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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 CB_1 receptor site functioning may produce promising medications.

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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.[1–4] 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 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.[4,5] 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.[6–9] 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.[10–18] 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/Medline 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,[19] 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,[20] 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.[21] 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 to14 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.[22] 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.[23] A second study compared a 14-session group CBT intervention, a 2-session individual MET intervention, and a delayed treatment control (DTC) condition.[24] 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.[25] 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.[26] 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.[27] *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".[28] 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-session comparison condition. 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.[25] 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 4-session MET, 14-session combined MET/CBT, and 14-session MET/CBT +CM.[29] MET/CBT+CM engendered significantly more weeks of continuous *cannabis* abstinence 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.[30] 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.[31] 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.[32] 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.[33] 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 highly 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.[30,31] 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.[34] 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,[35] family behavior therapy,[36] family support network intervention and community reinforcement approach counseling,[37] functional family therapy,[38] multidimensional family therapy,[39] and multisystemic therapy.[40] 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.[41] 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.[40] 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.[42,43] 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,[44] 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.[16–18,45] 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.[46,47] *Cannabis* users report that withdrawal symptoms adversely impact quit attempts, and report use of *cannabis* or other drugs to relieve these symptoms.[48,49] 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 CB_1 receptor. The primary psychoactive component of *cannabis*, Δ^9-tetrahydrocannabinol (Δ^9-THC), is a partial agonist of the CB_1 receptor and its reinforcing effects result from

activation of this receptor.[50] *Cannabis* use alters the functioning of several other neurotransmitter systems. Δ^9-THC and other CB_1 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 CB_1 receptor could impact *cannabis* use via multiple mechanisms. Agonist medications, those with similar neurobiological mechanisms of action as *cannabis* could 1) attenuate symptoms of withdrawal, 2) might blunt the reinforcing effects of *cannabis*, or 3) reduce cravings or urges for *cannabis* (i.e., substitution effect). Alternatively, CB_1 receptor antagonists, medications that block the receptor site but do not produce reinforcing effects, provide another viable pharmacological approach. Antagonists can reduce or prevent binding at the receptor site and thus suppress the reinforcing effects of *cannabis*. Another pharmacological approach has been to target pharmacological mechanisms different from that of *cannabis*, which could provide either withdrawal symptom relief, reduce the desire or liking of *cannabis*, or reduce conditions that might trigger *cannabis* use (e.g., depressed or anxious mood, sleep difficulties).

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.[51–58] 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 Δ^9-THC.[55] 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 CB_1 agonist, 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.[52,59,60] In one of these studies, dronabinol alone did not show positive effects in a laboratory analog model of relapse or *cannabis* self-administration.[59] 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-adrenergic receptor agonist, reduced the likelihood of "relapse" under these laboratory conditions. Two laboratory studies evaluating the partial CB_1 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.[61,62]

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.[63] 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.[64]

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.[65] 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.[66] Another randomized trial compared buspirone and placebo when combined with MET.[67] Some positive, but not robust *cannabis* use outcome effects were associated with buspirone, 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 buspirone with ten outpatients suggested that buspirone might reduce *cannabis* use and withdrawal symptoms, but adverse effects and a high drop out rate were also reported.[68] 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.[69] 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.[70] Last, an open label study of two patients prescribed dronabinol who had previously been unable to quit on their own reported sustained *cannabis* abstinence.[71] 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.[72] 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 CB_1 receptor.[72,73]

As reviewed above, one of these synthetic compounds, rimonabant, a CB_1 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 CB_1 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 CB_1 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 CB_1 agonists, partial CB_1 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.[72] 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 CB_1 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 cannabinioid 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. Cannabinioid 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.[22,74] 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 CB_1 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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References

