State of the Art Treatments for Cannabis Dependence

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KEYWORDS

- Cannabis • Dependence • Endocannabinoids • Marijuana • Therapy
- Treatment • Withdrawal

KEY POINTS

- The high prevalence of cannabis dependence, its strong association with comorbid mental health problems, and the difficulty of achieving cannabis cessation ensure that many psychiatrists will face patients with cannabis dependence.
- The comparatively lower "severity" of cannabis-associated consequences compared with other drugs of abuse creates a challenge for treatment providers since consensus has not been established about the value of nonabstinence goals, such as moderation and harm reduction.
- Cannabis intoxication is a syndrome recognized in DSM-IV and ICD-10, with psychological/behavioral and physical manifestations.
- Although no medication has been shown broadly effective in the treatment of cannabis dependence, evaluation is ongoing for 3 major strategies for treatment: agonist substitution, antagonist, and modulation of other neurotransmitter systems.
- A number of evidence-based psychotherapies have been shown to be efficacious for cannabis dependence, and efforts are underway to determine optimal combinations.

Worldwide, cannabis is the most commonly used illicit substance.[1] In the United States, 42% of persons over age 12 have used cannabis at least once in their lifetime, 11.5% have used within the past year, and 1.8% have met diagnostic criteria for cannabis abuse or dependence within the past year.[2,3] Among individuals who have

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ever used cannabis, conditional dependence (the proportion who go on to develop dependence) is 9%.[4] This rate is lower than many other drugs of abuse, but it is nonetheless significant considering the high prevalence of cannabis use across the population. Children and young adults have substantially higher rates of conditional dependence, a concerning notion given the fact that in recent years a decade-long trend of decreasing cannabis use has reversed. Between 2007 and 2010, past month use among youth aged 12 to 17 increased from 6.7 to 7.4%, corresponding with a decrease in perception of risk over that same period.[2,5] Altogether, there are 6600 new users of cannabis every day in the United States.[2]

Initial Characterization of Cannabis Addiction

Before the 1980s, cannabis was not thought to produce significant dependence.[6] Physical dependence, particularly the presence of a withdrawal syndrome, was not well characterized, animal models had not convincingly demonstrated reinforcing effects, and the neurobiology of cannabis was not well understood. Further, cannabis use did not seem to cause the dramatic harms typified by other drugs of abuse, such as alcohol, cocaine, and heroin. Discussion of adverse effects often focused on the "amotivational" syndrome,[7] a syndrome that was never fully disentangled from cannabis intoxication itself.

The primary psychoactive component of cannabis, tetrahydrocannabinol (THC), was identified in 1965,[8] but it was not until the 1990s, when the first cannabinoid receptor (CB1) was described, that researchers began to characterize the endocannabinoid system.[9] CB1 receptors were found to be localized throughout the brain, and although their purpose was not well-understood, cannabis exposure was shown to alter them.[10] The development of cannabinoid receptor antagonists permitted studies of precipitated withdrawal, which added to the mounting evidence of a clinically significant and specific cannabis withdrawal syndrome.[11] Cannabis was also shown to promote release of dopamine in the nucleus accumbens, one of the cornerstone features of reinforcing drugs.[12]

Broadening of Addiction Concept

Simultaneously, in the late 1970s and early 1980s, the conceptualization of addiction began to change. Rather than focusing on physical dependence, the phenomenology of addiction broadened to include such constructs as compulsivity, loss of control, consequences, salience, and relapse.[13] The DSM-III codified a view of substance dependence for which symptoms of physical dependence were neither necessary nor sufficient for establishing a diagnosis.[14] Among regular cannabis users, a dependence syndrome very similar to that described for other drugs of abuse was reliably described.[15] Users described unsuccessful attempts to cut down, use despite knowledge of persistent psychological or physical problems, excessive time spent buying, using or recovering from cannabis effects, and loss of control over use.[16] Perhaps the most important factor demonstrating the validity and clinical significance of cannabis dependence was that many heavy users sought help with problems related to cannabis use. Cannabis was the most common illicit drug responsible for substance abuse treatment admissions in the United States in 2007, and among youth under the age of 19, primary cannabis abuse accounted for over half of all admissions.[17]

