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State of the Art Treatments for Cannabis Dependence

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Synopsis

This article reviews established and emerging treatment options for cannabis dependence. Cannabis dependence poses some distinct challenges for treatment providers. The evolving sociocultural context of cannabis use for medical purposes, policy liberalization, and societal normalization has contributed to decreased perceived risk and increased acceptability of use. Simultaneously, the comparatively lower “severity” of cannabis-associated consequences 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.

Among treatment providers, consensus has not been established about the value of non-abstinence goals, such as moderation and harm reduction. Notwithstanding these challenges, the high prevalence of cannabis dependence, its strong association with co-morbid mental health problems, and the difficulty of achieving cannabis cessation ensure that many psychiatrists will face patients with cannabis dependence. While 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 treatment resources for patients in need.

Keywords

Cannabis; Marijuana; Endocannabinoids; Dependence; Withdrawal; Treatment; Therapy

Introduction

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

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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 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 to a decrease in perception of risk over that same period [2, 5]. Altogether, there are 6,600 new users of cannabis every day in the United States [2].

Adverse effects of cannabis

Prior to 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 appear 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.

Cannabis receptors

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 while 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]. DSMIII 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 US 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

Epidemiological 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 (i.e., pre-cannabis use) presence of the adverse outcome and known common risk factors (e.g., other substance use, psychiatric co-morbidity), 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 regards to mental health, individuals with cannabis dependence were found to be six-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 six 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 epidemiological 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 non-abstinence 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 co-morbid mental health problems, and the difficulty of achieving cannabis cessation ensure that many psychiatrists will face patients with cannabis dependence. While 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.

Pharmacotherapy

Cannabis intoxication

Cannabis intoxication is a syndrome recognized in DSM-IV and ICD-10, with psychological / behavioral and physical manifestations.

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	

Intoxication is usually mild and self-limiting, not requiring pharmacological treatment [46]. The most severe effects (anxiety, panic attack, psychosis) are best treated with a benzodiazepine or second-generation (atypical) anti-psychotic 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
- 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 US (Marinol®), as an oral medication for appetite stimulation and suppression of nausea and vomiting due 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), while 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 two small open-label clinical studies.

- In the first study, lithium (600 to 900 mg/day for 6 days) reduced withdrawal symptoms in 4 of the 9 participants, although one 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 2×/day 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 anti-convulsant and mood stabilizer divalproex (1500 mg/day for 29 days) and the anti-depressant bupropion (300 mg/day sustained release for 17 days) worsened, rather than improved, some withdrawal symptoms and had no positive effects [55, 60].
- A single dose of the anti-depressant nefazodone (450 mg/day) decreased some, but not the majority, of cannabis withdrawal symptoms [61].
- The combination of lofexidine (2.4 mg/day), an alpha2-adrenergic receptor agonist used to treat opiate withdrawal, and THC (60 mg/day) 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/day) 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 (COMT), 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/day 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 (NAC) 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, NAC (1,200 mg twice daily for 4 weeks) significantly decreased self-reported cannabis use and craving, with no significant change in semi-quantitative 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 (ADHD), 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/day) showed a trend towards 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 co-morbid ADHD, atomoxetine (25–100 mg/day escalating doses over 12 weeks) produced no significant change in cannabis use, although there was some improvement in ADHD symptoms [67].

Buspirone is a 5-HT_{1A} receptor agonist and a D₂ receptor antagonist that is used as an anxiolytic. In an open-label trial in 10 cannabis-dependent men, buspirone (up to 60 mg/day 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/day for 12 weeks) in conjunction with motivational interviewing significantly increased the proportion of cannabis-negative urine samples (95% CI for increase: 7 to 63%, $p < 0.05$) among the 24 patients who completed the entire trial [69]. There was a trend towards 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 anti-convulsant 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 daily for 6 weeks, with target plasma concentration of 50 to 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 anti-depressants nefazodone (300 mg/day) or bupropion (150 mg sustained release/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 co-morbid symptoms in cannabis users—Cannabis users frequently have co-morbid mood symptoms, especially depression [29]. Two studies evaluated the selective serotonin reuptake inhibitor (SSRI) anti-depressant 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 to 40 mg daily) 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 daily 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 pharmacological 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 which 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 daily) 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 physiological or psychological effects, suggesting that the observed effects were due 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 multi-national 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 US). 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 (FAAH) catalyzes the breakdown of anandamide. Inhibitors of FAAH, 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 FAAH 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 daily) 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, cognitive behavioral therapy, 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)