1. Australian Institute of Health and Welfare. Alcohol and other drug treatment services in Australia 2005–06: report on the National Minimum Data Set. Canberra, AU: 2007.
2. UNODC. World Drug Report - 2009. Journal [serial on the Internet]. [cited 2009 Nov 30]. Available from: http://www.unodc.org/unodc/en/data-and-analysis/WDR-2009.html
3. SAMHSA. National Survey on Drug Use and Health. 2009. [cited 2009 Nov 30]. Available from: http://www.oas.samhsa.gov/nsduh.htm
4. EMCDDA. Annual report on the state of the drugs problem. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2008.
5. SAMHSA. Treatment Episode Data Set. 2009. [cited 2009 Nov 30]. Available from: http://www.oas.samhsa.gov/2k2/TEDS/TEDS.cfm
6. Budney AJ. Are specific dependence criteria necessary for different substances: how can research on cannabis inform this issue? Addiction. 2006; 101(Supl 1):125–33. [PubMed: 16930169]
7. Gruber AJ, Pope HG, Hudson JI, Yurgelun-Todd D. Attributes of long-term heavy cannabis users: a case control study. Psychol Med. 2003; 33(8):1415–22. [PubMed: 14672250]
8. Levin FR, Brooks DJ, Bisaga A, Raby W, Rubin E, Aharonovich E, Nunes EV. Severity of dependence and motivation for treatment: comparison of marijuana- and cocaine-dependent treatment seekers. J Addict Dis. 2006; 25(1):33–41. [PubMed: 16597571]
9. Stephens RS, Babor TF, Kadden R, Miller M. The Marijuana Treatment Project Research Group. The Marijuana Treatment Project: rationale, design, and participant characteristics. Addiction. 2002; 97(S1):109–24. [PubMed: 12460133]
10. Denis C, Lavie E, Fatseas M, Auriacombe M. Psychotherapeutic interventions for cannabis abuse and/or dependence in outpatient settings. Cochrane Database Syst Rev. 2006; 3
11. Budney AJ, Roffman R, Stephens RS, Walker D. Marijuana dependence and its treatment. Addict Sci Clin Pract. 2007; 4(1):4–16. [PubMed: 18292704]
12. Budney, AJ.; Moore, BA.; Sigmon, S.; Higgins, ST. Contingency-management interventions for cannabis dependence. In: Roffman, R.; Stephens, R., editors. Cannabis dependence: its nature, consequences, and treatment. Cambridge University Press; 2006. p. 155-76.
13. Copeland J. Developments in the treatment of cannabis use disorder. Curr Opin Psychiatry. 2004; 17:161–8.
14. McRae AL, Budney AJ, Brady KT. Treatment of marijuana dependence: a review of the literature. J Subst Abuse Treat. 2003; 24(4):369–76. [PubMed: 12867212]
15. Roffman, R.; Stephens, R., editors. Cannabis dependence: its nature, consequences, and treatment. Cambridge, UK: Cambridge University Press; 2006.
16. Nordstrom BR, Levin FR. Treatment of cannabis use disorders: a review of the literature. Am J Addict. 2007; 16(5):331–42. [PubMed: 17882603]
17. Benyamina A, Lecacheux M, Blecha L, Reynaud M, Lukasiewcz M. Phamacotherapy and psychotherapy in cannabis withdrawal and dependence. Expert Rev Neurotherapeutics. 2008; 8(3): 479–91.
18. Vandrey R, Haney M. Pharmacotherapy for cannabis dependence: how close are we? CNS Drugs. 2009; 23(7):543–53. [PubMed: 19552483]
19. Roffman RK, Barnhart R. Assessing need for marijuana dependence treatment through an anonymous telephone interview. Int J Addict. 1987; 22(7):639–51. [PubMed: 3497886]
20. Miller, WR.; Rollnick, S. Motivational interviewing: preparing people for change. 2. New York: Guilford Press; 2002.
21. Steinberg, KL.; Roffman, R.; Carroll, KM.; McRee, B.; Babor, TF.; Miller, M., et al. Department of Health and Human Services: Substance Abuse and Mental Health Services Administration. Brief counseling for marijuana dependence: a manual for treating adults. 2005.
22. Budney, AJ.; Stanger, C. Marijuana treatment. In: Higgins, ST.; Silverman, KS.; Heil, S., editors. Contingency management in substance abuse. New York: Guilford Press; 2007.
23. Stephens RS, Roffman RA, Simpson EE. Treating adult marijuana dependence: a test of the relapse prevention model. J Consult Clin Psychol. 1994; 62(1):92–9. [PubMed: 8034835]