Adverse Effects of Cannabis

Epidemiologic surveys revealed subtle but significant adverse outcomes associated with cannabis dependence. Chronic heavy use was associated with poor educational

attainment among youth,[18] an unsurprising association given the fact that cannabis intoxication directly impairs cognition, and some studies,[19–21] but not all,[22,23] pointed to subtle but persistent long-term impairments. Cannabis use during adolescence may be distinct in that, alongside the putative neurobiological consequences of heavy cannabinoid exposure,[24] chronic intoxication may fundamentally alter developmental trajectories.[25,26] Heavy cannabis use has been linked to school failure, early pregnancy, crime, and progression to further drug use.[18,27,28] Even where these associations are demonstrated in prospective, longitudinal studies that control for baseline (ie, precannabis use) presence of the adverse outcome and known common risk factors (eg, other substance use, psychiatric comorbidity), it remains possible that the observed associations result from convergent risks and common predisposing factors, as much as direct effects of cannabis use.

Cannabis Dependence and Other Disorders

With regard to mental health, individuals with cannabis dependence were found to be 6-fold more likely to have mood or anxiety disorders,[29] and cannabis use was repeatedly correlated with poor clinical outcomes and exacerbation of symptoms across many psychiatric disorders.[30–33] A causal relationship between cannabis use and affective disorders has not been established. However, the link between cannabis use and risk of psychotic disorders has now been replicated across at least 6 well-controlled prospective longitudinal studies,[34] and specific genetic factors are emerging as plausible explanations for increased risk among subsets of users.[30,35,36] Demonstrating causality with epidemiologic or association studies is impossible because of the inability to ever completely exclude the presence of unmeasured shared predisposing or risk factors (common antecedent causality) or subtle presence of the adverse outcome at baseline (reverse causality),[37,38] but the consistency of the associations described above has fundamentally changed the appraisal of "hazard" associated with heavy cannabis use.

Cannabis dependence poses some distinct challenges for treatment providers. The evolving sociocultural context of use for medical (as opposed to recreational) purposes, policy liberalization, and societal normalization has contributed to decreased perceived risk and increased acceptability of use.[39–43] Simultaneously, the comparatively lower "severity" of cannabis-associated consequences (compared with other drugs of abuse)[44] makes it more difficult for some users to recognize the impact of their use and establish an enduring commitment to change. As a result, many treatment seekers are reluctant to accept traditional abstinence-based goals.[45] Among treatment providers, consensus has not been established about the value of nonabstinence goals, such as moderation and harm reduction.

Models and Approaches for Cannabis Dependence Treatment

Notwithstanding these challenges, the high prevalence of cannabis dependence, its strong association with comorbid mental health problems, and the difficulty of achieving cannabis cessation ensure that many psychiatrists will face patients with cannabis dependence. Although no pharmacotherapy has been approved for cannabis dependence, a number of promising approaches are in development. Psychotherapy studies are establishing a number of evidence-based models and techniques in the armamentarium of treatment resources for patients in need. This article reviews established and emerging treatment options for cannabis dependence.

Table 1
Manifestations of Cannabis intoxication

Psychological and Behavioral	Physical
Euphoria	Motor incoordination
Relaxation	Tachycardia
Increased appetite	Orthostatic hypotension
Impaired memory and concentration	
Anxiety, panic attack, psychosis	

PHARMACOTHERAPY FOR CANNABIS DEPENDENCE

Cannabis Intoxication

Cannabis intoxication is a syndrome recognized in DSM-IV and ICD-10, with psychological/behavioral and physical manifestations (**Table 1**). Intoxication is usually mild and self-limiting, not requiring pharmacologic treatment.[46] The most severe effects (anxiety, panic attack, psychosis) are best treated with a benzodiazepine or second-generation (atypical) antipsychotic medication, as appropriate to acutely control symptoms.[46] No medication is approved specifically for treatment of cannabis intoxication.

