Pharmacological and psychosocial interventions for cannabis use disorders

Intervenções farmacológica e psicossocial para os distúrbios de uso da cannabis

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Abstract

Objective: Cannabis remains the most widely used illicit substance in most developed countries. Its addictive potential has been established and the need for interventions for cannabis-related problems has become apparent. This article provides a review of the research evaluating potential treatments for cannabis use disorders. Method: A search of publication databases identified research studies and reviews of the scientific literature on psychosocial and pharmacological interventions for cannabis use disorders. Results: For adults, behaviorally-based interventions engender significant positive effects on abstinence and reductions in cannabis use. With adolescents, similar treatments and family-based interventions have demonstrated efficacy. Across studies, response rates appear modest even with the most potent psychosocial treatments. Evaluations of pharmacological approaches to cannabis use disorders have yet to provide clinical efficacy data for any specific medication. Agonist and antagonist approaches appear to offer the most promise. Advances in understanding of the neurobiology of the cannabinoid system provide optimism that the synthesis of compounds that alter CB1 receptor site functioning may produce promising medications. Conclusion: Clinical research has identified effective psychosocial treatments, but has yet to yield effective pharmacotherapies. Much work remains to enhance the potency of and access to interventions for those seeking treatment for cannabis use disorders.

Descriptors: Cannabis; Marijuana; Pharmacological process; Family relations; Treatment outcome

Introduction

Cannabis remains the most widely used illicit substance in most developed countries. The most recent United Nations Office on Drug and Crime (UNODC) estimates between 140 and 190 million users worldwide. The addictive potential of cannabis has

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been established through rigorous clinical and neurobiological research, and the need for primary and secondary interventions to address cannabis-related problems among youth and adults has become clear over the past 15 years. Thus, the debate over the addictive potential of cannabis has become obsolete. Treatment admissions for primary cannabis problems in the United States more than doubled between 1993 to 2003 and similar increases have been reported in Australia and the European Union. In response to this increase in demand, treatment research programs in multiple countries and continents: e.g., Australia, Brazil, Canada, France, Germany, Mexico, Spain, and the United States, have been established to investigate effective ways to assist those with cannabis use disorders. The extent of cannabis misuse and its associated consequences clearly indicates a public health problem that requires systematic efforts focused on prevention and intervention.

The problems and consequences reported by those enrolled in treatment for cannabis use disorders parallel what is observed among those in treatment for other addictive drugs, although problems associated with abuse of cannabis tend to be less severe than problems associated with abuse of drugs like cocaine and heroin. Treatment seeking cannabis users endorse the full range of abuse and dependence diagnostic criteria, including experiencing a withdrawal syndrome and failed attempts to quit or cut down. School or employment problems, relationship and family problems, guilt related to cannabis use, financial difficulties, low energy, low self esteem, dissatisfaction with productivity level, sleep and memory problems, and low life satisfaction are commonly reported.

This article will provide a summary and update of the scientific literature on psychosocial and pharmacological interventions focused on cannabis use and disorders. The psychosocial literature base has spanned approximately 20 years, but produced relatively few controlled treatment outcome studies. The pharmacotherapy literature spans less than 10 years and comprises primarily laboratory studies evaluating the potential of various medications, and only a few clinical trials. A general overview will alert the reader to the extant literature; more detailed analyses can be found in a number of recently published reviews. Comments and discussion will focus on the strengths and limitations of the current knowledge, needs for the future, and potential areas of future investigation.

Method

The studies included in this overview were selected by performing electronic searches of the PubMed and OVID/Embase databases, and by reviewing reference lists in located articles and book chapters. Both adult and adolescent studies are reviewed. The studies on adults include those seeking treatment specifically for cannabis, and typically exclude those with significant problems associated with other substances. The adolescent literature includes very few studies focused on adolescents seeking treatment specifically for cannabis, but rather include adolescents entering general substance use outpatient programs. The majority of these adolescents, however, are primary cannabis users. We review primarily randomized, controlled clinical trials except where noted. For the pharmacotherapy review, we included human laboratory studies targeting medications for cannabis, and clinical trials (both open label and controlled). We also provide comment on promising pharmacological targets gleaned from recent advances in cannabinoid neuroscience.

