to other substances.

As part of a complete assessment of cannabis use disorder we recommend review of (see "Substance use disorders: Clinical assessment"):

- Cannabis use including amount, frequency, route
- Attempts to cut back or stop cannabis use
- Effects on occupational, academic, or social functioning
- Use in high-risk situations
- Mental status examination
- Psychiatric history
- Medical history (including laboratory results and physical examination where clinically indicated)
- Social history
- Family history

Unhealthy use of one substance increases the likelihood of unhealthy use of other substances [3,42], thus clinicians should ask about all the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classes of substances (ie, alcohol, tobacco, cannabis, stimulants, opioids, and other drugs).

DIAGNOSIS

A cannabis use disorder is diagnosed if the patient's use, signs, symptoms, and functional impairment meet the thresholds established by the DSM-5 diagnostic criteria for the disorder. Cannabis intoxication and cannabis withdrawal are discussed in detail elsewhere. (See "Cannabis (marijuana): Acute intoxication" and "Cannabis withdrawal: Epidemiology, clinical features, diagnosis, and treatment".)

Cannabis use disorder — DSM-5 diagnostic criteria for cannabis use disorder are provided in a table (table 1) [3]. In the DSM-5, categories of mild, moderate, and severe cannabis use disorder replaced the DSM-IV terms "cannabis abuse" and "cannabis dependence."

Differential diagnosis — The differential diagnosis for cannabis use disorder includes nonproblematic cannabis use and other mental disorders that may resemble symptoms of cannabis use disorder.

Nonproblematic use of cannabis — The differential diagnosis from nonproblematic cannabis use relies on a careful assessment of the presenting problems or impairments, not on the quantity or frequency of cannabis use.

Key features suggesting the diagnosis of cannabis use disorder include patient denial of cannabis-related problems in the face of reports from reliable collateral sources (eg, family, school, employer) and patient denial of cannabis use in the face of objective evidence to the contrary (eg, urine drug testing).

Other mental disorders — Other mental disorders may resemble symptoms associated with cannabis use disorder. As examples, cannabis-related anxiety may resemble panic attacks, and chronic neglect of usual activities may resemble dysthymia or other mood disorders. Careful attention to history, in particular, the temporal relationship between cannabis use and symptoms and behavioral changes, is useful in differentiating these. For example, the onset of symptoms only after a period of heavy cannabis use and their resolution during a period of cannabis abstinence provides strong circumstantial evidence that they do not represent an independent psychiatric condition. (See 'Mood and anxiety symptoms' above.)

TREATMENT

Setting treatment goals and initiating treatment — The treatment goal for cannabis use disorder can be either sustained abstinence from cannabis use or reduced use that ameliorates cannabis-associated problems (so-called “harm reduction”) [43,44]. Reducing frequency of use is associated with greater improvement than reducing quantity of use [44,45]. Young adults and individuals with the DSM-5 mild cannabis use disorder tend to have harm reduction as their goal.

Regardless of the initial treatment goal, early sessions should focus on engaging the patient in treatment using motivational enhancement (or interviewing) techniques (see 'Motivational enhancement therapy' below). The patient is encouraged to explicitly identify the pros and cons of their cannabis use and balance them. Often a series of stepwise intermediate goals may be needed in order to engage the patient in the treatment process. As an example, an initial goal might be mild reduction of frequency or amount of cannabis use or limiting cannabis use to

low-risk situations. Other goals for treatment include improved psychological, social, and occupational functioning.

Approximately half of patients in treatment for cannabis use disorder experience a withdrawal syndrome on abrupt reduction or cessation of heavy or prolonged cannabis use [46]. These uncomfortable symptoms serve as a negative reinforcement for resumption of cannabis use in a large proportion of individuals [47]. Patients should be educated about the cannabis withdrawal syndrome at the start of treatment and monitored for symptoms. A variety of nonpharmacologic and pharmacologic approaches can be used to reduce withdrawal symptoms and minimize the risk of relapse. (See "Cannabis withdrawal: Epidemiology, clinical features, diagnosis, and treatment", section on 'Treatment'.)