24. 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]
25. Copeland J, Swift W, Roffman R, Stephens R. A randomized controlled trial of brief cognitive-behavioral interventions for cannabis use disorder. J Subst Abuse Treat. 2001; 21(2):55–64. [PubMed: 11551733]
26. Marijuana Treatment Project Research Group. Brief treatments for cannabis dependence: findings from a randomized multisite trial. J Consult Clin Psychol. 2004; 72(3):455–66. [PubMed: 15279529]
27. Jungerman FS, Andreoni S, Laranjeira R. Short term impact of same intensity but different duration interventions for cannabis users. Drug Alcohol Depend. 2007; 90(2–3):120–7. [PubMed: 17412530]
28. Stephens, RS.; Roffman, RA. College of problems of drug dependence. Orlando, FL: 2005. Marijuana dependence treatment PRN.
29. Budney AJ, Higgins ST, Radonovich KJ, Novy PL. Adding voucher-based incentives to coping-skills and motivational enhancement improves outcomes during treatment for marijuana dependence. J Consult Clin Psychol. 2000; 68(6):1051–61. [PubMed: 11142539]
30. Budney AJ, Moore BA, Rocha HL, Higgins ST. Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. J Consult Clin Psychol. 2006; 74(2):307–16. [PubMed: 16649875]
31. Kadden RM, Litt MD, Kabela-Cormier E, Petry NM. Abstinence rates following behavioral treatments for marijuana dependence. Addict Behav. 2007; 32(6):1220–36. [PubMed: 16996224]
32. Sinha R, Easton C, Renee-Aubin L, Carroll KM. Engaging young probation-referred marijuana-abusing individuals in treatment: a pilot trial. Am J Addict. 2003; 12(4):314–23. [PubMed: 14504024]
33. Carroll KM, Easton CJ, Nich C, Hunkele KA, Neavins TM, Sinha R, Ford HL, Vitolo SA, Doebrick CA, Rounsaville BJ. The use of contingency management and motivational/skills-building therapy to treat young adults with marijuana dependence. J Consult Clin Psychol. 2006; 74(5):955–66. [PubMed: 17032099]
34. Waldron HB, Turner CW. Evidence-based psychosocial treatments for adolescent substance abuse. J Clin Child Adolesc Psychol. 2008; 37(1):238–61. [PubMed: 18444060]
35. Szapocznik J, Kurtines WM, Foote FH, Perez-Vidal A, Hervis O. Conjoint versus one-person family therapy: some evidence for the effectiveness of conducting family therapy through one person. J Consult Clin Psychol. 1983; 51(6):889–99. [PubMed: 6655103]
36. Azrin NH, Donohue B, Besalel VA, Kogan ES, Acierno R. Youth drug abuse treatment: a controlled outcome study. J Child Adolesc Subst Abuse. 1994; 3(3):1–16.
37. Dennis M, Godley SH, Diamond G, Tims FM, Babor T, Donaldson J, Liddle H, Titus JC, Kaminer Y, Webb C, Hamilton N, Funk R. The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials. J Subst Abuse Treat. 2004; 27(3):197–213. [PubMed: 15501373]
38. Waldron HB, Slesnick N, Brody JL, Turner CW, Peterson TR. Treatment outcomes for adolescent substance abuse at 4- and 7- month assessments. J Consult Clin Psychol. 2001; 69(5):802–13. [PubMed: 11680557]
39. Liddle HA, Rowe CL, Dakof GA, Henderson CE, Greenbaum PE. Multidimensional family therapy for young adolescent substance abuse: twelve-month outcomes of a randomized controlled trial. J Consult Clin Psychol. 2009; 77(1):12–25. [PubMed: 19170450]
40. Henggeler SW, Halliday-Boykins CA, Cunningham PB, Randall J, Shapiro SB, Chapman JE. Juvenile drug court: enhancing outcomes by integrating evidence-based treatments. J Consult Clin Psychol. 2006; 74(1):42–54. [PubMed: 16551142]
41. Godley MD, Godley SH, Dennis ML, Funk RR, Passetti LL. The effect of assertive continuing care on continuing care linkage, adherence and abstinence following residential treatment for adolescents with substance use disorders. Addiction. 2007; 102(1):81–93. [PubMed: 17207126]
42. Kamon JL, Budney AJ, Stanger C. A contingency management intervention for adolescent marijuana abuse and conduct problems. J Am Acad Child Adolesc Psychiatry. 2005; 44(6):513–21. [PubMed: 15908833]