MET is a patient-centered therapy that seeks to help individuals resolve ambivalence in order to generate commitment to change [85]. MET views readiness to change as a dynamic process involving multiple stages: pre-contemplation, 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:" [87].

1. Maintain empathy and create a respectful, non-judgmental 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 re-framing 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 one to four sessions. MET has been shown to improve cannabis related outcomes among treatment-seeking adults [88], non-treatment seekers [89], and individuals with co-occurring disorders [90]. There have been efforts to computerize motivational interventions [91, 92], simplify them for use in community settings and busy primary practices, and utilize them in inpatient settings for patients with significant co-occurring disorders [93]. Studies of brief motivational interventions in adolescents show only minimal impact on cannabis use outcomes [94, 95]. However, these studies have reinforced the feasibility of brief motivational interventions for moderating use and

improving education [96]. 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 [94].

Cognitive Behavioral Therapy (CBT)

Cognitive behavioral therapy 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 [97]. 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 re-structuring, 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 [98, 99]. CBT was not superior to MET [49], but the synergies offered compelling rationale to integrate them [100]. Subsequent studies have demonstrated efficacy for CBT in the context of brief interventions [98], combination with motivational techniques and contingency management [101, 102], and for individuals with co-occurring disorders [90, 93, 103].

Contingency Management (CM)

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 [104]. 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, while relapse resets the reinforcer back to a minimal level) [104, 105]. Rewards are most effective when they are provided in close proximity to the desired behavior, and frequency of reinforcement increases efficacy [105]. Whereas traditionally CM links rewards to 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 [101]. 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, while not effective in isolation, CM reliably augments treatment outcomes of other effective psychotherapies [106, 107]. CM also improves engagement among non-treatment seeking adults with cannabis dependence, such as those referred by probation [108], and young adults referred by the criminal justice system [102]. At least one study showed promise for utilization of CM among adolescents [109], as well as for individuals with severe persistent mental illness [110].

Supportive-Expressive Psychotherapy (SEP)

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 [111]. Through self-understanding, SEP aims to help patients achieve greater mastery over problem behavior and improved personal well-being [112].

Supportive-Expressive psychotherapy is typically delivered in hour-long sessions, once or twice each week, over at least 4 months. In contrast to other therapies discussed, SEP 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 statistically significant gains were not maintained over the subsequent year [113].

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 intra-family communication, improving parental limit setting, and facilitating collaborative recovery work [114]. The Adolescent Community Reinforcement Approach (ACRA) is a multi-system behavioral therapy that seeks to integrate cognitive behavioral skills training with collaborative community support, and contingency management [115]. 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 [116].

In small randomized trials, MDFT has shown greater and more sustainable gains than CBT [117], group therapy, and MET interventions alone [118]. However, MDFT was not significantly better when compared with other high quality treatment interventions in the Cannabis Youth Treatment (CYT) study, which randomized 600 adolescents to five different treatment approaches across multiple sites [119, 120]. The treatment interventions included ACRA, Family Support Network, Multidimensional Family therapy, and a five-session and twelve-session version of combined MET and CBT. The CYT 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 [116].

12-Step Facilitation

Twelve-step programs are an integral part of the treatment of substance dependence [121], and manualized protocols for 12-step facilitation have been developed and implemented for

alcohol and many substance use disorders [122]. However, twelve-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 [123]. 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.

Conclusions

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 receive treatment in randomized trials, long-term abstinence is achieved by fewer than 20% [124]. 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 [93]. 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 pharmacological 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 [125]. 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 coping skills to prevent relapse. Among adolescents, family engagement and collaboration with community stakeholders adds substantial value.