Treatment for cannabis use disorder usually occurs in the outpatient setting. Residential treatment or inpatient treatment may be needed in refractory patients or in those patients with multiple concurrent substance use disorders. Inpatient hospital setting is indicated for patients with severe depression, suicidality, or psychosis.

Initial treatment

Patients identified by screening: Brief intervention — Cannabis users with cannabis-related problems who are identified by screening (ie, who do not present themselves for treatment) may respond to brief intervention, especially when they are an adolescent or young adult and are identified outside of health care settings; however, the evidence of efficacy is limited.

Brief intervention typically consists of no more than two short (no more than 15 to 20 minutes) sessions of patient-centered, nonjudgmental counseling using motivational enhancement techniques. (See "Brief intervention for unhealthy alcohol and other drug use: Efficacy, adverse effects, and administration", section on 'Treating unhealthy use of other drugs' and "Substance use disorders: Motivational interviewing".)

Studies have shown mixed and somewhat limited benefits. A meta-analysis of 26 published studies involved 6318 emerging adults (15 to 30 years old) enrolled primarily from non-health care settings (73 percent of studies non-health care) [48]. Brief intervention, compared with passive controls, increased the odds of cannabis abstinence one to three months later (odds ratio 1.73, 95% CI 1.13-2.66) and reduced symptoms of cannabis use disorder, but did not impact other outcomes. Another meta-analysis included six studies from health care settings involving more than 2000 primarily adult participants [49]. Brief intervention, compared with passive controls, had no significant effect on cannabis use within three months of or more than three months after the intervention.

Psychosocial interventions — For patients who desire treatment for cannabis use disorder, we suggest psychosocial treatment rather than medication treatment as initial therapy for cannabis use disorder. Controlled clinical trials have demonstrated efficacy for psychosocial treatments while there is no such consistent evidence of efficacy for any medication in the treatment of cannabis use disorder [50-52]. In a meta-analysis of seven published controlled clinical trials involving 1724 treatment-seeking adults with cannabis use disorder, patients receiving psychosocial treatment were twice as likely as those receiving no treatment to be abstinent at three- to four-month follow-up (21 percent versus 10 percent; relative risk 2.08, 95% CI 1.51-3.07) [35]. It is important to note, however, that most studies have short-term rather than long-term follow-up and rates of sustained abstinence are generally less than 50 percent.

Cognitive-behavioral therapy — We suggest cognitive-behavioral therapy (CBT; where available) as first-line treatment of cannabis use disorder. As compared with other therapies, CBT has the most robust evidence of efficacy for this disorder [50].

CBT is a psychotherapy approach that emphasizes identification and management of thoughts, behaviors, and external triggers that promote substance use. Coping skills and problem-solving skills that promote replacement of cannabis-related behaviors with healthier alternatives are taught. (See "Substance use disorders: Psychosocial management".)

Clinical trials have found that CBT reduces cannabis use among patients with moderate-severe cannabis use disorder [53]. One trial looking at effects of CBT on cannabis use randomly assigned 229 adults to six sessions of CBT over six weeks, one session of CBT, or delayed treatment [54]. The proportion of patients with continuous abstinence over the eight-month follow-up period favored six CBT sessions (15 versus 5 versus 0 percent). Another trial of 134 participants comparing CBT with inactive control in subjects with cannabis dependence showed a significant reduction in days of cannabis use (mean difference 10.94, 95% CI 7.44-14.44) [50].

Motivational enhancement therapy — Motivational enhancement therapy (MET) is another psychosocial treatment that is appropriate for initial therapy. Studies suggest efficacy for cannabis use disorder that is similar to CBT [53].

Motivational interviewing is a directive, nonjudgmental, patient-centered psychotherapy that focuses on encouraging patients to change maladaptive behaviors. When combined with personalized feedback and education regarding the patient's patterns of cannabis use, it is often termed motivational enhancement therapy. MET emphasizes the importance of self-efficacy and positive change and attempts to build motivation for treatment and abstinence in an empathic and nonjudgmental environment. Motivational interviewing for substance use

disorders is reviewed in greater detail separately. (See "Substance use disorders: Motivational interviewing".)

