Behavioral Interventions and Pharmacotherapies for Cannabis Use Disorder

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Opinion statement

Millions of Americans develop cannabis use disorder, which requires treatment to prevent numerous associated adverse outcomes. There are several evidence-based behavioral interventions, including motivational interviewing, motivational enhancement therapy, cognitive behavioral therapy, contingency management, and multidimensional family therapy, all with moderate effectiveness. None of the behavioral interventions are clearly superior to any of the others, whether in combination or alone. Thus, individual patient and therapist factors, such as patient preference and therapist expertise, should determine which is used. Currently, there are no FDA-approved medications for treatment of cannabis use disorder. Some pharmacologic agents have shown promise in early studies, most notably n-acetylcysteine and gabapentin, but none have been replicated. Given that gabapentin and buspirone have been widely used in psychiatric populations and have relatively few side effects, either could be considered as an augmenting agent to behavioral interventions, but neither should be continued for more than 12 weeks unless there is clear evidence of reduction in use. Evidence suggests venlafaxine and naltrexone are not effective in reducing use.

Introduction

Cannabis is the most commonly used illicit drug in the world [1] and in the United States [2]. It was used at least once by 42 % of all Americans and 45 % of 12th graders [3, 4••]. Potency of the active ingredient in marijuana, δ -9-tetrahydrocannabinol (THC), has

increased by a factor of six to seven from 1970 to 2010 [5]. Increased potency raises the risk of transitioning from use to addiction: 8–9 % of adults and 14–16 % of adolescents who use will become dependent [6].

As the decriminalization, legalization, and medical marijuana movements have progressed in recent years, perceived risk has decreased and use has increased. Among 12th graders, the proportion endorsing the perception of great risk in smoking marijuana occasionally decreased from 26 % to 20.6 % from 2008 to 2012; while the proportion using marijuana in the past year increased from 32.4 % to 36.4 % [4••].

Cannabis use disorder (see Table 1 for DSM-5 criteria) is associated with numerous adverse outcomes, such as impaired cognition, poor educational attainment, unemployment, risky sexual behaviors, early pregnancy, crime, progression to further drug use, development of psychotic disorders, and withdrawal syndrome [8, 9•]. Eighteen

percent of all substance use admissions are for primary cannabis dependence, an increase from 15 % in 2001 [10].

Systematic research on treating marijuana abuse and dependence began with psychosocial interventions in the 1980s and pharmacologic interventions in the 2000s [11], including motivational interviewing, motivational enhancement therapy, cognitive behavioral therapy, contingency management, multidimensional family therapy, and medications such as n-acetyl cysteine, gabapentin, buspirone, dronabinol, and others. However, guidelines for treating cannabis use disorder are sparse. Below is a summary of available treatment options with the evidence supporting their use.

Treatment

Pharmacologic agents

- There are no FDA-approved medications for the treatment of cannabis dependence. Below are medications which have been studied in trials with at least 20 participants. Thus, not included below are studies of baclofen ($n=10$) [12], bupropion sustained release (SR) ($n=10$) [13], divalproex ($n=7$) [14], mirtazapine ($n=11$) [12], and nefazodone ($n=7$) [15]. See Table 2 for a summary of medications listed below.

Agents with evidence suggesting reduced marijuana use in patients with cannabis use disorder

N-acetylcysteine

- N-acetylcysteine is an n-acetyl prodrug of the amino acid cysteine, and is thought to be involved in glutamate neurotransmission [16].
- Gray and colleagues [17] studied n-acetylcysteine (1200 mg divided into two oral doses daily) in an 8-week, randomized, double-blind, placebo-controlled trial, with 116 older adolescents with cannabis dependence. They found a statistically higher likelihood of a negative urine toxicology test among those taking n-acetylcysteine versus those taking placebo at the end of the study (40.9 % vs 27.2 %, $p=0.03$) and a non-significant trend at 1-month follow up (19.0 % vs 10.3 %, $p=0.13$). There were no serious adverse events associated with n-acetylcysteine use.

Standard dosage given the experimental nature of the use of this agent for this disorder, there is no known standard dosage.

Table 1. DSM-5 criteria for cannabis use disorder

A problematic pattern of cannabis use, with two or more of the following.