Results

1. Psychosocial/Behavioral treatment approaches

1) Adults

Since an initial survey study in 1987 reported that many adult cannabis users were interested in receiving help to stop or reduce their use, at least 11 randomized trials of psychosocial interventions for cannabis use disorders have been published. This literature clearly demonstrates that a number of behaviorally-based outpatient treatments are effective for promoting reduction in and abstinence from cannabis use. Motivational enhancement therapy (MET), cognitive behavioral therapy (CBT), and contingency management (CM) approaches reflect the majority of interventions tested, all of which have been tested and deemed efficacious with other substance use disorders. Table 1 provides a summary of the types of interventions that have received empirical support in controlled studies.

MET, based on the motivational interviewing theory and technique, addresses ambivalence about quitting and seeks to strengthen motivation to change. Therapists use a non-confrontational, empathic style of counseling to guide the person towards commitment to and action towards change. MET is delivered in 45-90 minute individual sessions, and may involve 1-4 sessions. CBT focuses on teaching skills relevant to quitting cannabis and to avoiding or coping with other problems that might interfere with good outcomes. Examples of session targets are: analysis of recent cannabis use or cravings, coping with situations that trigger use, cannabis refusal, mood management, and problem solving. CBT usually involves 6 to 14 individual or group counseling sessions, each lasting 45-60 minutes. CM involves the systematic use of consequences (reward and punishment) to motivate cannabis abstinence. The most frequently studied CM interventions tested with cannabis use disorders involve abstinence-based incentive programs that provide tangible (monetary-based) incentives contingent on abstinence documented via once or twice-weekly urine testing. Participants receive vouchers indicating their earnings, which are then exchangeable for retail items or gift cards.

MET/CBT studies: The Roffman and Stephens research group conducted the initial tests of MET and CBT treatments. A series of four trials have demonstrated the efficacy of CBT and MET for adults with cannabis use disorders. The first trial showed promising, but comparable cannabis use outcomes for CBT group and social support group interventions. A second study compared a 14-session group CBT intervention, a 2-session individual MET intervention, and a delayed treatment control (DTC) condition. For both active treatments, days of cannabis...
use, amount used per day, the number of dependence symptoms, and problems related to cannabis decreased compared with the DTC group, yet no differences were observed between CBT and MET conditions. This finding raised the possibility that brief MET treatments might produce equivalent outcomes to the longer CBT interventions. An Australian study employed a similar experimental design comparing a 6-session, hybrid MET/CBT, a 1-session hybrid MET/CBT, and a DTC group. Results again showed that both active treatments produced better outcomes than DTC, with little difference observed between the active treatment groups, although some trends emerged suggestive of better abstinence rates for those receiving 6-session MET/CBT.

The final trial in this series was conducted at 3 sites in the U.S. with a sample size of 450 cannabis users. A 9-session MET/CBT intervention, a 2-session MET intervention, and a DTC condition were compared. The MET/CBT and MET interventions again produced better cannabis reduction and abstinence outcomes than the DTC. However, in this larger trial, results clearly indicated better cannabis use outcomes for the 9-session MET/CBT treatment compared with the brief MET only intervention. Findings generalized across sites and were not moderated by ethnicity or gender.

Most recently, a Brazilian study compared an MET/CBT intervention in which 4 sessions were delivered weekly (1 month duration) with an intervention that delivered the same 4 sessions over the course of 3 months. Cannabis use outcome measures improved in both treatment conditions compared to a delayed treatment group, but did not differ from each other. There was a trend towards greater reduction in use over time and greater reductions in dependence for the longer duration treatment.

In recognition of the moderate overall outcomes achieved with the usual course of MET/CBT, the Stephens and Roffman group has begun to develop and test a chronic-care model of treatment termed “cannabis dependence treatment PRN”. Following an initial four sessions of MET/CBT, participants can choose to attend more MET/CBT sessions as desired over a 28-month period. Unfortunately, in the first study only a minority (25%) made use of the continuing care sessions, and the PRN group did not show increased abstinence rates compared with a fixed-treatment follow-ups. However, individuals who had high utilization of PRN sessions showed high levels of abstinence (60%) at follow up.

