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Pharmacotherapy for Cannabis Dependence: How Close Are We?

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Abstract

Cannabis is the most widely used illicit drug in the world. Treatment admissions for cannabis use disorders have risen considerably in recent years, and the identification of medications that can be used to improve treatment outcomes among this population is a priority for researchers and clinicians. To date, several medications have been investigated for indications of clinically desirable effects among cannabis users (e.g. reduced withdrawal, attenuation of subjective or reinforcing effects, reduced relapse). Medications studied have included those 1) known to be effective in the treatment of other drug use disorders, 2) known to alleviate symptoms of cannabis withdrawal (e.g. dysphoric mood, irritability), or 3) that directly affect endogenous cannabinoid receptor function. Results from controlled laboratory studies and small open-label clinical studies indicate that buspirone, dronabinol, fluoxetine, lithium, lofexedine, and rimonabant may have therapeutic benefit for those seeking treatment for cannabis-related problems. However, controlled clinical trials have not been conducted and are needed to both confirm the potential clinical efficacy of these medications and to validate the laboratory models being used to study candidate medications. While the recent increase in research towards the development of pharmacotherapy for cannabis use disorders has yielded promising leads, the published research conducted to date is not sufficient to support broad clinical use of these medications to treat cannabis-use disorders.

Introduction

Cannabis (also known as marijuana or hashish) is obtained from the plant *Cannabis sativa*. Cannabis contains many psychoactive compounds that affect the endogenous cannabinoid receptor system, of which delta-9-tetrahydrocannabinol (THC) has been identified as the compound primarily responsible for the subjective “high” experienced by users [1]. The acute effects of cannabis include subjective feelings of euphoria, relaxation, dream-like state, altered sensory perception, slowing of time, anxiety/paranoia, and increased appetite. Cannabis also increases heart rate and, in rare instances, can induce hallucinations or psychosis.

THC is a partial agonist of the CB1 receptor, a G-protein-coupled receptor that is expressed in the brain at the highest concentrations in the basal ganglia (motor control), cerebellum (sensorimotor coordination), hippocampus (memory), and cortex (higher-order cognition) [2]. Like most, if not all, addictive drugs, exposure to psychoactive cannabinoids stimulates brain-reward areas and can induce appetitive drug-seeking and drug-taking behaviors. Evidence of these effects include studies in which exposure to cannabis increased dopamine (DA) release in the mesolimbic-dopamine reward pathway, enhanced electrical brain-

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stimulation reward, established conditioned place preference, and established drug self-administration [3]. Similarly, abrupt cessation of chronic cannabinoid exposure produces cellular changes in the brain reward pathway (increased corticotropin releasing factor, decreased DA) that have been linked to the dysphoric effects associated with withdrawal from drugs such as alcohol, opiates, and cocaine, and are thought to contribute to relapse [4,5]. Recognizing that cannabis shares neurobiological features associated with dependence on other drugs is important when considering pharmacological treatment of cannabis-use disorders.

The rationale for developing pharmacological treatments for cannabis-use disorders is clear. There are an estimated 160 million current cannabis users world wide, and the number of people who meet criteria for cannabis dependence exceeds that for dependence on any other illicit drug [6]. Treatment admissions for cannabis-use disorders in many areas have steadily increased in the past decade, including a two-fold increase in the U.S. and three-fold increases in Australia and Europe [7-9]. Clinical trials have demonstrated that evidence-based psychosocial interventions (e.g. Motivational Enhancement, Contingency Management, Cognitive-Behavior Therapy) result in overall improved clinical outcomes compared with usual care or delayed-control conditions [10,11]. However, as is common with other drugs (e.g. opiates, cocaine, nicotine), adults and adolescents seeking treatment for cannabis-related disorders have great difficulty achieving and sustaining periods of abstinence: the majority relapsing to use following therapeutic interventions [12-21]. Thus, there exists a clear need for the development and dissemination of interventions that improve clinical outcomes (e.g. reduced use/abstinence, fewer drug-related problems) for the increasing number of those seeking treatment for their cannabis use.

One method of improving clinical outcomes for patients seeking treatment for cannabis-use disorders is to identify medications that exhibit clinical benefit and could be added to existing evidence-based psychosocial treatments. There is evidence that a combination of pharmacotherapy and psychosocial therapy can significantly improve treatment outcomes relative to psychosocial treatments alone [22-24]. Pharmacotherapy medications can aid in the treatment of drug dependence in several ways. One approach is to identify medications that attenuate symptoms of withdrawal. This can be achieved with agonist/substitute medications (e.g. nicotine patch for tobacco dependence, methadone for opiate dependence), or by use of medications known to alleviate specific withdrawal symptoms (e.g. clonidine for sweating, GI disturbance, and hypertension during opiate withdrawal). Another approach for pharmacotherapy is the use of medications that attenuate the reinforcing effects of the target drug. One way this can be done is by directly blocking the receptor with an antagonist (e.g. naltrexone for opiate dependence) or partial agonist (e.g., buprenorphine for opiate dependence). A third approach is the use of medications that induce adverse effects when combined with the drug of dependence (e.g. disulfiram induces nausea when combined with alcohol).