Cannabis Withdrawal

Increasing evidence from human laboratory and clinical studies indicates that there is a true cannabis withdrawal syndrome,[11] which has been proposed for inclusion in DSM-V.[47] The commonest symptoms of cannabis withdrawal are dysphoric mood (anxiety, irritability, depressed mood, restlessness), disturbed sleep, gastrointestinal symptoms, and decreased appetite. Most symptoms begin during the first week of abstinence and resolve after a few weeks. Up to one half of patients in treatment for cannabis use disorders report symptoms of a withdrawal syndrome.[11,48–50] Although not medically serious, cannabis withdrawal should be a focus of treatment, because it may serve as negative reinforcement for relapse to cannabis use in individuals trying to abstain.[48,51]

Treatment approaches for cannabis withdrawal

No medications are approved for the treatment of cannabis withdrawal, but several medications have been evaluated in small clinical studies.[52,53] One approach is cross-tolerant (cannabinoid CB1 receptor) agonist substitution to suppress the withdrawal syndrome (analogous to using an opiate to suppress heroin withdrawal). This approach can be implemented using synthetic THC (dronabinol), which is legally marketed in many countries, including the United States (Marinol, Solvay Pharmaceuticals, Marietta, GA, USA), as an oral medication for appetite stimulation and suppression of nausea and vomiting owing to chemotherapy. Dronabinol has shown efficacy in several human laboratory studies and open-label case series, at doses up to 30 mg tid, with minimal side effects.[54–56] A controlled, clinical trial of dronabinol (20 mg bid), although not showing efficacy for reducing cannabis use (see below), did significantly reduce cannabis withdrawal symptoms.[57]

Lithium, a mood stabilizer used primarily in the treatment of bipolar disorder, has been evaluated in 2 small open-label clinical studies. In the first study, lithium (600–900 mg/d for 6 days) reduced withdrawal symptoms in 4 of the 9 participants, although 1 of the 4 continued to smoke some cannabis.[58] Abstinence was not verified in the other 8

participants. In the second study, lithium (500 mg bid for 7 days) was given to 20 cannabis-dependent in-patients undergoing detoxification.[59] Twelve patients completed the 7-day detoxification program. Over 90 days of follow-up, participants reported being abstinent on 88% of days, with 64% abstinence on day 10, 65% on day 24, and 41% on day 90. Five participants reported continuous abstinence, with cannabis-negative urine tests on day 90. These results suggest a possible persisting therapeutic effect of lithium given during the withdrawal (detoxification) period.

Another approach, which has been evaluated in human laboratory studies, tries to alleviate symptoms of cannabis withdrawal (e.g., dysphoric mood, disturbed sleep) by influencing the brain circuits that mediate these symptoms, using medications already approved for other psychiatric conditions. Human laboratory studies found that the anticonvulsant and mood stabilizer divalproex (1500 mg/d for 29 days) and the antidepressant buproprion (300 mg/d sustained release for 17 days) worsened, rather than improved, some withdrawal symptoms and had no positive effects.[55,60] A single dose of the antidepressant nefazodone (450 mg/d) decreased some, but not the majority, of cannabis withdrawal symptoms.[61] The combination of lofexidine (2.4 mg/d), an alpha2-adrenergic receptor agonist used to treat opiate withdrawal, and THC (60 mg/d) produced more improvement over 3 days in symptoms of cannabis withdrawal than either medication alone.[62]

Cannabis Dependence

No medication has been shown broadly effective in the treatment of cannabis dependence, nor is any medication approved for this condition by any regulatory authority. Ongoing research is evaluating 3 major strategies for treatment: Agonist substitution, antagonist, and modulation of other neurotransmitter systems.