In summary, adults with cannabis use disorders respond positively to individual and group models of MET, CBT and their combination. Longer duration MET/CBT interventions may produce more robust outcomes than much briefer models, but even 1-2 session MET interventions show efficacy. Also, therapist experience may be related to achieving better outcomes these treatments. This literature suggests that combining MET and CBT reflects the current state-of-the-art counseling intervention for adults with cannabis use problems. Note that reduced cannabis use, rather than abstinence, is the more common outcome observed across studies. Such reductions in use appear important as these are correlated with reductions in problems and symptoms of dependence. That said, abstinence and reduction rates across MET/CBT studies suggest that the majority of participants do not make substantial clinical progress.

CM studies: In an effort to enhance outcomes, Budney et al. added an abstinence-based voucher CM intervention to the types of MET/CBT previously described. An initial trial compared

### Table 1 - Randomized trials of psychosocial treatments for cannabis use disorders (adults)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT vs Social Support</td>
<td>Significant reductions in cannabis use, but no differences between groups.</td>
<td></td>
</tr>
<tr>
<td>CBT, MET vs DTC</td>
<td>CBT and MET produced superior cannabis outcomes than DTC. No differences between CBT and MET.</td>
<td></td>
</tr>
<tr>
<td>MET/CBT vs DTC</td>
<td>MET/CBT produced superior cannabis outcomes than DTC; no differences between active conditions.</td>
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</tr>
<tr>
<td>MET/CBT vs DTC</td>
<td>MET/CBT and MET produced superior cannabis outcomes than DTC; 9-session MET/CBT produced superior outcomes than MET.</td>
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<tr>
<td>MET/CBT vs DTC</td>
<td>Both MET/CBT groups produced superior cannabis outcomes than DTC; longer duration MET/CBT marginally superior to shorter duration.</td>
<td></td>
</tr>
<tr>
<td>MET/CBT vs DTC</td>
<td>No differences between treatment groups.</td>
<td></td>
</tr>
<tr>
<td>MET/CBT vs DTC</td>
<td>MET/CBT/CM produced greater cannabis abstinence than MET or CBT.</td>
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</tr>
<tr>
<td>MET/CBT vs DTC</td>
<td>MET/CBT/CM and CM produced superior abstinence outcomes during treatment; MET/CBT/CM had superior post-treatment abstinence compared to CM or MET/CBT.</td>
<td></td>
</tr>
<tr>
<td>MET/CBT vs DTC</td>
<td>Both CM conditions produced superior abstinence outcomes. MET/CBT/CM showed the highest rates of abstinence at later post-treatment follow-ups.</td>
<td></td>
</tr>
<tr>
<td>MET/CBT vs DTC</td>
<td>CM enhanced treatment attendance, did not affect cannabis use. Note that CM targeted attendance and not abstinence.</td>
<td></td>
</tr>
<tr>
<td>MET/CBT vs DTC</td>
<td>CM enhanced treatment retention and cannabis abstinence, with MET/CBT/CM producing the best cannabis outcomes.</td>
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</tbody>
</table>
Both CM groups received incentives for attendance during treatment than MET/CBT or MET alone. A second trial compared MET/CBT+CM with MET/CBT alone, and CM alone (no counseling), and evaluated outcomes out to one year post treatment. CM alone and MET/CBT+CM engendered greater rates of abstinence during treatment than MET/CBT alone, but they did not differ from each other. During the post-treatment period, however, MET/CBT+CM evidenced greater rates abstinence than CM alone highlighting the potential importance of the MET/CBT and CM combination to longer-term maintenance of abstinence. No differences in abstinence rates between CM alone and MET/CBT alone were observed during the post-treatment period.

These outcomes were replicated by another research group in a study that included a more diverse and larger treatment sample, and that used a lower magnitude voucher earning schedule. Again during treatment, MET/CBT+CM and CM alone produced abstinence outcomes similar to each other, but superior to MET/CBT alone. During the post-treatment year, MET/CBT+CM sustained these positive outcomes better than CM alone.

Two studies evaluated CM for cannabis use with probation-referred young adults (ages 18-25). An initial trial compared 3-session MET with MET plus an attendance-based voucher CM program. MET+CM engendered greater rates of attendance and treatment completion and attendance, but did not enhance effects on cannabis abstinence. A follow-up study compared MET/CBT+CM, MET/CBT alone, Drug Counseling (DC) alone, and DC+CM. Both CM groups received incentives for attendance and cannabis abstinence. CM enhanced rates of attendance, treatment completion, and cannabis abstinence, MET/CBT engendered higher rates of attendance than DC. Overall, MET/CBT+CM showed the highest rates of abstinence throughout post-treatment, but this effect did not reach statistical significance.