There are currently no accepted pharmacological treatment interventions for cannabis use disorders. Identification of such medications is an increasing priority among researchers and clinicians working with cannabis users and has been addressed in a number of recent papers. Below, we review the extant research investigating medications of potential therapeutic efficacy for the treatment of cannabis dependence. Due to space constraints and the clinical focus of this review, preclinical laboratory studies will not be covered, but can be found in other reviews [25-27]. Areas of focus will include human laboratory studies, clinical case reports and small open-label trials, and controlled clinical trials. This paper will complement and extend previous reviews on the topic [10,11,25,28].

Human Laboratory Studies

Attenuation of withdrawal symptoms

Research dating back to the 1970s provides clear evidence that a valid and reliable cannabis withdrawal syndrome occurs. Common symptoms of withdrawal in humans include: anger and aggression, anxiety, depressed mood, irritability, restlessness, sleep difficulty and strange dreams, decreased appetite, and weight loss [29,30]. Chills, headaches, physical tension, sweating, stomach pain, and general physical discomfort have also been observed during cannabis withdrawal, but are less common [29]. Most symptoms begin within the first 24 hours of cessation, peak within the first week, and last approximately 1-2 weeks [31-33]. Because there is evidence that cannabis withdrawal contributes to the high relapse rates among heavy cannabis users [30,34-36], amelioration of cannabis withdrawal symptoms may be an important target for the development of pharmacological treatment interventions for heavy cannabis users.

Much of the current research in humans has been conducted by a group of researchers at Columbia University in the U.S. There, an inpatient human laboratory model was designed to characterize the effects of medications on the consequences of abstinence from cannabis (e.g. withdrawal symptoms). Research volunteers who smoked cannabis multiple times per day and who were not seeking treatment for their cannabis use were enrolled in a series of studies investigating several medications. Participants smoked cannabis (active or placebo) and received oral medication (active or placebo) each day under double blind conditions. The protocol used a within-subjects crossover design so that each participant received each active and placebo combination of cannabis. Further, most of the laboratory studies administered medication repeatedly each day until steady-state levels were attained prior to assessing the effects of marijuana. The effect of receiving placebo versus active medication during the periods of cannabis abstinence (placebo cannabis) was then evaluated. Outcome variables included round-the-clock data on mood and physical symptoms, psychomotor task performance, food intake, social behavior and sleep.

Medications investigated in this model to date have been bupropion, divalproex, nefazodone, lofexidine, and dronabinol. Buproprion is used clinically as an antidepressant and for smoking cessation, and is thought to exert clinical effects by inhibiting reuptake of NE and DA, and possibly by acting as a nicotine receptor antagonist [37]. Divalproex is used clinically as a mood stabilizer as well as to treat epilepsy and migraine headaches. Divalproex dissociates valproate ions in the GI tract, and, though uncertain, clinical effects are thought to be mediated by increased GABA concentrations in the CNS [38]. Nefazodone is an antidepressant and is believed to operate by blocking post-synaptic 5HT-2a receptors and, to a lesser extent, by inhibiting pre-synaptic 5HT and NE reuptake [39]. Lofexidine is used to treat symptoms of opiate withdrawal and acts as an agonist at the alpha2-adrenergic receptor [40]. Dronabinol is used clinically as an antiemetic and appetite stimulant, and is a partial agonist of cannabinoid CB1 receptor [41].

In laboratory studies using the methods described above, administration of bupropion (0, 300 mg/day for 17 days) and divalproex (0, 1500 mg/day for 29 days) during periods of cannabis abstinence significantly worsened mood compared with placebo [42,43]. Nefazodone (0, 450 mg/day for 26 days) significantly decreased ratings of anxiety and muscle pain during abstinence, but did not alter other essential features of cannabis withdrawal [44]. Lofexidine (2.4 mg/day for 8 days) significantly reduced ratings of chills, restlessness and upset stomach, and improved sleep, but was associated with increased sedation during the day [45].