A meta-analysis including four trials with a total of 612 participants with the DSM-IV cannabis dependence (equivalent to moderate to severe cannabis use disorder in the DSM-5) found that MET reduced days of cannabis use at early follow-up as compared with inactive or delayed treatment (mean difference 4.45 days, 95% CI 1.90-7.00) [50]. However, no difference was seen in one-month abstinence rates. Individual trials have had more favorable results. As an example, a trial of 291 treatment-seeking adult cannabis users were assigned to 14 sessions of CBT versus two sessions of motivational interviewing versus delayed treatment [53]. At four months, subjects in the motivational interviewing group and in the cognitive therapy group showed lower cannabis use compared with those assigned to delayed treatment (7 versus 6 versus 17 days per month).

Monitoring treatment — We suggest monitoring patients at least weekly at the start of treatment. The frequency and type of monitoring may vary with the goals and the stability of the patient's condition. Assessment of progress in achieving a treatment goal of abstinence is often done with drug testing to objectively evaluate cannabis use status. Monitoring should involve the patient's family and close social network as much as possible, always with the patient's permission. Such collateral monitoring often provides the earliest indications of potential relapse. A patient who has maintained their treatment goals for several months may need monitoring only monthly or less often.

Patients who need further treatment — If treatment with CBT or MET is not effective after several weeks or the patient relapses after initial treatment response, combination therapy is suggested; CBT and MET can be combined or contingency management can be added. Both of these approaches have enhanced the effectiveness of psychosocial therapy in clinical trials [50].

Combined interventions — Where available, we suggest combined treatment with CBT and MET for patients who are unable to achieve their treatment goal with either therapy alone. Indirect comparisons suggest that combination treatment may be more effective than individual psychotherapy. A meta-analysis of three clinical trials with 398 participants found that the combination of MET and CBT reduced patients' mean days per month of cannabis use at early follow-up compared with delayed treatment (mean difference 7.38, 95% CI 3.18-11.57) [50].

In another trial involving 450 adults with cannabis use disorder, treatment with two sessions of combined CBT and MET over six weeks was compared with nine sessions of the combination therapy over 12 weeks and also to a delayed treatment control [55]. At four months follow-up,

both the nine-session and the two-session treatment groups showed higher rates of complete abstinence than the delayed treatment group (23 versus 9 versus 4 percent).

Augmentation with contingency management — Contingency management has not been shown to be effective for cannabis use disorder as a stand-alone treatment [50]. However, studies examining its efficacy as an adjunctive treatment suggest a benefit.

Contingency management uses behavioral reinforcement techniques (typically a voucher incentive) to encourage specific behaviors that promote treatment adherence or abstinence.

Clinical trials have found that the addition of contingency management to other psychosocial treatments (eg, CBT, MET) reduces cannabis use as compared with nonaugmented intervention alone [50,56-60]. As an example, in a trial of 240 participants with cannabis dependence treated with combination of contingency management with combined CBT/MET, the combined treatment had a higher percentage of 90-day abstinence rates at 14 months (28 percent) than MET/CBT alone (20 percent), case management (19 percent), or contingency management alone (13 percent) [60].

Clinical trials comparing contingency management with other active interventions for cannabis dependence have reported mixed results with some reports suggesting benefit and others no apparent benefit [61,62].

The theoretical foundation, components, and implementation of contingency management are reviewed separately. (See "Substance use disorders: Principles, components, and monitoring during treatment with contingency management" and "Substance use disorders: Training, implementation, and efficacy of treatment with contingency management".)

Other treatments — Any psychosocial intervention incorporating one or more of the following strategies has an element of a potentially effective intervention [50]:

- Enhance motivation to reduce or end cannabis use
- Improve social skills
- Improve social support and interpersonal functioning
- Manage painful feelings
- Education about consequences of cannabis use

Less structured treatments may be useful for those who cannot access the above therapies. (See 'Drug or addiction counseling' below and 'Mutual help groups' below.)

Among those patients who are unable to maintain abstinence through psychosocial interventions alone, trials of adjunctive medications may be helpful. (See 'Potentially beneficial

medications' below.)

Patients unable to access structured treatments

Drug or addiction counseling — There is little evidence to support the use of drug or addiction counseling in cannabis use disorder. Nonetheless, their efficacy in other clinical situations supports their use when other structured treatments are unavailable.