In summary, these CM studies provide consistent evidence for the efficacy of abstinence-based incentive programs facilitating high rates of cannabis abstinence during treatment. Moreover, combining MET/CBT with CM would appear to produce the most potent and enduring positive effects on cannabis abstinence compared with other interventions tested to date.

**Limitations of treatment outcomes for adults:** Even with the most efficacious treatment for adults, MET/CBT+CM, only about half of those who enroll in treatment achieve a substantial period of abstinence, and among those, approximately half return to use or relapse within a year. Moreover, 1-year abstinence rates across studies of MET/CBT and MET alone have ranged between 19%-29% and 9%-28%, respectively. An additional number of participants significantly reduce their use, but still a substantial proportion does not show evidence of progress. There clearly remains much room for improvement in rates of change in cannabis use and abstinence for adults who enter outpatient treatment.

2) Treatment for youth/adolescents

Most treatment outcome data on cannabis use interventions for youth come from studies that include adolescents who use multiple substances, with the most common being cannabis and alcohol. Empirical support for the efficacy of group or individual MET/CBT and family-based treatments has emerged across multiple randomized trials. The MET/CBT interventions studied have been similar to those for adults in scope and duration. Specific forms of family-based treatments that have been tested include brief strategic family therapy, family behavior therapy, family support network intervention and community reinforcement approach counseling, functional family therapy, multidimensional family therapy, and multisystemic therapy.

The duration, intensity, and content of each of these treatment models vary considerably, but detailed descriptions are beyond the scope of this paper. Generally, the family interventions engage social networks (parents, schools, judicial system, other social agencies) to facilitate change and identify problem areas. They also may address maladaptive family patterns (e.g. parent drug use, parent-child relationships, parent supervision, house rules etc.).

Although yet to be clearly supported by the empirical literature, family approaches may produce more potent and enduring outcomes than those without family involvement.

As with adult outcomes, reductions in cannabis and other substance use reported in adolescent trials have been modest and robust effects on abstinence rates have been difficult to demonstrate. Recent trials investigating adjuncts to standard treatments have appeared in the literature. Assertive continuing care (ACC) was designed to maintain treatment gains (reduce relapse) achieved during residential treatment. For 90 days following treatment, case managers made weekly home visits to facilitate use of other social services, development of a supportive social network, and use of coping strategies to maintain abstinence. ACC was more effective in increasing adolescents’ engagement and retention in continuing care and resulted in longer-term abstinence than the usual care condition.

Three CM intervention studies have also tried to boost outcomes of established treatments. An abstinence-based incentive CM program added to Drug Court and the multisystemic therapy did not clearly enhance outcomes. Note that all youth involved in the study were already receiving incentives and consequences based on drug testing results through a Drug Court program, and the CM program employed may not have included optimal methods for delivering abstinence-based incentives. Second, a more elaborate CM-based treatment did enhance abstinence outcomes when integrated with MET/CBT. This CM program included a clinic delivered abstinence-based voucher program and a parent-based CM program that instructed parents to systematically provide rewards and consequences contingent on their teen’s use of or abstinence from cannabis and other substances. Unfortunately, the positive effects on abstinence were not as robust during post-treatment assessments. Note that a twice-weekly urine testing program with results systematically reported to parents was used in both the CM and comparison conditions. This type of testing program was unique to this study.
and may be an active treatment component in its own right. Last, another innovative CM program utilizing a prize drawing reward program to increase prosocial, goal-oriented activities appeared to show promise, although results from a controlled study have yet to be reported.

In summary, multiple types of behavioral and family-based interventions have demonstrated efficacy for treating adolescent cannabis and other substance use disorders. The family-based treatments may have some advantages over interventions that only involve the adolescent. Moreover, adding CM interventions to individual or family interventions may further enhance outcomes, particularly for engendering abstinence. Nonetheless, similar to the adult outcomes, the majority of youth do not show a substantial positive response even to the most potent interventions. There remains a clear and pressing need for continued treatment development research.