- Cannabis is taken in larger amounts, or over a longer period, than was intended
- Persistent desire, or unsuccessful efforts, to cut down or control use
- A great deal of time is spent in activities necessary to obtain, use, or recover from cannabis
- Craving, or a strong desire to use
- Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home
- Continued use despite persistent or recurrent social or interpersonal problems caused, or exacerbated, by the effects of cannabis
- Tolerance: either a need for markedly increased amounts to achieve intoxication or desired effect, or a markedly diminished effect with continued use of the same amount
- Withdrawal: either the characteristic cannabis withdrawal syndrome, or cannabis is used to relieve or avoid withdrawal symptoms

The symptoms occur within a 12-month period and cause clinically significant impairment or distress.

Classify as mild (two or three symptoms), moderate (four or five symptoms), or severe (six or more symptoms).

DSM-5 criteria for cannabis use disorder [7].

Contraindications	relatively few. Some serious anaphylactoid reactions have been reported with both intravenous and oral administration [18].
Main drug interactions	no known interactions.
Main side effects	hypotension, tachycardia, angioedema, pruritis, urticaria, nausea, vomiting, and bronchospasm [18, 19].
Cost	inexpensive.

Gabapentin

- Gabapentin is an alkylated analog of gamma-amino-butyric acid (GABA), FDA approved for the treatment of seizures and post-herpetic neuralgia. It is believed to modulate GABAergic mechanisms by blocking the α -2d subunit of the voltage-gated calcium channel [20].
- Mason and colleagues [21] studied gabapentin (1200 mg divided into three oral doses daily) in a 12-week, randomized, double-blind, placebo-controlled, phase IIa trial, in 50 adults with cannabis dependence. They found statistically significant reductions in grams used and days of use in participants receiving gabapentin, along with reductions in cannabis withdrawal symptoms, marijuana cravings, sleep problems, and depression scores, with improvements in mea-

Table 2. Medications for cannabis use disorder

Evidence	Medication
Evidence suggests that the medication leads to reduced marijuana use	N-acetylcysteine, gabapentin, buspirone, dronabinol
Evidence does not suggest that the medication leads to reduced marijuana use	Nefazodone, bupropion SR, divalproex, venlafaxine, naltrexone

	<p>tures of executive functioning. There were no serious adverse events associated with gabapentin use. However, both those receiving gabapentin and those receiving placebo had dramatic reductions in use (less than 0.5 grams of marijuana use per week, and less than 1 day of use per week, at the end of the study).</p>
Standard dosage	given the experimental nature of the use of this agent for this disorder, there is no known standard dosage.
Contraindications	no absolute contraindications.
Main drug interactions	may enhance the effect of other CNS depressants.
Main side effects	dizziness, drowsiness, ataxia, and fatigue, among others.
Cost	expensive.

Buspirone

	<ul style="list-style-type: none"> • Buspirone is a non-benzodiazepine anxiolytic, FDA approved for the treatment of generalized anxiety disorder. • McRae-Clark and colleagues [22] studied buspirone (60 mg daily, orally) in a 12-week, randomized, double-blind, placebo-controlled trial, in 50 adults with cannabis dependence. They found a trend showing a higher percentage of negative drug screens among those receiving buspirone than among those receiving placebo (29 % vs 11 %, $p=0.07$); the trend was significant when only examining the 24 participants who completed the trial ($p=0.01$). There were no group differences in withdrawal symptoms.
Standard dosage	given the experimental nature of the use of this agent for this disorder, there is no known standard dosage.
Contraindications	no absolute contraindications.
Main drug interactions	may enhance the effect of other CNS depressants. Monitor for serotonin syndrome if given with other serotonergic medications.
Main side effects	dizziness, drowsiness, and headache.
Cost	expensive.

Dronabinol

- Dronabinol is an orally bioavailable synthetic form of THC, which is the main psychoactive component of marijuana acting at the cannabinoid 1 receptor [23]. It is approved for AIDS-related anorexia and chemotherapy-associated nausea and vomiting refractory to other antiemetics.
- Levin and others [23] studied dronabinol (40 mg divided into two oral doses daily) in a 12-week, randomized, double-blind, placebo-controlled trial, in 156 adults with cannabis dependence. They found no significant difference in abstinence at weeks 7 and 8 (17.7 % and 15.6 % for dronabinol and placebo, respectively), although they did find higher treatment retention (77 % vs 61 %, respectively) and lower withdrawal symptoms in the dronabinol group. There were four serious adverse events, but none was deemed to be study related.