Though 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, while 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 [126]. Additionally, there is a need for further investigation of genetic underpinnings and endophenotypes underlying cannabis dependence in order to identify neurobiological mechanisms for targeted intervention [127]. 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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References

1. Vienna, Austria: United Nations Office on Drugs and Crime, World Drug Report 2011 (United Nations Publication, Sales No. E.11.XI.10).
2. Substance Abuse and Mental Health Services Administration, Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-41, HHS Publication No. (SMA) 11-4658. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011.
3. Degenhardt L, et al. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. *PLoS Med.* 2008; 5(7):e141. [PubMed: 18597549]
4. Swift W, Hall W, Teesson M. Characteristics of DSM-IV and ICD-10 cannabis dependence among Australian adults: results from the National Survey of Mental Health and Wellbeing. *Drug Alcohol Depend.* 2001; 63(2):147–153. [PubMed: 11376919]
5. Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. Monitoring the Future national survey results on drug use, 1975–2010. Volume I: Secondary school students. Ann Arbor: Institute for Social Research, The University of Michigan; 2011.
6. Dennis M, et al. Changing the focus: the case for recognizing and treating cannabis use disorders. *Addiction.* 2002; 97(Suppl 1):4–15. [PubMed: 12460125]
7. McGlothlin WH, West LJ. The marihuana problem: an overview. *Am J Psychiatry.* 1968; 125(3):126–134. [PubMed: 5667203]
8. Mechoulam R, Gaoni Y. A Total Synthesis of Δ^1 -Tetrahydrocannabinol, the Active Constituent of Hashish. *J Am Chem Soc.* 1965; 87:3273–3275. [PubMed: 14324315]
9. Howlett AC, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev.* 2002; 54(2):161–202. [PubMed: 12037135]
10. Cooper ZD, Haney M. Cannabis reinforcement and dependence: role of the cannabinoid CB1 receptor. *Addict Biol.* 2008; 13(2):188–195. [PubMed: 18279497]
11. Budney AJ, et al. Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry.* 2004; 161(11):1967–1977. [PubMed: 15514394]
12. Tanda G, Loddo P, Di Chiara G. Dependence of mesolimbic dopamine transmission on Δ^9 -tetrahydrocannabinol. *Eur J Pharmacol.* 1999; 376(1–2):23–26. [PubMed: 10440085]
13. Edwards G, Gross MM. Alcohol dependence: provisional description of a clinical syndrome. *Br Med J.* 1976; 1(6017):1058–1061. [PubMed: 773501]
14. Diagnostic and Statistical Manual of Mental Disorders - Third Edition (DSM-III). American Psychiatric Association; 1981.
15. Teesson M, et al. The structure of cannabis dependence in the community. *Drug Alcohol Depend.* 2002; 68(3):255–262. [PubMed: 12393220]
16. Stephens RS, et al. The Marijuana Treatment Project: rationale, design and participant characteristics. *Addiction.* 2002; 97(Suppl 1):109–124. [PubMed: 12460133]
17. Treatment Episode Data Set (TEDS) Highlights-2007: National Admissions to Substance Abuse Treatment Services (Office of Applied Studies, DASIS Series: S-45, DHHS Publication No SMA 09-4360. Rockville, MD: 2008.
18. Fergusson DM, Horwood LJ, Beaudrais AL. Cannabis and educational achievement. *Addiction.* 2003; 98(12):1681–1692. [PubMed: 14651500]
19. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med.* 5(1):1–8. [PubMed: 21321675]
20. Solowij N, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA.* 2002; 287(9):1123–1131. [PubMed: 11879109]

21. Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: a review. *Curr Drug Abuse Rev.* 2008; 1(1):81–98. [PubMed: 19630708]
22. Dregan A, Gulliford MC. Is Illicit Drug Use Harmful to Cognitive Functioning in the Midadult Years? A Cohort-based Investigation. *Am J Epidemiol.* 175(3):218–227. [PubMed: 22193170]
23. Pope HG Jr, et al. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry.* 2001; 58(10):909–915. [PubMed: 11576028]
24. Medina KL, et al. Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. *J Int Neuropsychol Soc.* 2007; 13(5):807–820. [PubMed: 17697412]
25. Brook JS, et al. Developmental trajectories of marijuana use from adolescence to adulthood: personality and social role outcomes. *Psychol Rep.* 108(2):339–357. [PubMed: 21675549]
26. Fontes MA, et al. Cannabis use before age 15 and subsequent executive functioning. *Br J Psychiatry.* 198(6):442–447. [PubMed: 21628706]
27. Fergusson DM, Boden JM. Cannabis use and later life outcomes. *Addiction.* 2008; 103(6):969–976. discussion 977–8. [PubMed: 18482420]
28. Macleod J, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. *Lancet.* 2004; 363(9421):1579–1588. [PubMed: 15145631]
29. Stinson FS, et al. Cannabis use disorders in the USA: prevalence, correlates and co-morbidity. *Psychol Med.* 2006; 36(10):1447–1460. [PubMed: 16854249]
30. Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. *Arch Gen Psychiatry.* 68(2):138–147. [PubMed: 20921112]
31. Bovasso GB. Cannabis abuse as a risk factor for depressive symptoms. *Am J Psychiatry.* 2001; 158(12):2033–2037. [PubMed: 11729021]
32. de Graaf R, et al. Early cannabis use and estimated risk of later onset of depression spells: Epidemiologic evidence from the population-based World Health Organization World Mental Health Survey Initiative. *Am J Epidemiol.* 172(2):149–159. [PubMed: 20534820]
33. Kuepper R, et al. Continued cannabis use and risk of incidence and persistence of psychotic symptoms. 10 year follow-up cohort study. *BMJ.* 342:d738.
34. Moore TH, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet.* 2007; 370(9584):319–328. [PubMed: 17662880]
35. Verweij KJ, et al. Genetic and environmental influences on cannabis use initiation and problematic use: a meta-analysis of twin studies. *Addiction.* 105(3):417–430. [PubMed: 20402985]
36. van Winkel R. Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: sibling analysis and proband follow-up. *Arch Gen Psychiatry.* 68(2):148–157. [PubMed: 21041608]
37. Arseneault L, et al. Causal association between cannabis and psychosis: examination of the evidence. *Br J Psychiatry.* 2004; 184:110–117. [PubMed: 14754822]
38. Harder VS, Morral AR, Arkes J. Marijuana use and depression among adults: Testing for causal associations. *Addiction.* 2006; 101(10):1463–1472. [PubMed: 16968348]
39. Aggarwal SK, et al. Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions. *J Opioid Manag.* 2009; 5(3):153–168. [PubMed: 19662925]
40. Arbour-Nicitopoulos KP, et al. Social norms of alcohol, smoking, and marijuana use within a Canadian university setting. *J Am Coll Health.* 59(3):191–196. [PubMed: 21186449]
41. Gates P, et al. Barriers and facilitators to cannabis treatment. *Drug Alcohol Rev.* 2011 **Epub ahead of print.**
42. Hoffmann DE, Weber E. Medical marijuana and the law. *N Engl J Med.* 362(16):1453–1457. [PubMed: 20410512]
43. Lewis TF, Mobley AK. Substance abuse and dependency risk: the role of peer perceptions, marijuana involvement, and attitudes toward substance use among college students. *J Drug Educ.* 40(3):299–314. [PubMed: 21313988]