Pharmacotherapy development

Over the past decade, increased recognition of the 1) need for effective interventions for cannabis use disorder treatment, 2) validity of the cannabis withdrawal syndrome, and 3) structure and functioning of the endogenous cannabinoid system has stimulated research on the potential use of medications to treat cannabis use disorders. Unfortunately, there is no robust empirical support for the efficacy of any medication for use in the treatment of cannabis use disorders to date. The pharmacotherapy development literature related to cannabis use disorders has been reviewed and summarized in considerable detail by others. Here we discuss potential pharmacological targets, briefly review the laboratory studies and few clinical trials that have been reported, and discuss promising areas for future investigation. Table 2 provides a summary of these studies and results.

The cannabis withdrawal syndrome has been a primary focus of the medication evaluation research efforts because of the recent establishment of its validity and clinical importance. Cannabis users report that withdrawal symptoms adversely impact quit attempts, and report use of cannabis or other drugs to relieve these symptoms. As such, suppressing or alleviating cannabis withdrawal symptoms would seem a promising target for promoting cessation attempts.

A primary neurobiological target for pharmacological interventions has been the CB₁ receptor. The primary psychoactive component of cannabis, Δ⁹-tetrahydrocannabinol (Δ⁹-THC), is a partial agonist of the CB₁ receptor and its reinforcing effects result from activation of this receptor. Cannabis use alters the functioning of several other neurotransmitter systems. Δ⁹-THC and other CB₁ receptor agonists increase dopamine (DA) release in the mesolimbic-dopamine reward pathway and enhance electrical brain-stimulation reward, effects associated with appetitive drug-seeking and drug-taking behaviors. Intervention at the CB₁ receptor could

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Study type/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine⁷⁹</td>
<td>norepinephrine reuptake inhibitor</td>
<td>Open label trial/No effect on cannabis use, gastrointestinal side effects.</td>
</tr>
<tr>
<td>Bupropion⁶¹,⁶⁶</td>
<td>norepinephrine and dopamine reuptake inhibitor</td>
<td>Lab study/Exacerbated withdrawal but reduced effects of cannabis. Randomized clinical trial/No effects on withdrawal or cannabis use.</td>
</tr>
<tr>
<td>Buspirone⁶⁷,⁶⁸</td>
<td>serotonin 5HT receptor partial agonist</td>
<td>Lab study/Reduced cannabis use, craving, and irritability but high drop out. Randomized clinical trial/No effects on cannabis use and high drop out.</td>
</tr>
<tr>
<td>Clonidine⁵⁴</td>
<td>α₂ adrenergic agonist</td>
<td>Lab study/Reduced tachycardia, but not subjective effects of cannabis.</td>
</tr>
<tr>
<td>Divalproex⁵²,⁶⁵</td>
<td>unknown</td>
<td>Randomized clinical trial/No effect on cannabis use. Lab study/Exacerbated withdrawal and increased subjective effects of cannabis.</td>
</tr>
<tr>
<td>Dronabinol⁵²,⁵⁶,⁵⁰,⁷¹</td>
<td>CB₁ receptor agonist</td>
<td>Lab studies (2)/Reduced cannabis withdrawal. Lab study/Reduced subjective effects, but not choice to administer cannabis. Lab study/Increased subjective effects of cannabis and did not reduce &quot;relapse&quot;. Open label trial/Associated with cannabis abstinence.</td>
</tr>
<tr>
<td>Lithium⁶⁹,⁷⁰</td>
<td>unknown</td>
<td>Open label trials (2)/Associated with reduced withdrawal and cannabis use.</td>
</tr>
<tr>
<td>Lofexidine⁶⁶</td>
<td>α₂ adrenergic agonist</td>
<td>Lab study/Alone and in combination with dronabinol, reduced withdrawal and &quot;relapse&quot;.</td>
</tr>
<tr>
<td>Naltrexone⁵⁵,⁵⁷</td>
<td>mu-opioid receptor antagonist</td>
<td>Lab studies/Variable, but mostly negative impact on subjective effects of cannabis; dose and history of subjects may moderate effects.</td>
</tr>
<tr>
<td>Nefazodone⁵⁵,⁶⁶</td>
<td>norepinephrine and serotonin reuptake inhibitor, 5HT₂ receptor antagonist</td>
<td>Lab study / Reduced select withdrawal symptoms, no effect on overall severity, and did not alter subjective effects of cannabis. Randomized clinical trial/No effects on withdrawal or cannabis use.</td>
</tr>
<tr>
<td>Rimonabant⁵¹,⁶²</td>
<td>cannabinoid CB₁ receptor antagonist</td>
<td>Attenuated subjective and physiological effects of cannabis in laboratory studies. Reduced cannabis use in small open-label clinical study. Side effect concerns.</td>
</tr>
</tbody>
</table>
Another viable pharmacological approach. Antagonists can reduce the receptor site but do not produce reinforcing effects, provide non-treatment seeking, daily sleep difficulties). A recent follow-up study of Bupropion, clonidine, nefazodone, naltrexone, and divalproex have not shown robust effects across multiple measures that would suggest therapeutic efficacy, and in some cases have produced effects opposite of those desired. A recent follow-up study of naltrexone, an opioid antagonist, showed that naltrexone dose and cannabis use history moderated its impact on the subjective affects of ∆9-THC. Such findings suggest that more research may be warranted on opioid antagonists, and highlight the importance of testing a wider range of doses during initial laboratory tests of pharmacological agents.