Not surprisingly, the medication that has demonstrated the most clinical potential in reducing cannabis withdrawal has been dronabinol. Dronabinol is a synthetic formulation of THC, the

primary psychoactive component in cannabis. In that regard it is similar to using nicotine replacement products to suppress withdrawal during tobacco abstinence. In one study by the Columbia University researchers, dronabinol (10 mg, 5 times/day for 6 days) significantly decreased ratings of cannabis craving, anxiety, misery, chills, self-reported sleep disturbance, and reversed the anorexia and the weight loss associated with cannabis withdrawal [43]. This attenuation of withdrawal symptoms occurred even though participants in this study were unable to reliably distinguish dronabinol from placebo. In a follow-up study, dronabinol administered at a higher dose and less frequently (20 mg, 3 times/day for 8 days) again decreased ratings of restless and chills and reversed anorexia, but was associated with significant increases in drug effect, drug liking, irritability, and latency to sleep compared with placebo [45]. In this same study, however, a combination of dronabinol (20 mg, 3 times/day) and lofexidine (2.4 mg/day) decreased ratings of restless, chills, craving, and upset stomach and improved multiple measures of sleep, but also increased sedation during the day and drug effect ratings.

The effects of dronabinol (0, 10, and 30 mg, 3 times/day for 15 days) on cannabis withdrawal were also recently reported in an outpatient study of daily cannabis users not seeking treatment [46]. Dronabinol dose-dependently decreased withdrawal during 5-day periods of abstinence while participants were in their home environment. Compared with placebo, the 10 mg dose reduced participant ratings of aggression, craving, irritability, sleep difficulty, and total withdrawal. Though withdrawal was attenuated at the 10 mg dose, it remained significantly elevated compared with a baseline period when participants smoked cannabis as usual. When participants received the 30 mg dose, withdrawal symptom severity was significantly reduced compared with both the placebo and 10 mg conditions, and, more importantly, none of the withdrawal symptom ratings differed from the cannabis-as-usual baseline condition indicating a maximum therapeutic effect at this dose. Consistent with the initial study described above [43], the 10 mg dose regimen was not associated with increased ratings of intoxication and was not reliably distinguished from placebo. However, the 30 mg dose was distinguished from placebo by all participants and resulted in significantly increased drug effect ratings.

Attenuation of subjective and reinforcing effects

Laboratory studies have also investigated the ability of medications to reduce the acute effects of smoked cannabis or orally administered THC. In one experiment, pretreatment with the cannabinoid (CB1) receptor antagonist rimonabant significantly attenuated the physiological and subjective effects of smoked cannabis administered 2 hours later [47,48]. Acute administration of 90 mg rimonabant reduced participant ratings of the strength and liking of the smoked cannabis by approximately 40% and reduced cannabis-induced tachycardia by 59%. In a subsequent study, acute rimonabant (90 mg) again reduced cannabis-induced tachycardia, but an attenuation of subjective drug effects was not replicated [49]. In this same study, repeated daily doses of rimonabant (40 mg/day) administered for 15 consecutive days to a second group of participants reduced cannabis-induced tachycardia following acute cannabis administration on Days 8 and 15. The subjective effects of cannabis were also reduced by rimonabant in this group, but that reduction was only significantly different from placebo on Day 8 and not Day 15.

Studies have also investigated whether the mu-opioid receptor antagonist naltrexone, which has been shown to decrease cannabinoid self-administration in nonhumans [50], [51], can reduce the subjective effects of cannabinoids in humans. In cannabis users, pretreatment with high doses of naltrexone (50-200 mg) failed to attenuate or enhanced the subjective effects of dronabinol [52,53] and smoked cannabis [54]. By contrast, a lower, more opioid-selective dose of naltrexone (12 mg) decreased the intoxicating effects of 20 mg but not 40 mg of dronabinol in a recent study [55]. These findings indicate that the influence of naltrexone on cannabinoid

effects may vary as a function of naltrexone dose, but also that the effect of naltrexone can be overcome with higher doses of cannabis.

The effect of dronabinol on the subjective and reinforcing effects of smoked cannabis has also been investigated [56]. Participants received 0, 10, or 20 mg dronabinol, 4 times per day, for three consecutive days. Each day, participants sampled the dose of cannabis cigarette available that day and were then given 4 choices to smoke that dose of cannabis or receive a voucher worth $2 that would be added to their study earnings. Subjective drug effect ratings were obtained following the sample dose of cannabis under each dronabinol dose condition. Dronabinol attenuated the subjective effects of smoked cannabis, but did not affect the choice to smoke cannabis (reinforcing effects). Of note, the competing reinforcer, a voucher worth $2, may not have been sufficiently sensitive to detect changes in cannabis reinforcing efficacy. Also, each dronabinol dose condition only lasted for three days, whereas more time may be needed to see an effect of maintenance medication. Thus, more data are needed to determine whether dronabinol disrupts ongoing cannabis use.

The subjective effects of cannabis have also been evaluated in single studies for several other medications. In a small laboratory study, 0.4 mg clonidine (alpha$_2$ receptor agonist; opiate withdrawal medication) administered 3 hours prior to smoked cannabis reduced cannabis-induced tachycardia, but did not reduce subjective effects [57]. Bupropion (300 mg) decreased ratings of “high” following smoked cannabis, but, as described above, this dose also exacerbated withdrawal effects during a period of abstinence [42]. In two other laboratory studies described above [43] [44] the subjective effects of smoked cannabis were not altered by nefazodone (450 mg), and were increased following administration of divalproex (1500 mg).