Drug or addiction counseling refers to general individual and group psychotherapies whose goal is to help patients reduce substance use. Counseling typically provides fact-based education regarding drug use and health risks along with suggestions for minimizing harm. Counseling may also incorporate various elements of more focused therapy approaches, such as cognitive-behavioral, motivational enhancement, and insight-oriented psychotherapies [50]. (See "Substance use disorders: Psychosocial management", section on 'Addiction counseling'.)

Low-quality clinical trials have not found a difference between drug counseling and a control intervention in patients with moderate to severe cannabis use disorder [63,64]. As an example, a trial randomly assigned 50 cannabis-using university students to receive a single 15- to 20-minute session of drug counseling or a session about health promotion unrelated to substance use [63]. At 3- and 12-month follow-up no difference was reported between groups in the frequency of cannabis-smoking days or joints used per day.

Mutual help groups — Mutual help groups have not been well evaluated in this setting. They may be useful, however, in patients who do not have other therapies available to them.

Mutual help groups (eg, Marijuana Anonymous) consist of individuals with a common experience or problem coming together to share their experiences and provide help and support to one another without professional direction. The goal of mutual help groups for addiction recovery is to help individuals with substance use disorders to achieve and maintain remission and recovery. Mutual help groups are reported to be used by approximately half of adults with current cannabis use disorder [65].

Marijuana Anonymous is based on the 12-step principles of Alcohol Anonymous. Its effectiveness has not been evaluated via formal studies. In our clinical experience, participation may have some benefit as an adjunct to professional psychosocial treatment. These groups are readily available in larger cities in the United States and other countries.

Potentially beneficial medications — No medication is approved for this indication by the US Food and Drug Administration (FDA) or any other national regulatory authority.

We are unable to recommend any specific medication as stand-alone treatment until there are more clinical trials supporting their use.

Medications that have shown limited benefit in reducing cannabis use in small trials are mentioned below. None of these medications have been shown to produce extended abstinence or to reduce the severity of cannabis use disorder [66].

- N-acetylcysteine – The antioxidant n-acetylcysteine (NAC), an N-acetyl prodrug of the naturally occurring amino acid cysteine, has been tested in the treatment of cannabis use disorder. Evidence of efficacy is not consistent among trials [67,68]. It is available as an over-the-counter supplement.

  One trial assigned 116 treatment-seeking, cannabis-dependent adolescents/young adults (15 to 21 years old) to treatment with NAC (2400 mg daily) or placebo for eight weeks [67]. All subjects received brief weekly individual supportive counseling and twice weekly contingency management reinforcing adherence and abstinence. The NAC group had greater adjusted odds of a urine test negative for delta-9-tetrahydrocannabinol (THC) during the trial (odds ratio 2.4, 95% CI 1.1-5.2) and a higher proportion of delta-9-THC-negative urine specimens over the treatment period (41 versus 27 percent) as compared with placebo. The two-week point prevalence abstinence rate at end of treatment showed a trend towards favoring NAC (36 versus 21 percent).

  Another trial assigned 302 treatment-seeking, cannabis-dependent adults (18 to 50 years old) to NAC (2400 mg daily) or placebo for 12 weeks [68]. All subjects received brief weekly individual supportive counseling and twice weekly contingency management reinforcing adherence and abstinence. At the end of the study the same proportion of negative urine tests for cannabinoids was found in both treatment groups (22 percent each group; odds ratio 1.00, 95% CI 0.63-1.59).

  NAC was well tolerated in both trials. There were no differences between treatment and placebo groups in retention rates or adverse effects.

- Gabapentin – Gabapentin, a GABAergic agent used in the treatment of seizures and neuropathic pain has been shown to reduce cannabis use in a small trial of adults with cannabis use disorder [69].

  In this trial, 50 treatment-seeking cannabis-dependent adults were assigned to either gabapentin 1200 mg daily or placebo daily for 12 weeks. All subjects received psychosocial support in the form of weekly individual “abstinence-oriented” counseling. The gabapentin group had reduced cannabis use verified by cannabinoid-negative urine tests and self-

reported cannabis use, decreased cannabis withdrawal symptoms (Marijuana Withdrawal Checklist), and greater improvement on cognitive tests of executive function as compared with placebo.