Human laboratory studies
Multiple inpatient and outpatient laboratory studies with non-treatment seeking, daily cannabis users have examined medication effects on cannabis withdrawal, the reinforcing and subjective effects of smoked cannabis, and analog models of relapse. Bupropion, clonidine, nefazodone, naltrexone, and divalproex have not shown robust effects across multiple measures that would suggest therapeutic efficacy, and in some cases have produced effects opposite of those desired. A recent follow-up study of naltrexone, an opioid antagonist, showed that naltrexone dose and cannabis use history moderated its impact on the subjective affects of ∆9-THC. Such findings suggest that more research may be warranted on opioid antagonists, and highlight the importance of testing a wider range of doses during initial laboratory tests of pharmacological agents.

Positive findings have been observed in studies targeting cannabis withdrawal with oral doses of the CB1 antagonist, dronabinol (synthetic encapsulated THC). Across three studies, dronabinol produced dose-dependent reductions in most symptoms of cannabis withdrawal with higher doses engendering almost complete suppression of withdrawal effects. In one of these studies, dronabinol alone did not show positive effects in a laboratory analog model of relapse or cannabis self-administration. An earlier study showed that dronabinol attenuated the subjective effect of cannabis, but not the choice to smoke cannabis. However, dronabinol in combination with lofexidine, an α2-agonist, reduced the likelihood of “relapse” under these laboratory conditions. Two laboratory studies evaluating the partial CB1 antagonist, rimonabant, have produced mixed results. An initial study showed substantially reduced subjective effects of smoked cannabis, but a subsequent study showed inconsistent effects suggesting a need to further explore dosing regimens.

Last, an initial study using extended-release zolpidem to target sleep difficulty, a robust symptom of cannabis withdrawal, reported an attenuation of sleep disturbance during a period of cannabis abstinence. Across laboratory and survey studies, sleep difficulty is one of the most common and highest magnitude cannabis withdrawal effects, and was the withdrawal symptom most associated with relapse to cannabis use across multiple studies.

Clinical trials
Three randomized, pharmacotherapy trials for cannabis use disorders have been reported. A 6-week trial showed that adding divalproex to a CBT intervention did not enhance cannabis use outcomes compared to placebo. A second trial compared nefazodone, sustained-release bupropion, and placebo, and observed high drop out rates and no effects on cannabis use outcomes for either medication. Another randomized trial compared bupropion and placebo when combined with MET. Some positive, but not robust cannabis use outcome effects were associated with bupropione, but the majority of participants did not complete the study and multiple side-effects associated with the medication were reported.