Standard dosage	given the experimental nature of the use of this agent for this disorder, there is no known standard dosage.
Contraindications	hypersensitivity to marijuana, cannabinoids, or sesame seed oil.
Main drug interactions	may enhance the effect of other CNS depressants.
Main side effects	euphoria, abnormal thinking, dizziness, paranoia, somnolence, nausea, vomiting, among others.
Cost	expensive.

Agents without evidence suggesting reduced marijuana use in patients with cannabis use disorder

Nefazodone and bupropion SR

- Nefazodone is a serotonin and norepinephrine reuptake inhibitor and a serotonin 2a receptor antagonist, FDA approved for the treatment of depression. Bupropion is a norepinephrine and dopamine reuptake inhibitor, FDA approved for the treatment of depression and for smoking cessation.
- Carpenter and colleagues [24] studied nefazodone (600 mg divided into two oral doses daily) and bupropion SR (300 mg divided into two oral doses daily) in a 13-week, randomized, double-blind, placebo-controlled trial, in 116 adults with cannabis dependence. They found no difference in abstinence or withdrawal symptoms among those receiving nefazodone, bupropion SR, or placebo.

Divalproex

- Divalproex is an anticonvulsant with effects upon GABA transmission, approved for the treatment of seizures and bipolar disorder, as well as for migraine prophylaxis.
- Levin and colleagues [25] studied divalproex (up to 2000 mg daily, orally, with target plasma concentrations of 50–120 ng/mL) in a 6-week, randomized, placebo-controlled trial, in 25 adults with cannabis dependence. They found no difference in use rates among those receiving divalproex or placebo.

Venlafaxine

- Venlafaxine is a serotonin and norepinephrine reuptake inhibitor, FDA approved for the treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder.
- Levin and colleagues [26] studied venlafaxine extended release (XR) (up to 375 mg/day, orally) in a 12-week, randomized, double-blind, placebo-controlled trial, with 103 adults with comorbid cannabis dependence and major depressive disorder or dysthymia. They found less abstinence in those receiving venlafaxine versus placebo (11.8 % and 36.5 %, respectively, $p < 0.01$).

Naltrexone

- Naltrexone is an opioid μ antagonist, FDA approved for treatment of alcohol and opioid dependence.
- Cooper and Haney [27] studied the interaction of naltrexone (0, 12, 25, 50, and 100 mg, orally) with smoked marijuana (0 or 3.27 % THC) in a within-subject, randomized, double-blind trial, with 29 adults who used marijuana daily. They found that naltrexone alone (with 0 % THC) reduced ratings of 'liking', 'take again', and 'stimulated,' but, when used with 3.27 % THC, naltrexone increased ratings of 'liking', 'take again', 'stimulated', 'high', 'good', and 'strength.' They concluded that naltrexone may increase the abuse liability of cannabinoids.
- Haney and colleagues [28] studied the interaction of naltrexone (0 or 50 mg, orally) with oral THC in a within-subject, randomized, double-blind trial, in 23 adults who smoked marijuana heavily. They found that naltrexone increased the positive subjective effects and reinforcing effects of THC without altering THC plasma levels.

Behavioral interventions

- Motivational interviewing (MI), motivational enhancement therapy (MET), cognitive behavioral therapy (CBT), contingency management (CM), multidimensional family therapy (MDFT), and combinations thereof are all effective in the treatment of cannabis use disorder. Most comparison studies do not find significant differences between treatments. In studies of treatment-seeking patients, all interventions lead to reductions in use of between 20–60 % after short-term therapy, with less effect at long-term follow up (see below). In a meta-analysis, Dutra and colleagues [29] found an effect size of 0.81 [95 % CI 0.25–1.36] for psychosocial interventions of marijuana dependence, which compared favorably with studies of all substance use disorders (effect size 0.45 [0.27–0.63]). The mean dropout rate in studies of psychosocial treatment for cannabis dependence was 28 % and the mean abstinence rate was 26 %.

Brief motivational interviewing (MI) and motivational enhancement therapy (MET)

- MI is a conversational, person-centered, collaborative, goal-oriented style of communication, with special emphasis on the language of change. It is designed to address ambivalence about change and increase motivation for change. The four processes of MI are engaging,

focusing, evoking, and planning; the core skills include open-ended questions, affirming, reflecting listening, summarizing, and informing and advising; and the core values of MI are partnership, acceptance, compassion, and evocation [30]. Motivational enhancement therapy (MET) is an approach to therapy based on the principles of MI, typically involving one to four 45- or 90-minute sessions [11].