Gabapentin was well tolerated, though occasional headache, insomnia, and mood changes were reported. There was no difference between treatment and placebo groups in study retention rates mean number of adverse events, or rates of specific adverse events.

The FDA issued a safety alert in December 2019, based upon case reports and human studies, warning that gabapentin may be associated with respiratory depression when administered to patients receiving central nervous system depressants or patients with underlying respiratory impairment [70].

- Nabiximols – Nabiximols is a cannabis whole-plant extract containing a 1:1 ratio of THC and cannabidiol. It is approved for the treatment of muscle spasticity associated with multiple sclerosis in Canada and several European countries.

  Small clinical trials have demonstrated mixed outcomes using nabiximols for reducing cannabis use over up to 12 weeks when combined with psychosocial interventions [71,72].

  - A trial compared nabiximols (self-titrated up to eight sprays four times daily) with placebo in 128 treatment-resistant cannabis-dependent patients [71]. All patients received weekly individual CBT for the first six weeks. After 12 weeks, nabiximols treatment was associated with fewer mean number of days of cannabis use (35 versus 53 days) and a higher proportion of patients who reduced cannabis use by at least 50 percent (54 versus 29 percent). At 24-week follow-up (12 weeks after end of study period) 23 percent of those in the treatment group reported abstinence versus 9 percent of the placebo group [73].

  - A trial compared nabiximols (titrated up to maximum of 42 sprays daily over the first 10 days) with placebo in 40 cannabis-dependent adults [72]. All patients also received weekly motivational enhancement and CBT for 12 weeks. There was no statistically significant difference in average decrease in cannabis use from baseline between the nabiximols (70 percent) and placebo (43 percent) groups.

- Cannabidiol – Cannabidiol is a major cannabinoid constituent of the *Cannabis* plant. In a clinical trial, 82 adults with moderate-severe cannabis use disorder were randomly assigned to oral synthetic cannabidiol 200, 400, or 800 mg/day for four weeks versus placebo [74]. All participants received six 30-minute sessions of motivational interviewing.

Both the 400 mg dose and the 800 mg dose reduced urine THC metabolite (THC-COOH):creatinine ratio and increased cannabis abstinence days per week compared with placebo. In each case, 400 mg was marginally more efficacious than 800 mg as compared with placebo. Cannabidiol 200 mg/day was no different from placebo. Cannabidiol was well tolerated; there were no serious adverse effects.

- Topiramate – Topiramate, an antiepileptic agent, has effects on several membrane ion channels and neurotransmitter receptors. In one clinical trial, 66 participants (both adults and adolescents, 15 to 25 years) with at least twice weekly cannabis use were randomly assigned to oral topiramate (titrated from 25 to 200 mg/day over six weeks) plus motivational enhancement therapy (MET) versus placebo plus MET [75]. Percent use days were similar between treatment groups throughout the course of the trial. However, a trend towards less grams use per day during the final week of the trial was noted. The topiramate group had a higher dropout rate than the placebo group (53 versus 23 percent, p = 0.018), which may have biased the findings. Dropout was attributed to significantly higher incidence of adverse effects (impaired concentration, confusion, dizziness, anxiety, paresthesias) in the topiramate group.

- Varenicline – Varenicline, a selective nicotinic acetylcholine receptor agonist, approved for smoking cessation, may be effective as a treatment for cannabis use disorder. In one trial, 72 adults with cannabis use disorder using cannabis at least three days per week were randomly assigned to six weeks of treatment with varenicline (escalating dose schedule) versus placebo [76]. All participants received three individual sessions of brief motivational enhancement therapy. Individuals in the treatment group had a higher rate of weekly self-reported abstinence at each study visit with the greatest difference at week 6 (17 versus 5 percent [relative risk 3.2, 95% CI 0.7-14.7]). Additionally, while both groups showed decreases in percentage of days with cannabis use, individuals in the varenicline group showed a greater decrease than individuals in the placebo group (42 [95% CI 26.3-57.0] versus 27 [95% CI 13-42] percent). Urine cannabinoid test results were consistent with self-reported cannabis use in both groups.