An open label study of bupropione with ten outpatients suggested that bupropione might reduce cannabis use and withdrawal symptoms, but adverse effects and a high drop out rate were also reported. Two open label studies of lithium carbonate, a mood stabilizer, for cannabis withdrawal were suggestive of positive effects. First, lithium dosing during a 7-day residential episode was associated with good cannabis outcomes during the year following treatment without substantial safety or side effects concerns. A second study reported that 4 of 9 outpatients prescribed lithium reported reduced withdrawal symptoms. An 11-week open label trial of atomoxetine with 13 treatment seekers reported a non-significant reduction in cannabis use, but relatively severe side effects were also reported. Last, an open label study of two patients prescribed dronabinol who had previously been unable to quit on their own reported sustained cannabis abstinence. One patient was tapered off dronabinol without relapse, the other stayed on a course of dronabinol maintenance. Multiple confounds and no control conditions make it difficult to interpret these open label studies.

Additional pharmacological targets
The characterization of the endogenous cannabinoid system has provided valuable targets that can be manipulated for therapeutic gain. Two G-protein coupled receptors and arachidonic-acid based endogenous ligands for those receptors, as well as the enzymes to control synthesis and degradation of the more well-known ligands, have been identified as its principal components. These components have been located in key areas that correspond well to the known effects of cannabis. Medicinal chemists have been generating synthetic compounds that target specific elements of the endogenous cannabinoid system, including those that function as selective agonists, antagonists, indirect agonists and allosteric modulators at the CB1 receptor.

As reviewed above, one of these synthetic compounds, rimonabant, a CB1 partial antagonist, has been tested in humans and may be effective in blocking the subjective effects of cannabis. Unfortunately, due to significant psychiatric adverse events observed during clinical trials and post-marketing surveillance...
in the European Union, rimonabant has been pulled from the market world-wide. Thus, development of second generation CB₁ antagonists that can block the reinforcing effects of cannabis without producing significant adverse effects has become a working target for drug development. Similarly, oral preparations of THC (dronabinol), a CB₁ agonist, have shown promise in laboratory studies, but concern has been raised about possible adverse cognitive and behavioral effects and the abuse liability of THC. Synthesis of alternative CB₁ agonists, partial CB₁ agonists or alternative formulations of THC (e.g., transdermal patch, sustained release depot devices) that do not produce such effects offer alternative targets for medication development.

Another alternative target of preclinical drug development has been endogenous brain endocannabinoid levels. Frequent cannabis use may stimulate down-regulation of endocannabinoid signaling in the brain. In turn, pharmacological agents that elevate brain levels of the endocannabinoid neurotransmitters might alleviate cannabis withdrawal and dependence.²⁻³ Fatty-acid amide hydrolase (FAAH), an enzyme that assists with the deactivation of anandamide, has become a specific target because its inhibition may trigger indirect activation of the CB₁ receptor. A FAAH inhibitor, URB597, has shown some promise in nonhuman studies and is hypothesized as a potential agent for attenuating cannabis withdrawal.

In summary, effective medications for cannabis use have yet to clearly identified. The most promising laboratory findings have been reported with dronabinol, a cannabinoid agonist, which if implemented, would parallel the agonist (substitution) therapy model that has been successful in the treatment of opioid (methadone, buprenorphine, LAAM) and nicotine (nicotine replacement medications) dependence and withdrawal. Randomized clinical trials of an agonist therapy for cannabis have yet to be completed, although a number of studies are currently under way. Further study of combinations of agents, like dronabinol and lofexidine also appears warranted based on an initial laboratory study. Cannabinoid antagonist treatments paralleling the effective opioid antagonist model (naltrexone) also hold promise, however, the only cannabinoid antagonist evaluated to date, rimonabant, has concomitant adverse effects that make its use untenable. Synthesis and testing of alternative antagonists with fewer adverse effects would seem a worthwhile avenue for additional research. Targeting specific and clinically important withdrawal symptoms, such as sleep difficulty, with already approved medications provides another promising target for treating cannabis dependence. Last, our rapidly expanding knowledge of the endogenous cannabinoid system is facilitating exciting opportunities for medicinal chemists to synthesize agents that can impact cannabinoid modulation and effects, providing multiple possibilities for development of novel medications.

Conclusion
The last 20 years has provided great advances in the empirical understanding of the addictive potential of cannabis. This includes neurobiological evidence that cannabis affects brain reward systems in a manner similar to other abused drugs, characterization of a clinically significant and pharmacologically specific withdrawal syndrome, and the observation that a considerable number of both adults and adolescents experience significant problems related to their use of cannabis and seek treatment for them. Such recognition has lead to a recent surge in research aimed at the development and validation of treatment interventions that are effective in helping the treatment-seeking cannabis use population. Not surprisingly, the interventions that have been shown to be effective largely parallel those that are effective in the treatment of other substance use disorders.