Agonist substitution with antagonist

One treatment strategy is substitution with a cross-tolerant agonist drug to suppress withdrawal and drug craving, analogous to using nicotine itself to treat tobacco dependence or methadone for heroin dependence. For treatment of cannabis dependence, this strategy can be implemented using the legally available agonist, dronabinol. Oral dronabinol (10–50 mg/d) successfully reduced cannabis use and suppressed cannabis withdrawal in several outpatient cases.[54] Controlled clinical trials of oral THC are currently underway. In a controlled clinical trial, dronabinol (20 mg bid for 8 weeks) significantly improved treatment retention and reduced cannabis withdrawal symptoms, but did not improve rates of abstinence.[57]

Neuromodulation

Another strategy is modulation of other neurotransmitter systems to reduce the reinforcing effects of and craving for cannabis. This strategy has been implemented using a variety of medications approved for other psychiatric conditions.

Entacapone inhibits catechol-O-methyl transferase, an enzyme that metabolizes catecholamine neurotransmitters and regulates dopamine levels in the synapse. In an open-label trial in 36 patients with cannabis dependence (DSM-IV), entacapone (up to 2000 mg/d for 12 weeks) significantly decreased craving for cannabis in 52.7% of the patients (no data on cannabis use was reported).[63] The medication was well tolerated; there were no serious adverse events.

N-acetylcysteine reverses the down-regulation of the cystine-glutamate exchanger associated with chronic drug exposure in animals, thereby restoring normal regulation of glutamate release and reducing compulsive drug-seeking behaviors.[64] In an open-label trial in 24 cannabis-dependent outpatients, *N*-acetylcysteine (1200 mg

twice daily for 4 weeks) significantly decreased self-reported cannabis use and craving, with no significant change in semiquantitative urine cannabinoid levels.[65] The medication was well tolerated.

Atomoxetine is a selective norepinephrine reuptake inhibitor used in the treatment of attention deficit/hyperactivity disorder, and considered to have low abuse potential. In an 11-week, open-label study in 13 cannabis-dependent outpatients, atomoxetine (25, 40, or 80 mg/d) showed a trend toward reduction in cannabis use and increase in proportion of abstinent days only in the 8 patients who completed the trial.[66] The majority of patients experienced gastrointestinal adverse events. In a double-blind, placebo-controlled clinical trial in 38 cannabis-dependent outpatients with comorbid attention deficit/hyperactivity disorder, atomoxetine (25–100 mg/d escalating doses over 12 weeks) produced no significant change in cannabis use, although there was some improvement in attention deficit/hyperactivity disorder symptoms.[67]

Buspirone is a 5-HT($_{1A}$) receptor agonist and a D_2 receptor antagonist that is used as an anxiolytic. In an open-label trial in 10 cannabis-dependent men, buspirone (up to 60 mg/d for 12 weeks) significantly reduced frequency and duration of cannabis craving and use and reduced irritability and depression.[68] In a placebo-controlled clinical trial in 50 cannabis-dependent outpatients, buspirone (up to 60 mg/d for 12 weeks) in conjunction with motivational interviewing significantly increased the proportion of cannabis-negative urine samples (95% confidence interval for increase, 7%–63%; $P<.05$) among the 24 patients who completed the entire trial.[69] There was a trend toward faster initiation of abstinence (first cannabis-negative urine) among those receiving buspirone. These findings support the promise of buspirone as a treatment for cannabis dependence.

Divalproex is an anticonvulsant used as a mood stabilizer in the treatment of bipolar disorder. In a 6-week, placebo-controlled clinical trial in 25 cannabis-dependent outpatients, divalproex (1500–2000 mg/d for 6 weeks, with target plasma concentration of 50–120 ng/mL) in conjunction with weekly relapse prevention psychotherapy was not significantly more effective than placebo in reducing cannabis use and was poorly tolerated by participants.[70]

In a 13-week, placebo-controlled clinical trial in 106 cannabis-dependent outpatients, the antidepressants nefazodone (300 mg/d) or bupropion (150 mg sustained release per day) in conjunction with weekly, individual coping skills therapy were not significantly better than placebo in reducing cannabis use or symptoms of cannabis withdrawal.[71]