44. Nutt D, et al. Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet*. 2007; 369(9566):1047–1053. [PubMed: 17382831]
45. Lozano BE, Stephens RS, Roffman RA. Abstinence and moderate use goals in the treatment of marijuana dependence. *Addiction*. 2006; 101(11):1589–1597. [PubMed: 17034438]
46. Wilkins, JN.; DI; Gorelick, DA. Management of stimulant, hallucinogen, marijuana, phencyclidine, and club drug intoxication and withdrawal. In: F, D.; Ries, RI.; Miller, SC.; Saitz, R., editors. *Principles of Addicition Medicine*. 4th Edition. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 607-628.
47. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 2011. [cited; Available from: <http://www.dsm5.org/>].
48. Budney AJ, Hughes JR. The cannabis withdrawal syndrome. *Curr Opin Psychiatry*. 2006; 19(3): 233–238. [PubMed: 16612207]
49. Stephens RS, Roffman RA, Curtin L. Comparison of extended versus brief treatments for marijuana use. *J Consult Clin Psychol*. 2000; 68(5):898–908. [PubMed: 11068976]
50. Budney AJ, Moore BA. Development and consequences of cannabis dependence. *J Clin Pharmacol*. 2002; 42(11 Suppl):28S–33S. [PubMed: 12412833]
51. Levin KH, et al. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. *Drug Alcohol Depend*. 111(1–2):120–127. [PubMed: 20510550]
52. Weinstein AM, Gorelick DA. Pharmacological treatment of cannabis dependence. *Curr Pharm Des*. 17(14):1351–1358. [PubMed: 21524266]
53. Vandrey R, Haney M. Pharmacotherapy for cannabis dependence: how close are we? *CNS Drugs*. 2009; 23(7):543–553. [PubMed: 19552483]
54. Levin FR, Kleber HD. Use of dronabinol for cannabis dependence: two case reports and review. *Am J Addict*. 2008; 17(2):161–164. [PubMed: 18393061]
55. Haney M, et al. Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology*. 2004; 29(1):158–170. [PubMed: 14560320]
56. Budney AJ, et al. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend*. 2007; 86(1):22–29. [PubMed: 16769180]
57. Levin FR, et al. Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend*. 116(1–3):142–150. [PubMed: 21310551]
58. Bowen R, et al. Lithium and marijuana withdrawal. *Can J Psychiatry*. 2005; 50(4):240–241. [PubMed: 15898465]
59. Winstock AR, Lea T, Copeland J. Lithium carbonate in the management of cannabis withdrawal in humans: an open-label study. *J Psychopharmacol*. 2009; 23(1):84–93. [PubMed: 18515451]
60. Haney M, et al. Bupropion SR worsens mood during marijuana withdrawal in humans. *Psychopharmacology (Berl)*. 2001; 155(2):171–179. [PubMed: 11401006]
61. Haney M, et al. Nefazodone decreases anxiety during marijuana withdrawal in humans. *Psychopharmacology (Berl)*. 2003; 165(2):157–165. [PubMed: 12439626]
62. Haney M, et al. Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. *Psychopharmacology (Berl)*. 2008; 197(1):157–168. [PubMed: 18161012]
63. Shafa R. COMT- Inhibitors may be a Promising Tool in Treatment of Marijuana Addiction. *The American Journal on Addictions*. 2009; 18:322. (AAAP 19th Annual Meeting Poster Abstracts).
64. Kau KS, et al. Blunted cystine-glutamate antiporter function in the nucleus accumbens promotes cocaine-induced drug seeking. *Neuroscience*. 2008; 155(2):530–537. [PubMed: 18601982]
65. Gray KM, et al. N-acetylcysteine (NAC) in young marijuana users: an open-label pilot study. *Am J Addict*. 19(2):187–189. [PubMed: 20163391]
66. Tirado CF, et al. Atomoxetine for treatment of marijuana dependence: a report on the efficacy and high incidence of gastrointestinal adverse events in a pilot study. *Drug Alcohol Depend*. 2008; 94(1–3):254–257. [PubMed: 18182254]
67. McRae-Clark AL, et al. A placebo-controlled trial of atomoxetine in marijuana-dependent individuals with attention deficit hyperactivity disorder. *Am J Addict*. 19(6):481–489. [PubMed: 20958842]