- Several studies have shown reduction in use after only two sessions of MI or MET
- Walker and colleagues [31] compared two 1-hour sessions of MET with educational feedback in 310 non-treatment-seeking adolescents. They found more reduction in use in the MET group than in the educational feedback group at 3 months (21 % vs 8 %) but not at 12 months (16 % vs 9 %).
- Stein and colleagues [32] compared two sessions of MI with an assessment-only group in 332 non-treatment-seeking young women who regularly used marijuana. They found less use in the MI group than in the assessment-only group at 3 months (OR 0.53, $p=0.01$) but not at 1 or 6 months. Among participants expressing some desire to quit, those in the MI group were less likely to use at all three time points (OR 0.42, OR 0.31, and OR 0.35 for 1, 3, and 6 months, respectively; $p<0.05$).
- Stephens and colleagues [33] compared two sessions of MI with educational feedback in 188 adult marijuana users who were ambivalent about change. They found more reduction in use in the MI group than in the educational feedback group at 7 weeks (18 % vs 6 %) and 1 year (19 % vs 4 %).
- Stephens and colleagues [34] compared two sessions of MI with 14 sessions of CBT in 291 adult marijuana users. They found significant reductions in use in both groups at 4 months (67 % and 74 %) and 16 months (46 % and 52 %), without significant differences between groups. Both were superior to the waitlist group (which had a 31 % reduction in use at 4 months).

Cognitive behavioral therapy (CBT)

- CBT links thoughts, emotions, and behaviors in an interactional model. As applied to substance use disorders, CBT aims to develop and enhance coping strategies, including exploring the consequences of use, self-monitoring, recognizing and coping with triggers and cravings, and identifying situations that could lead to use [35]. Typical courses of CBT for substance abuse consist of 6–14 hour-long sessions [11].
- Most studies of CBT for cannabis dependence include CBT as part of a larger intervention (e.g., CBT plus contingency management), though some studies investigate CBT alone.
- Hendriks and others [36] compared CBT with MDFT in 109 adolescents with cannabis dependence. They found no difference in reduction in use between groups at 6 months (31 % and 36 %) or

12 months (24 % and 32 %). In post-hoc analyses, they found that adolescents aged 17 and 18 years and those without coexisting psychiatric problems benefited more from CBT; while younger adolescents and those with conduct disorder, oppositional defiant disorder, or internalizing problems benefited more from MDFT.

- Liddle and colleagues [37] compared CBT with MDFT in 224 adolescents with cannabis dependence or abuse. They found no difference in reduction in use at 3 months (17 % and 51 %) or 12 months (46 % and 59 %). However, MDFT was found to be superior in decreasing drug abuse problem severity.

Multidimensional family therapy (MDFT)

- MDFT includes sessions with adolescents and their parents individually and together, addressing personal and interpersonal issues, family functioning, parenting skills, family monitoring, and limit setting, as well as specific strategies for finding alternatives to drug use [38].
- See the section on CBT for evidence showing MDFT is generally equivalent to CBT for treating cannabis dependence.

Contingency management (CM)

- CM is a behavioral approach based on operant conditioning in which patients are given rewards (typically, vouchers or cash) contingent upon targeted outcomes (e.g., providing negative urine samples, attending therapy sessions, or doing CBT homework). Typically, the value of the reward increases for each consecutive desired behavior and reverts back to the original, lower value if the patient engages in the undesired behavior.
- Litt and colleagues [39] compared CM for being abstinent with CM for completing homework in 215 adults with marijuana dependence, all of whom received MET plus CBT. Also included was a case management control condition. All groups improved, including the case management control condition, with an increase in abstinent days from about 10 % to 50 %, with no differences between groups in use, abstinence, or marijuana-related problems.
- Stanger and colleagues [40] compared abstinence-based CM with attendance-based CM in 69 adolescents with problematic marijuana use who all received combination MET plus CBT. Participants in both groups had reductions in use from 45–55 % of days using marijuana (at baseline), to 9–12 % (at 14 weeks), to 15–30 % (at 9 months), with less use at all time points for those receiving abstinence-based CM. Those receiving abstinence-based CM were also more likely to have 8 or more weeks of abstinence (53 % vs 30 %, $p=0.06$) and 10 or more weeks of abstinence (50 % vs 18 %, $p=0.01$).
- Carroll and colleagues [41] compared MET plus CBT with or without CM with drug counseling with or without CM in 136 young adults

with cannabis dependence. Adding CM to either MET plus CBT or drug counseling resulted in significantly longer durations of continuous abstinence and significantly more negative urine samples. They also found that those in the MET plus CBT group reduced their use over time as compared with those in the drug counseling group.