43. Stanger C, Budney AJ, Kamon JL, Thostensen J. A randomized trial of contingency management for adolescent marijuana abuse and dependence. Drug Alcohol Depend. 2009; 105(3):240–7. [PubMed: 19717250]
44. Godley SH, Godley MD, Wright KL, Funk RR, Petry NM. Contingent reinforcement of personal goal activities for adolescents with substance use disorders during post-residential continuing care. Am J Addict. 2008; 17(4):278–86. [PubMed: 18612882]
45. Hart CL. Increasing treatment options for cannabis dependence: a review of potential pharmacotherapies. Drug Alcohol Depend. 2005; 80(2):147–59. [PubMed: 15899556]
46. Budney AJ, Hughes JR. The cannabis withdrawal syndrome. Curr Opin Psychiatry. 2006; 19(3): 233–8. [PubMed: 16612207]
47. Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry. 2004; 161(11):1967–77. [PubMed: 15514394]
48. Budney AJ, Vandrey RG, Hughes JR, Thostenson JD, Bursac Z. Comparison of cannabis and tobacco withdrawal: Severity and contribution to relapse. J Subst Abuse Treat. 2008; 35(4):362–8. [PubMed: 18342479]
49. Copersino ML, Boyd SJ, Tashkin DP, Huestis MA, Heishman SJ, Dermand JC, Simmons MS, Gorelick DA. Cannabis withdrawal among non-treatment-seeking adult cannabis users. Am J Addict. 2006; 15(1):8–14. [PubMed: 16449088]
50. Cooper ZD, Haney M. Actions of delta-9-tetrahydrocannabinol in cannabis: relation to use, abuse, dependence. Int Rev Psychiatry. 2009; 21(2):104–12. [PubMed: 19367504]
51. Haney M, Ward AS, Comer SD, Hart CL, Foltin RW, Fischman MW. Bupropion SR worsens mood during marijuana withdrawal in humans. Psychopharmacology (Berl). 2001; 155(2):171–9. [PubMed: 11401006]
52. Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubaran C, Fohin RW. Marijuana withdrawal in humans: effects of oral THC or divalproex. Neuropsychopharmacology. 2004; 29(1):158–70. [PubMed: 14560320]
53. Haney M, Hart CL, Ward AS, Foltin RW. Nefazodone decreases anxiety during marijuana withdrawal in humans. Psychopharmacology (Berl). 2003; 165(2):157/65. [PubMed: 12439626]
54. Cone EJ, Welch P, Lange WR. Clonidine partially blocks the physiologic effects but not the subjective effects produced by smoking marijuana in male human subjects. Pharmacol Biochem Beh. 1988; 29(3):649–52.
55. Haney M. Opioid antagonism of cannabinoid effects: differences between marijuana smokers and nonmarijuana smokers. Neuropsychopharmacology. 2007; 32(6):1391–403. [PubMed: 17091128]
56. 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]
57. 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):251–60. [PubMed: 10812285]
58. Hart CL, Haney M, Ward AS, Fischman MW, Foltin RW. Effects of oral THC maintenance on smoked marijuana self-administration. Drug Alcohol Depend. 2002; 67(3):301–9. [PubMed: 12127201]
59. Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Foltin RW. Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. Psychopharmacology (Berl). 2008; 197(1):157–68. [PubMed: 18161012]
60. Budney AJ, Vandrey RG, Hughes JR, Moore BA, Bahrenburg B. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. Drug Alcohol Depend. 2007; 86(1):22–9. [PubMed: 16769180]
61. Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, Frank RA. Blockade of effects of smoked marijuana by the CB1-sective cannabinoid receptor antagonist SR141716. Arch Gen Psychiatry. 2001; 58(4):322–8. [PubMed: 11296091]
62. Huestis MA, Boyd SJ, Heishman SJ, Preston KL, Bonnet D, Le Fur G, Gorelick DA. Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users. Psychopharmacology (Berl). 2007; 194(4):505–15. [PubMed: 17619859]