Treatment of Comorbid Symptoms in Cannabis Users

Cannabis users frequently have comorbid mood symptoms, especially depression.[29] Two studies evaluated the selective serotonin reuptake inhibitor antidepressant fluoxetine in such a population. A post hoc analysis of 13 cannabis-using patients among a larger sample of alcohol-abusing, depressed adolescents treated with fluoxetine (20–40 mg/d) showed reduction in both cannabis and alcohol use and depressive symptoms.[72] Five-year follow-up of 10 patients showed that cannabis and alcohol dependence were reduced and academic ability improved, but clinical depression remained problematic. In a placebo-controlled clinical trial in 70 adolescents and young adults with comorbid major depression and cannabis use disorder, fluoxetine (20 mg/d for 12 weeks) in conjunction with cognitive behavioral/motivational enhancement psychotherapy was no better than placebo in reducing either depressive symptoms or cannabis-related symptoms.[73]

Emerging Pharmacologic Targets for Cannabis Dependence

Growing knowledge about the endogenous cannabinoid (endocannabinoid) system in the brain and its role in mediating behavior offers potential new targets for the treatment of cannabis use disorders. The endocannabinoid system includes the cannabinoid (CB1) receptor, a G-protein–coupled receptor located on neuronal membranes in several brain regions, and several endogenous cannabinoids (endocannabinoids) which act as agonists at this receptor.[74,75] These endocannabinoids are primarily phospholipid esters, including anandamide and 2-arachidonoylglycerol (2-AG). Plant-derived cannabinoids such as THC are also ligands at this receptor, which mediates their actions. The synthetic and metabolic pathways for endocannabinoids are being worked out, and compounds that modulate these pathways or bind to the CB1 receptor have been developed.

Studies with the selective CB1 receptor antagonist/inverse agonist rimonabant suggest that CB1 receptors mediate many of the acute effects of cannabis in humans. In human laboratory studies, a single, double-blind oral dose of rimonabant (90 mg) produced significant dose-dependent attenuation of the subjective intoxication and tachycardia caused by an active (2.64% THC) cannabis cigarette smoked (double-blind) 2 hours later.[76] Subacute (2-week) treatment with rimonabant (40 mg/d) also attenuated the subjective intoxication and tachycardia caused by an active cannabis cigarette (2.78% THC) smoked double-blind.[77] Rimonabant alone did not significantly affect THC pharmacokinetics or produce significant physiologic or psychological effects, suggesting that the observed effects were owing to CB1 receptor blockade and not reduced brain THC concentrations. This pattern of findings suggests that CB1 receptor blockade might be beneficial acutely in the treatment of cannabis intoxication or overdose (analogous to the use of the mu-opiate receptor antagonist naloxone in the treatment of opiate overdose), and beneficial as a chronic treatment for cannabis dependence (analogous to the use of the long-acting mu-opiate receptor antagonist naltrexone in the treatment of opiate dependence).

Several CB1 receptor antagonists/inverse agonists were in clinical development by major multinational pharmaceutical companies, albeit for the treatment of obesity (activation of the CB1 receptor mediates increased appetite and weight gain). Rimonabant earned regulatory approval in more than 50 countries (but not the United States). However, its clinical use was associated with significant psychiatric side effects (anxiety, depression, suicidality), leading to suspension of marketing in the European Union in November 2008.[78] Further clinical development of rimonabant and other CB1 receptor antagonists/inverse agonists was subsequently halted worldwide. Thus, no such medication is currently available for human use.