68. McRae AL, Brady KT, Carter RE. Buspirone for treatment of marijuana dependence: a pilot study. *Am J Addict.* 2006; 15(5):404. [PubMed: 16966201]
69. McRae-Clark AL, et al. A placebo-controlled trial of buspirone for the treatment of marijuana dependence. *Drug Alcohol Depend.* 2009; 105(1–2):132–138. [PubMed: 19699593]
70. Levin FR, et al. Pharmacotherapy for marijuana dependence: a double-blind, placebo-controlled pilot study of divalproex sodium. *Am J Addict.* 2004; 13(1):21–32. [PubMed: 14766435]
71. Carpenter KM, et al. A preliminary trial: double-blind comparison of nefazodone, bupropion-SR placebo in the treatment of cannabis dependence. *Am J Addict.* 2009; 18(1):53–64. [PubMed: 19219666]
72. Cornelius JR, et al. Acute phase and five-year follow-up study of fluoxetine in adolescents with major depression and a comorbid substance use disorder: a review. *Addict Behav.* 2005; 30(9): 1824–1833. [PubMed: 16102905]
73. Cornelius JR, et al. Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. *Drug Alcohol Depend.* 112(1–2):39–45. [PubMed: 20576364]
74. Kano M, et al. Endocannabinoid-mediated control of synaptic transmission. *Physiol Rev.* 2009; 89(1):309–380. [PubMed: 19126760]
75. Parolaro D, et al. The endocannabinoid system and psychiatric disorders. *Exp Neurol.* 224(1):3–14. [PubMed: 20353783]
76. Huestis MA, et al. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Arch Gen Psychiatry.* 2001; 58(4):322–328. [PubMed: 11296091]
77. Huestis MA, et al. Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users. *Psychopharmacology (Berl).* 2007; 194(4):505–515. [PubMed: 17619859]
78. Le Foll B, Gorelick DA, Goldberg SR. The future of endocannabinoid-oriented clinical research after CB1 antagonists. *Psychopharmacology (Berl).* 2009; 205(1):171–174. [PubMed: 19300982]
79. Clapper JR, Mangieri RA, Piomelli D. The endocannabinoid system as a target for the treatment of cannabis dependence. *Neuropharmacology.* 2009; 56(Suppl 1):235–243. [PubMed: 18691603]
80. Greenwald MK, Stitzer ML. Antinociceptive, subjective and behavioral effects of smoked marijuana in humans. *Drug Alcohol Depend.* 2000; 59(3):261–275. [PubMed: 10812286]
81. Wachtel SR, de Wit H. Naltrexone does not block the subjective effects of oral Delta(9)-tetrahydrocannabinol in humans. *Drug Alcohol Depend.* 2000; 59(3):251–260. [PubMed: 10812285]
82. Haney M, Bisaga A, Foltin RW. Interaction between naltrexone and oral THC in heavy marijuana smokers. *Psychopharmacology (Berl).* 2003; 166(1):77–85. [PubMed: 12491025]
83. Haney M. Opioid antagonism of cannabinoid effects: differences between marijuana smokers and nonmarijuana smokers. *Neuropsychopharmacology.* 2007; 32(6):1391–1403. [PubMed: 17091128]
84. Cooper ZD, Haney M. Opioid antagonism enhances marijuana's effects in heavy marijuana smokers. *Psychopharmacology (Berl).* 211(2):141–148. [PubMed: 20490465]
85. Miller, W.; Rollnick, S. *Motivational Interviewing: Preparing People for Change* (second edition). New York City: The Guilford Press; 2002.
86. Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. *Am Psychol.* 1992; 47(9):1102–1114. [PubMed: 1329589]
87. William, R.; Miller, SR. *Motivational Interviewing, Second Edition: Preparing People for Change.* Second Edition. The Guilford Press; 2002. edition
88. Babor TF. Brief treatments for cannabis dependence: findings from a randomized multisite trial. *J Consult Clin Psychol.* 2004; 72(3):455–466. [PubMed: 15279529]
89. Stein LA, et al. Motivational interviewing for incarcerated adolescents: effects of depressive symptoms on reducing alcohol and marijuana use after release. *J Stud Alcohol Drugs.* 72(3):497–506. [PubMed: 21513687]
90. Baker A, et al. The long and the short of treatments for alcohol or cannabis misuse among people with severe mental disorders. *Addict Behav.* 2009; 34(10):852–858. [PubMed: 19299087]