For adults, substantial evidence now indicates that behaviorally-based interventions such as MET, CBT, and CM can help individuals make significant changes to their problematic use of cannabis. With adolescents, these same treatment approaches have also demonstrated efficacy, as have a number of family-based approaches. Nonetheless, more potent treatment approaches and intervention strategies are clearly needed to address the modest response rates and substantial relapse rates observed with the current interventions. Optimistic expectations for continued enhancements to current approaches appears warranted given that incremental gains in efficacy have been observed as innovative applications such as combining MET and CBT, and integrating CM with standard or family-based treatments. Better understanding of the moderators of treatment outcome and mechanisms of action of the specific treatments should also lead to innovations that can better match individuals to particular treatment modalities, or result in modifications to treatment approaches that deliver more of the active ingredients necessary for change. For example, with MET and CBT, the optimal number of sessions or length of treatment is unknown, and with CM interventions, the optimal frequency, duration, and magnitude of the incentive schedule used to reinforce abstinence has not been determined, but these variables are likely to be related to the potency of CM interventions.²⁻²⁴ Moreover, the recent exploration of chronic care models of treatment reflects a growing understanding and acceptance that substance use disorders (including cannabis) are chronic conditions that may require ongoing interventions to maintain gains and limit relapse.

The development and evaluation of pharmacological approaches to cannabis use disorders has yet to provide clinical efficacy data for any specific medication, however this area of investigation is relatively young. Agonist and antagonist approaches appear to offer the most promise based on human laboratory reports, although concerns remain related to abuse liability and adverse effects. Rapid advances in the neurobiology of cannabis and the cannabinoid system provide optimism that novel agonist- or antagonist-like compounds that indirectly alter CB₁ receptor site functioning may be synthesized and show efficacy without adverse effects. Most of the laboratory studies that have focused on cannabis withdrawal symptom suppression with compounds that do not target the cannabinoid receptor have failed to show promise, However,
initial findings targeting sleep dysfunction show some promise, and there remain many additional agents and dosing schedules to evaluate. Multiple pharmacotherapy development and evaluation studies underway in the U.S. and elsewhere will hopefully result in identification of pharmacological agents that will improve outcomes for those with cannabis use disorders.

In addition to the need to develop more potent models of treatment is the need to address issues related to the dissemination and translation of effective treatments. Substance abuse services delivery systems lag well behind research. For example, the availability of MET, CBT, and CM remains low, even though evidence for these approaches with substance dependence problems other than cannabis has been documented for many years. Few community-based substance abuse counselors are currently trained to provide quality MET/CBT, although slow but steady progress seems apparent. Treatment providers remain ambivalent about CM interventions because of their cost and CM’s basic premise, i.e., providing incentives for not using substances.75,76

The treatment system in general experiences difficulty recruiting, training and retaining treatment staff, inadequate financing to provide treatment, insufficient treatment availability to meet demand, and slow adoption of research-based treatment innovations, which all contribute to limited access to the most effective treatments.77,78 Treatment services research must continue to investigate novel, efficient, and effective methods for treatment dissemination and implementation, including the use of innovative technologies (computer, internet, telephone) to enhance or assist in the delivery of treatment, exploration of cost effective training and adherence procedures, and restructuring of current service delivery systems.

In conclusion, independent of whether or not cannabis has valid medical applications, it clearly has addictive potential. Heavy cannabis use may contribute to the development of significant psychosocial and health-related problems, and a growing number of people are seeking treatment for these problems, most of whom are unsuccessful in their attempts to quit. Clinical research has provided us with a number of effective psychosocial treatment interventions, but has yet to yield effective pharmacotherapies. Much work remains to increase the potency of and access to the interventions we develop for those seeking treatment for cannabis use disorders.

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Disclosures

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* Modest
** Significant
*** Significant: Amounts given to the author’s institution or to a colleague for research in which the author has participation, not directly to the author.
Note: UAMS = University of Arkansas for Medical Sciences; NIH = National Institutes of Healths.

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