An alternative approach to receptor blockade is modulation of brain concentrations of endocannabinoids. The enzyme fatty acid amide hydrolase catalyzes the breakdown of anandamide. Inhibitors of fatty acid amide hydrolase inhibitor, such as URB597, selectively increase brain anandamide concentrations in rodents and primates. In rodent studies, URB597 produced analgesic, anxiolytic-like, and antidepressant-like effects, but had no effects suggestive of abuse liability, such as self-administration. These findings suggest that enhancing brain endocannabinoid activity with a fatty acid amide hydrolase inhibitor might offer benefit for the treatment of acute cannabis withdrawal.[79]

Animal studies show that mu-opiate receptor antagonists block acute effects of THC, suggesting that such medications might be useful in the treatment of cannabis intoxication or overdose. Several human laboratory studies have explored this possibility by evaluating whether naltrexone reduces the subjective effects of

cannabinoids in humans. Most findings to date have been disappointing. Pretreatment with high doses of naltrexone (50–200 mg) failed to attenuate or enhanced the subjective effects of THC.[80–82] A lower, more mu-selective dose of naltrexone (12 mg) decreased the intoxicating effects of 20 mg, but not 40 mg, of THC.[83] A recent placebo-controlled study in 29 heavy cannabis smokers found that opioid receptor blockade by naltrexone (12, 25, 50, or 100 mg/d) enhanced the subjective and cardiovascular effects of cannabis.[84] This pattern of human experimental findings suggests that naltrexone would not be an effective treatment for cannabis dependence.

PSYCHOTHERAPY FOR CANNABIS DEPENDENCE

Psychotherapy for cannabis dependence has its origins in psychotherapy for substance dependence in general. Randomized studies of psychotherapy for cannabis dependence have manualized and studied various iterations of motivational enhancement therapy (MET), cognitive–behavioral therapy (CBT), and contingency management, as well as community and family interventions. Because the underpinnings of these therapeutic models are complementary, researchers have been less focused on treatment superiority and more on identifying effective combinations.

Motivational Enhancement Therapy

MET is a patient-centered therapy that seeks to help individuals resolve ambivalence to generate commitment to change.[85] MET views readiness to change as a dynamic process involving multiple stages: Precontemplation, contemplation, preparation, action, and maintenance (consider using a figure to demonstrate these), and proposes that the role of the therapist is to create the conditions that promote the patient's intrinsic motivation.[86] Five core tenets characterize the motivational "style"[85]:

1. Maintain empathy and create a respectful, nonjudgmental therapeutic frame through the use of open-ended questions and validation.
2. Develop cognitive discrepancy by identifying goals that are meaningful to the patient and incrementally linking them to contrary behaviors.
3. Avoid arguments that cause patients to become defensive by letting the patient lead and working from within their perspective.
4. Roll with resistance by using reflective interpretations and reframing rather than confrontations.
5. Support self-efficacy to engender confidence in the ability to make and sustain change by utilizing support and validation.

Whereas in clinical practice MET may be used repeatedly over time as the targets for behavioral change evolve, in clinical studies, MET sessions are typically 60 to 90 minutes long, with treatment occurring over 1 to 4 sessions. MET has been shown to improve cannabis related outcomes among treatment-seeking adults,[87] non-treatment seekers,[88] and individuals with co-occurring disorders.[89] There have been efforts to computerize motivational interventions,[90,91] simplify them for use in community settings and busy primary practices, and utilize them in inpatient settings for patients with significant co-occurring disorders.[92] Studies of brief motivational interventions in adolescents show only minimal impact on cannabis use outcomes.[93,94] However, these studies have reinforced the feasibility of brief motivational interventions for moderating use and improving education.[95] It remains to be seen whether brief interventions for non–treatment-seeking cannabis users will

increase the possibility of self-directed change by facilitating openness to education and consideration of future intervention.[93]

Cognitive–Behavioral Therapy

CBT views drug use as a learned behavior. CBT posits that by identifying the associative links and chain of events precipitating use, patients can identify opportunities to alter their behavioral repertoire and use alternative, healthy coping mechanisms.[96] CBT begins by establishing a therapeutic framework and teaching self-monitoring of underlying triggers. The therapy then moves to the development of relapse prevention skills, such as relaxation techniques, mindfulness, cognitive restructuring, positive self-talk, and assertiveness. The therapist may impart these skills through instruction, modeling, and role playing, but eventually the patient is encouraged to practice those skills outside of therapy, such that they develop the skills to adaptively deal with high-risk situations without relapsing.