91. Kay-Lambkin FJ, et al. Computer-based psychological treatment for comorbid depression and problematic alcohol and/or cannabis use: a randomized controlled trial of clinical efficacy. *Addiction*. 2009; 104(3):378–388. [PubMed: 19207345]
92. Walker DD, et al. The check-up: in-person, computerized, and telephone adaptations of motivational enhancement treatment to elicit voluntary participation by the contemplator. *Subst Abuse Treat Prev Policy*. 2007; 2:2. [PubMed: 17210075]
93. Baker AL, Hides L, Lubman DI. Treatment of cannabis use among people with psychotic or depressive disorders: a systematic review. *J Clin Psychiatry*. 71(3):247–254. [PubMed: 20331929]
94. Martin G, Copeland J. The adolescent cannabis check-up: randomized trial of a brief intervention for young cannabis users. *J Subst Abuse Treat*. 2008; 34(4):407–414. [PubMed: 17869051]
95. Walker DD, et al. Motivational enhancement therapy for adolescent marijuana users: a preliminary randomized controlled trial. *J Consult Clin Psychol*. 2006; 74(3):628–632. [PubMed: 16822119]
96. Stephens RS, et al. The Marijuana Check-up: promoting change in ambivalent marijuana users. *Addiction*. 2007; 102(6):947–957. [PubMed: 17523990]
97. Beck, AT., et al. *Cognitive Therapy of Substance Abuse*. New York City: The Guilford Press; 2001.
98. Copeland J, et al. A randomized controlled trial of brief cognitive-behavioral interventions for cannabis use disorder. *J Subst Abuse Treat*. 2001; 21(2):55–64. discussion 65–6. [PubMed: 11551733]
99. Stephens RS, Roffman RA, Simpson EE. Treating adult marijuana dependence: a test of the relapse prevention model. *J Consult Clin Psychol*. 1994; 62(1):92–99. [PubMed: 8034835]
100. Stephens, R., et al. Cognitive-Behavioral and Motivational Enhancement Treatments for Cannabis Dependence, in *Cannabis Dependence; Its Nature, Consequences and Treatment*. In: Roffman, R.; Stephens, R., editors. Cambridge: Cambridge University Press; 2006.
101. Budney AJ, et al. Adding voucher-based incentives to coping skills and motivational enhancement improves outcomes during treatment for marijuana dependence. *J Consult Clin Psychol*. 2000; 68(6):1051–1061. [PubMed: 11142539]
102. Carroll KM, et al. The use of contingency management and motivational/skills-building therapy to treat young adults with marijuana dependence. *J Consult Clin Psychol*. 2006; 74(5):955–966. [PubMed: 17032099]
103. Baker A, et al. Cognitive-behavioural therapy for substance use disorders in people with psychotic disorders: Randomised controlled trial. *Br J Psychiatry*. 2006; 188:439–448. [PubMed: 16648530]
104. Budney, A., et al. Contingency-Management Interventions for Cannabis Dependence, in *Cannabis Dependence; Its Nature, Consequences, and Treatment*. In: Roffman, R.; Stephens, R., editors. Cambridge: Cambridge University Press; 2007.
105. Petry NM. A comprehensive guide to the application of contingency management procedures in clinical settings. *Drug Alcohol Depend*. 2000; 58(1–2):9–25. [PubMed: 10669051]
106. Budney AJ, et al. Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. *J Consult Clin Psychol*. 2006; 74(2):307–316. [PubMed: 16649875]
107. Kadden RM, et al. Abstinence rates following behavioral treatments for marijuana dependence. *Addict Behav*. 2007; 32(6):1220–1236. [PubMed: 16996224]
108. Sinha R, et al. Engaging young probation-referred marijuana-abusing individuals in treatment: a pilot trial. *Am J Addict*. 2003; 12(4):314–323. [PubMed: 14504024]
109. Stanger C, et al. A randomized trial of contingency management for adolescent marijuana abuse and dependence. *Drug Alcohol Depend*. 2009; 105(3):240–247. [PubMed: 19717250]
110. Sigmon SC, et al. Contingent reinforcement of marijuana abstinence among individuals with serious mental illness: a feasibility study. *Exp Clin Psychopharmacol*. 2000; 8(4):509–517. [PubMed: 11127422]
111. Misch DA. Basic strategies of dynamic supportive therapy. *J Psychother Pract Res*. 2000; 9(4): 173–189. [PubMed: 11069130]
112. Brin F, Grenyer LL, Solowij Nadia. Treatment manual for supportive-expressive dynamic psychotherapy: special adaptation for treatment of cannabis (marijuana) dependence. National Drug and Alcohol Research Centre (Australia). 1995:51.