63. Vandrey, R.; McCann, U.; Smith, M.; Budney, AJ. Sleep dysfunction during cannabis withdrawal. Annual Scientific Meeting of the College on Problems of Drug Dependence; 2009; Reno, NV. 2009.
64. Haney, M. Role of withdrawal in relapse to marijuana use. Annual Scientific Meeting of the College on Problems of Drug Dependence; Reno, NV. 2009.
65. Levin FR, McDowell D, Evans SM, Nunes E, Akerele E, Donovan S, Vosburg SK. Pharmacotherapy for marijuana dependence: a double-blind, placebo-controlled pilot study of divalproex sodium. Am J Addict. 2004; 13(1):21–32. [PubMed: 14766435]
66. Carpenter KM, McDowell D, Brooks DJ, Cheng WY, Levin FR. A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. Am J Addict. 2009; 18(1):53–64. [PubMed: 19219666]
67. McRae-Clark AL, Carter RE, Killeen TK, Carpenter MJ, Wahlquist AE, Simpson SA, Brady KT. A placebo-controlled trial of buspirone for the treatment of marijuana dependence. Drug Alcohol Depend. 2009; 105(1–2):132–8. [PubMed: 19699593]
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. 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]
70. Bowen R, McIlwrick J, Baetz M, Zhang X. Lithium and marijuana withdrawal. Can J Psychiatry. 2005; 50(4):240–1. [PubMed: 15898465]
71. Levin FR, Kleber HD. Use of dronabinol for cannabis dependence: two case reports and review. Am J Addict. 2008; 17(2):161–4. [PubMed: 18393061]
72. Clapper JR, Mangieri RA, Piomelli D. The endocannabinoid system as a target for the treatment of cannabis dependence. Neuropharmacology. 2009; 56 (Suppl 1):235–43. [PubMed: 18691603]
73. Janero DR, Vadivel SK, Makriyannis A. Pharmacotherapeutic modulation of the endocannabinoid signalling system in psychiatric disorders: drug-discovery strategies. Int Rev Psychiatry. 2009; 21(2):122–33. [PubMed: 19367506]
74. Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. Addiction. 2006; 101(2):192–203. [PubMed: 16445548]
75. Kirby KC, Benishek LA, Dugosh KL, Kerwin ME. Substance abuse treatment providers' beliefs and objections regarding contingency management: implications for dissemination. Drug Alcohol Depend. 2006; 85(1):19–27. [PubMed: 16650657]
76. Ritter A, Cameron J. Australian clinician attitudes towards contingency management: comparing down under with America. Drug Alcohol Depend. 2007; 87(2–3):312–5. [PubMed: 16971057]
77. McLellan AT, Carise D, Kleber HD. Can the national addiction treatment infrastructure support the public's demand for quality care? J Subst Abuse Treat. 2003; 25(2):117–21. [PubMed: 14680015]
78. Carroll KM, Rounsaville BJ. A vision of the next generation of behavioral therapies research in the addictions. Addiction. 2007; 102(6):850–62. [PubMed: 17523974]
79. Tirado CF, Goldman M, Lynch K, Kampman KM, Obrien CP. 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):254–7. [PubMed: 18182254]