CBT is typically provided over 6 to 12 individual or group sessions. The earliest randomized psychotherapy studies for cannabis dependence showed small but significant benefits.[97,98] CBT was not superior to MET,[49] but the synergies offered compelling rationale to integrate them.[99] Subsequent studies have demonstrated efficacy for CBT in the context of brief interventions,[97] combination with motivational techniques and contingency management,[100,101] and for individuals with co-occurring disorders.[89,92,102]

Contingency Management

Contingency management posits that behaviors will increase or decrease as a function of immediate and directly associated consequences. By manipulating the quality and immediacy of external consequences, contingency management attempts to systematically increase the likelihood of desired behaviors, and minimize undesired behaviors. Studies of CM show that rewards are generally more effective than punishments and that they do not have to be large or monetary to substantially alter behaviors.[103] For goals such as abstinence, that require continuous behavior, escalating values of reward can be very effective (i.e., longer periods of continuous abstinence increase the value of the reinforcer, whereas relapse resets the reinforcer back to a minimal level).[103,104] Rewards are most effective when they are provided in close proximity to the desired behavior, and frequency of reinforcement increases efficacy.[104] Whereas traditionally CM links rewards with abstinence confirmed by urine monitoring, CM can be effectively tied to a broader set of therapeutic goals, including attendance of counseling sessions, completion of therapy-related assignments, and adherence to medications.

The first randomized study of CM for cannabis dependence demonstrated that adding voucher-based incentives could improve responses to a motivational behavioral coping skills intervention.[100] CM is not a replacement for motivational enhancement or skill building, but can be used to augment the decisional balance among patients who would not otherwise be ready to address their substance use. In accordance with this, studies consistently show that, although not effective in isolation, CM reliably augments treatment outcomes of other effective psychotherapies.[105,106] CM also improves engagement among non–treatment-seeking adults with cannabis dependence, such as those referred by probation,[107] and young adults referred by the criminal justice system.[101] At least 1 study showed promise for utilization of CM among adolescents,[108] as well as for individuals with severe persistent mental illness.[109]

Supportive-Expressive Psychotherapy

Supportive-expressive psychotherapy has many characteristics similar to motivational and skills-based treatment. The supportive element of the therapy involves establishing a helpful, optimistic, encouraging, and empathic relationship between the patient and therapist. The development of a strong therapeutic alliance enables an expressive component, in which the therapist utilizes reflective listening and interpretation to explore the patient's subjective experience, point out patterns that manifest within the therapeutic relationship, and facilitate development of self-awareness, insight, and adaptive coping.[110] Through self-understanding, supportive-expressive psychotherapy aims to help patients achieve greater mastery over problem behavior and improved personal well-being.[111]

Supportive-expressive psychotherapy is typically delivered in hour-long sessions, once or twice each week, over at least 4 months. In contrast with the other therapies, supportive-expressive psychotherapy has not been studied in well-controlled randomized trials, but is worth mention because it is a commonly utilized technique among community providers of psychotherapy. One poorly controlled study compared a 16-week supportive-expressive intervention to a single session self-help intervention for cannabis dependence—significant abstinence—was achieved at the close of therapy, but significant gains were not maintained over the subsequent year.[112]

Family and Systems Interventions

Recognizing the complex interplay of psychosocial factors for many cannabis-dependent youth, system-based interventions have been established to involve family, utilize case managers to decrease obstacles, incorporate community supports to navigate environmental challenges, and collaborate with other stakeholders such as schools. Three manualized "systems" interventions have been studied among cannabis-using adolescents. Family therapy views the family as the patient, taking a family systems approach to resolving problems, by enhancing intrafamily communication, improving parental limit setting, and facilitating collaborative recovery work.[113] The Adolescent Community Reinforcement Approach is a multisystem behavioral therapy that seeks to integrate cognitive behavioral skills training with collaborative community support, and contingency management.[114] Multidimensional family therapy (MDFT) is a comprehensive systems therapy that targets the functioning of the individual within the context of his or her environment by integrating individual therapy, parent coaching, family systems therapy, and engagement of key community stakeholders, such as school, medical supports, juvenile justice, and social services.[115]