Combinations of MI, MET, CBT, CM, and MDFT

- Given that MI, MET, CM, CBT, and MDFT have all been found to be effective, many recent studies have investigated whether combining two or more modalities is more effective than using any one particular modality. No clear consensus emerges: some studies find no differences, while other studies offer conflicting evidence as to which combination or single modality treatment is best.
- Budney and colleagues [42] compared CBT alone, CBT plus CM, and CM alone, in 90 adults with cannabis dependence. They found reductions in use in all groups at 14 weeks (67 %, 61 %, and 56 %, respectively) and 1 year (30 %, 50 %, 30 %, respectively), with evidence for more continuous abstinence with CM alone compared with CBT alone at 14 weeks, no difference between CM alone and CM plus CBT at 14 weeks, and better effects for CBT plus CM than either treatment alone at 1 year.
- Carroll and colleagues [43] compared CBT alone, CBT plus CM (for abstinence, attendance, and homework completion), and CM alone, in 127 adults with cannabis dependence. At 12 weeks, they found a reduction in use in all groups, ranging from 29 % to 63 %, highest for those getting CBT alone. The reductions tended to last: at 1-year follow up, use was down by between 35 and 50 % from baseline values in all groups. Surprisingly, they found worse outcomes among those getting CBT plus CM for negative drug screens than among those getting CM alone.
- Kadden and colleagues [44] compared CM, MET plus CBT, MET plus CBT plus CM, and case management control in 240 adults with cannabis dependence. All groups had reduced use, from 85–95 % of days used at baseline to 35–55 % (at 2 months) to 40–55 % (at 1 year). The CM-only group had the highest abstinence rates at 2 months; the MET plus CBT plus CM group had the highest abstinence rates at follow up.
- The Marijuana Treatment Project Research Group [45] compared two sessions of MET with nine sessions of a combination of MET plus CBT with a waitlist condition, in 450 adults with cannabis dependence. The nine-session group reduced use by 59 % and 50 % (at 4 and 9 months, respectively), which was greater than the two-session group (35 % and 31 %, respectively), and the waitlist group (16 % at 4 months).
- Dennis and colleagues [46] compared (i) five sessions of MET plus CBT, (ii) 12 sessions of MET plus CBT, (iii) family education and therapy, (iv) adolescent community reinforcement approach, and (v) MDFT in 600 adolescents with cannabis dependence or abuse. They

found similar reductions in use in all groups, with an average of 24 % increase in days abstinent.

- Hoch and colleagues [47] compared a combination of CBT plus MET plus problem-solving training with a waitlist group in 279 adults with cannabis dependence. Those receiving active treatment had significantly improved rates of abstinence (46 %, 32 %, and 36 % at 10, 22, and 36 weeks, respectively) compared with those in the waitlist group (18 % at 10 weeks).
- Gates and colleagues [48] compared four 1-hour telephone sessions of MI plus CBT with a waitlist group in 110 adults with cannabis dependence. Those receiving the intervention reduced their use more than those in the waitlist group at both 4 weeks (62 % vs 38 %) and 12 weeks (68 % vs 44 %).

Conclusion

Clinicians working with patients with cannabis use disorder should first assess their patient's motivation to reduce or abstain from using. If a patient is not interested in treatment or is ambivalent, evidence suggests that as little as two sessions of MI or MET can still lead to reductions in use [31–33]. If a patient is seeking treatment, any of the behavioral interventions described above, including MI, MET, CBT, CM, and MDFT, alone or in combination, can lead to moderate reductions in use. Clinicians should consider adding medication, such as n-acetylcysteine, gabapentin, bupirone, or dronabinol, to augment behavioral interventions, while being aware that none are FDA approved and all require replication of evidence showing reduction in use.

Compliance with Ethics Guidelines

Conflict of Interest

This work has been supported by NIDA grant K99RO0DA029115 granted to Kevin Hill. Aaron J. Bobb declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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