Other medications with no established benefit — Antidepressants (ie, bupropion, fluoxetine, venlafaxine, and vilazodone), atomoxetine, divalproex, lithium, buspirone, and cannabinoid receptor agonists (synthetic THC [ie, dronabinol], nabilone) have been found to be comparable to placebo or ineffective in promoting abstinence or reducing cannabis use [51,52]. In one trial, 130 adults with moderate-severe cannabis use disorder and using cannabis at least five days per week were randomly assigned to treatment with quetiapine (a second-generation antipsychotic) 300 mg nightly or placebo for 12 weeks, plus weekly supportive behavioral

treatment sessions. Treatment with quetiapine was associated with greater likelihood of transitioning from heavy cannabis use to moderate cannabis use, but there was no significant medication group difference in overall cannabis use [77]. Many trials investigating treatment for cannabis use disorder were small and thus may have been underpowered to detect a difference between active drug and placebo.

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".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Cannabis hyperemesis syndrome (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Cannabis use and disorder** – Cannabis is the third most commonly used psychoactive substance worldwide, after alcohol and tobacco (nicotine). (See 'Introduction' above.)

  Cannabis use disorder presents as a problematic pattern of cannabis use that results in at least two manifestations of clinically significant functional impairment or distress occurring within a period of 12 months. (See 'Clinical manifestations' above.)

- **Acute intoxication** – Acute intoxication from cannabis causes physiologic signs such as tachycardia, psychological symptoms such as euphoria or anxiety, and neurocognitive impairments. (See 'Acute intoxication' above.)

- **Chronic cannabis use** – Chronic cannabis use is associated with persistent mood changes and psychosocial impairment. Chronic use, particularly during adolescence, is associated with increased risk of psychosis and the development of schizophrenia. Association with long term neurocognitive impairments is unclear. (See 'Persistent symptoms' above.)

- **Screening** – Screening for cannabis use disorder may be prompted by otherwise unexplained impairment in social, academic, or vocational functioning, exacerbation of conditions known to be worsened by cannabis (ie, depression, anxiety), chronic conjunctival injection, yellowing of fingertips, cannabis odor on clothing, or increase in appetite. (See 'Indicators for screening' above.)

  Brief patient questionnaires are effective means of screening for cannabis use, supplemented by drug testing in appropriate contexts. (See 'Screening' above.)

- **Assessment** – We perform assessment of risk level in all individuals who screen positive for cannabis use. We review patterns of use, attempts to cut back use, symptoms of tolerance or withdrawal, and effects on social, occupational or academic functioning. (See 'Assessment' above.)

- **Treatment goals** – We develop the goal of treatment for cannabis use disorder in collaboration with the patient. Examples of treatment goals may be sustained abstinence from cannabis use or sustained reduction in use to avoid harmful consequences. The goal of moderation in use may be needed to engage some patients in the treatment process. (See 'Setting treatment goals and initiating treatment' above.)

- **Treatment**

  - **Brief intervention** – We typically do a brief intervention of patient centered, nonjudgmental counseling for individuals identified by screening.

  - **Psychosocial intervention** – We suggest a psychosocial intervention such as cognitive-behavioral therapy (CBT) or motivational enhancement therapy (MET) rather than medication as the first choice of treatment for cannabis use disorder (**Grade 2C**). (See 'Psychosocial interventions' above.)

  - **Combined intervention** – We suggest combined treatment with CBT and MET, rather than other interventions for individuals who are unable to achieve their treatment goal

with the initial psychosocial intervention. (**Grade 2C**). (See 'Patients who need further treatment' above and 'Combined interventions' above.)

- **Addiction counseling and mutual help groups** – For patients who lack access to one of these structured psychotherapies, treatment options include generic addiction counseling and referral to a mutual help group such as Marijuana Anonymous. (See 'Drug or addiction counseling' above and 'Mutual help groups' above.)

- **Medication** – Trials of adjunctive medication may be helpful for patients who are unable to achieve their treatment goal with psychosocial interventions. Medications have shown limited benefit in reducing cannabis use or severity of cannabis use disorder; none are US Food and Drug Administration-approved for this indication. (See 'Potentially beneficial medications' above and 'Other medications with no established benefit' above.)

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