Table 1

Randomized trials of psychosocial treatments for *cannabis* use disorders (adults)

CBT[23]	CBT vs Social Support	Significant reductions in *cannabis* use, but no differences between groups.
CBT, MET[24]	14-session CBT vs 2-session MET vs DTC	CBT and MET produced superior *cannabis* outcomes than DTC. No differences between CBT and MET.
MET/CBT[25]	6-session MET/CBT vs 1-session MET/CBT vs DTC	MET/CBT produced superior *cannabis* outcomes than DTC; no differences between active conditions
MET/CBT[26]	Multi-site, 9-session MET/CBT vs 2-session MET vs DTC	MET/CBT and MET produced superior *cannabis* outcomes than DTC; 9-session MET/CBT produced superior outcomes than MET.
MET/CBT[27]	1-month MET/CBT vs 4-month MET/CBT vs DTC	Both MET/CBT groups produced superior *cannabis* outcomes than DTC; longer duration MET/CBT marginally superior to shorter duration.
MET/CBT[28]	4-session MET/CBT + PRN sessions vs 9-session MET/CBT	No differences between treatment groups
CM[29]	MET vs MET/CBT vs MET/CBT/CM	MET/CBT/CM produced greater *cannabis* abstinence than MET or MET/CBT.
CM[30]	MET/CBT vs MET/CBT/CM vs CM	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.
CM[31]	MET/CBT vs MET/CBT/CM vs DC vs DC/CM	Both CM conditions produced superior abstinence outcomes. MET/CBT/CM showed the highest rates of abstinence at later post-treatment follow-ups.
CM[32]	MET vs MET/CM	CM enhanced treatment attendance, did not affect *cannabis* use. Note that CM targeted attendance and not abstinence
CM[33]	MET/CBT vs. MET/CBT/CM vs CM vs. Case Management	CM enhanced treatment retention and *cannabis* abstinence, with MET/CBT/CM producing the best *cannabis* outcomes.

Table 2

Studies of potential medications for *cannabis* use disorders

Medication	Mechanism of action	Study type/Results
Atomoxetine[79]	norepinephrine reuptake inhibitor	Open label trial/No effect on *cannabis* use, gastrointestinal side effects.
Bupropion[51,66]	norepinephrine and dopamine reuptake inhibitor	Lab study/Exacerbated withdrawal but reduced effects of *cannabis.* Randomized clinical trial/No effects on withdrawal or *cannabis* use.
Buspirone[67,68]	serotonin 5HT receptor partial agonist	Open label trial/Reduced *cannabis* use, craving, and irritability but high drop out. Randomized clinical trial/No effects on *cannabis* use and high drop out.
Clonidine[54]	a_2 adrenergic agonist	Lab study/Reduced tachycardia, but not subjective effects of *cannabis.*
Divalproex[52,65]	unknown	Randomized clinical trial/No effect on *cannabis* use. Lab study/Exacerbated withdrawal and increased subjective effects of *cannabis.*
Dronabinol[52,58–60,71]	CB_1 receptor agonist	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 "relapse". Open label trial/Associated with *cannabis* abstinence.
Lithium[69,70]	unknown	Open label trials (2)/Associated with reduced withdrawal and *cannabis* use.
Lofexedine[59]	a_2 adrenergic agonist	Lab study/Alone and in combination with dronabinol, reduced withdrawal and "relapse".
Naltrexone[55–57]	mu-opioid receptor antagonist	Lab studies/Variable, but mostly negative impact on subjective effects of *cannabis*; dose and history of subjects may moderate effects.
Nefazodone[53,66]	norepinephrine and serotonin reuptake inhibitor, $5HT_2$ receptor antagonist	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.
Rimonabant[61,62]	cannabinoid CB_1 receptor antagonist	Attenuated subjective and physiological effects of *cannabis* in laboratory studies. Reduced *cannabis* use in small open-label clinical study. Side effect concerns.