In small, randomized trials, MDFT has shown greater and more sustainable gains than CBT,[116] group therapy, and MET interventions alone.[117] However, MDFT was not significantly better when compared with other high-quality treatment interventions in the Cannabis Youth Treatment study, which randomized 600 adolescents to 5 different treatment approaches across multiple sites.[118,119] The treatment interventions included Adolescent Community Reinforcement Approach, Family Support Network, MDFT, and a 5-session and 12-session version of combined MET and CBT. The Cannabis Youth Treatment study had good retention rates, acceptability of manual-based interventions to therapists, treatment efficacy (across all arms), and economic feasibility (costs were comparable to national outpatient program costs). Long-term follow-up data are anticipated, as are initial findings from a large international study of MDFT, which is currently under way.[115]

Twelve-Step Facilitation

Twelve-step programs are an integral part of the treatment of substance dependence,[120] and manualized protocols for 12-step facilitation have been developed and implemented for alcohol and many substance use disorders.[121] However, 12-step programs are notably absent from the literature on psychosocial interventions for cannabis dependence. In 2008, the Marijuana Anonymous World Service published a 12-step workbook.[122] The extent to which 12-step programs are utilized, long-term efficacy and potential role as an integrated component of psychosocial interventions for cannabis dependence has not been examined.

SUMMARY

The treatment of cannabis dependence can be viewed as a cup half empty or half full. On the one hand, few people who might benefit from treatment actually receive it. Among those who undergo treatment in randomized trials, long-term abstinence is achieved by fewer than 20%.[123] Moderate use goals have been associated with decreases in consequences, but the differential impact of such goals on the long-term course of cannabis dependence is unknown. Optimal duration of treatment is unclear, and certain populations, particularly patients with co-occurring disorders, have not been studied adequately.[92] Twelve-step programs are low cost, effective for other substance use disorders, and readily available in most regions of the world. However, their role and efficacy in cannabis dependence has not been examined. Finally, effective pharmacologic treatments are under development, but none have yet been firmly established.

On the other hand, psychotherapeutic strategies used to treat other substance use disorders can be effective for cannabis dependence. A recent meta-analysis of psychosocial interventions for illicit substance use disorders found that treatments for cannabis dependence had comparatively larger effect sizes than treatments for other substance use disorders.[124] Combination therapies have proven most effective, particularly those that begin with a motivational intervention, utilize incentives to enhance the commitment to change, and teach behavioral and cognitive copings skills to prevent relapse. Among adolescents, family engagement and collaboration with community stakeholders adds substantial value.

Although only 9% of cannabis users develop cannabis dependence, the volume of people who smoke cannabis ensures that the total number of people in need of help is larger than the capacity of substance abuse specialty services. Thus, although efforts to refine and improve the efficacy of treatment interventions continue, innovations that increase the availability and accessibility of treatment are also needed. Computer- and phone-based interventions, social media, and brief interventions that can be implemented in primary care settings are areas that may hold promise for reaching at-risk populations. Adolescents and persons with co-occurring mental illness are at particularly high risk of cannabis dependence, and may suffer disproportionately from cannabis's adverse effects. As in the treatment of other substance use disorders, there is a need for a continuing care model with long-term follow-up that extends past the periods typically evaluated in treatment studies.[125] Additionally, there is a need for further investigation of genetic underpinnings and endophenotypes underlying cannabis dependence to identify neurobiological mechanisms for targeted intervention.[126] One benefit of the societal focus on cannabis has been a prominent increase in research covering everything from the basic science to public health impact of cannabis. Over the next decade, physicians who provide treatment for individuals with cannabis dependence are likely to see their

armamentarium of effective interventions expand, to the ultimate betterment of patients, their families, and society at large.

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