113. Grenyer BSN, Peters R. A comparison of brief versus intensive treatment for cannabis dependence. *Australian journal of psychology*. 1996; 48(Suppl 106)
114. Diamond, G., et al. The Cannabis Youth Treatment Study: The Treatment Models and Preliminary Findings. *Cannabis Dependence; Its Nature, Consequences and Treatment*. In: AS; Roffman, R., editors. Cambridge: Cabridge University Press; 2006.
115. Waldron HB, et al. Engaging resistant adolescents in drug abuse treatment. *J Subst Abuse Treat*. 2007; 32(2):133–142. [PubMed: 17306722]
116. Rigter H, et al. INCANT: a transnational randomized trial of multidimensional family therapy versus treatment as usual for adolescents with cannabis use disorder. *BMC Psychiatry*. 10:28. [PubMed: 20380718]
117. Liddle HA, et al. Treating adolescent drug abuse: a randomized trial comparing multidimensional family therapy and cognitive behavior therapy. *Addiction*. 2008; 103(10):1660–1670. [PubMed: 18705691]
118. Liddle HA, et al. Multidimensional family therapy for adolescent drug abuse: results of a randomized clinical trial. *Am J Drug Alcohol Abuse*. 2001; 27(4):651–688. [PubMed: 11727882]
119. Dennis M, et al. The Cannabis Youth Treatment (CYT) experiment: rationale, study design and analysis plans. *Addiction*. 2002; 97 Suppl 1:16–34. [PubMed: 12460126]
120. Diamond G, et al. Five outpatient treatment models for adolescent marijuana use: a description of the Cannabis Youth Treatment Interventions. *Addiction*. 2002; 97(Suppl 1):70–83. [PubMed: 12460130]
121. Brigham GS. 12-step participation as a pathway to recovery: the Maryhaven experience and implications for treatment and research. *Sci Pract Perspect*. 2003; 2(1):43–51. [PubMed: 18552722]
122. Humphreys K. Professional interventions that facilitate 12-step self-help group involvement. *Alcohol Res Health*. 1999; 23(2):93–98. [PubMed: 10890802]
123. [cited 2011 October 21] Marijuana 12 Step Workbook. 2008. Available from: <http://www.marijuana-anonymous.org/ma12stepworkbook.shtml>.
124. Stephens, R.; Roffman, A. The Nature, Consequences and Treatment of Cannabis Dependence: Implications for Future Research and Policy, in *Cannabis Dependence; Its Nature, Consequences and Treatment*. In: Roffman, A.; Stephens, R., editors. Cambridge: Cabridge University Press; 2006.
125. Dutra L, et al. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry*. 2008; 165(2):179–187. [PubMed: 18198270]
126. McLellan AT, et al. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000; 284(13):1689–1695. [PubMed: 11015800]
127. Solowij N, Michie PT. Cannabis and cognitive dysfunction: parallels with endophenotypes of schizophrenia? *J Psychiatry Neurosci*. 2007; 32(1):30–52. [PubMed: 17245472]

Key Points

- The high prevalence of cannabis dependence, its strong association with co-morbid 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 non-abstinence 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.
- Though 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, evaluation is ongoing for three major strategies for treatment: agonist substitution, antagonist, and modulation of other neurotransmitter systems.