Relapse Prevention

In one recent study, relapse was modeled in non-treatment seekers by structuring laboratory conditions (charging participants $10 for a single initial puff of cannabis) so that a return to cannabis use was costly [45]. The effect of dronabinol (20 mg, 3 times/day) and lofexidine (2.4 mg/day) were evaluated both when administered alone and when administered together. In this study, neither dronabinol nor lofexidine alone reduced the number of participants who elected to smoke any amount of cannabis compared with placebo during a 4-day maintenance period, but the combination of the two drugs doubled the rate of complete abstinence (25% abstinent for each medication alone, 50% for the combination). Compared with the dronabinol alone condition, the average amount of money spent per day on cannabis was reduced in both the lofexidine alone and the combined medication conditions.

Case Reports and Small Open-Label Studies

Several studies have investigated the efficacy of potential treatment medications for cannabis dependence in small clinical samples. One recent open-label study investigated atomoxetine as a potential pharmacotherapy in adults presenting for treatment of cannabis dependence [58]. Atomoxetine is a non-stimulant medication that inhibits NE reuptake, and is used to treat ADHD [59]. Thirteen participants received atomoxetine (25 - 80 mg/day; mean 62 mg/day) for 11 weeks. A non-significant reduction in cannabis use was observed, however, several adverse events were reported by a majority of participants, including clinically significant GI problems in 77% of participants. Two participants withdrew from the study due to these adverse effects.

An open-label investigation was also conducted with the anxiolytic medication buspirone, a 5HT-1a agonist and DA$_2$ mixed agonist/antagonist [60]. Ten treatment-seeking cannabis users received buspirone (up to 60 mg/day; mean 39 mg/day) for up to 12 weeks. Self-reported

cannabis use declined from use on 73% of days prior to treatment to use on 39% of days during treatment, and 44% of urine drug screens conducted during treatment were negative for cannabis (100% positive at intake). Significant decreases in craving and irritability during treatment were also observed. However, several adverse events were reported during the trial and only 2 participants completed the entire 12-week study.

Following a preclinical study showing that lithium, a mood stabilizer that enhances oxytocin expression, attenuated cannabis withdrawal in rats [61], two small open-label clinical studies have been conducted. In one study, lithium was administered to 9 adults presenting for treatment of cannabis dependence [62]. All participants indicated that previous quit attempts resulted in significant withdrawal and that abstinence failed to extend beyond a few days or weeks. Lithium (600 to 900 mg/day) was administered for 6 days and resulted in reduced withdrawal in 4 of the 9 participants. However, cannabis was admittedly smoked during this period by one of these 4 participants and cannabis abstinence was not verified in the others. In the second study, 20 cannabis dependent participants received lithium (500 mg 2x/day) for 7 days in an inpatient detoxification facility [63]. Twelve participants (60%) completed the 7-day inpatient detoxification (2 removed due to adverse events). Cannabis abstinence at post-treatment follow-up sessions was 64% (Day 10), 65% (Day 24), and 41% (Day 90). Participants also self-reported cannabis abstinence on 88% of days post-treatment with 5 participants reporting continuous abstinence that was corroborated with urine toxicology tests on Day 90.

To date, the only published report in which dronabinol has been used clinically to treat cannabis dependence is a paper describing 2 case studies [64]. In both cases, the patients used cannabis daily and had repeatedly failed in prior quit attempts. Dronabinol was started at 30 mg (10 mg, 3 times/day) and then adjusted in both cases. Both patients were able to achieve sustained periods of abstinence, however, adjunct medications were required (divalproex for Case 1 and venlafaxine in Case 2). In Case 1, the patient was successfully tapered off dronabinol without relapse. In Case 2, removal of dronabinol resulted in either relapse or heavy alcohol use. This patient continued using dronabinol (5 mg, 2-3 times/day) as a maintenance medication.

A case report has also been published in which the atypical antipsychotic medication quetiapine was administered to 8 cannabis-dependent patients with a diagnosis of either schizophrenia or bipolar disorder [65]. Following mean quetiapine administration of 388 mg (range 100 - 1200 mg) for an average of approximately 6 months, cannabis use in these 8 patients was reported as being reduced from an average of 35.6 g/week to 1.1 g/week. Concomitant medications administered during the quetiapine treatment period included unspecified antidepressants (N=4), gabapentin (N=2), and methadone (N=1). It is unclear from the report whether cannabis use rates were verified via objective measures (e.g. urine toxicology), or if the medication was well tolerated by all patients who received it.

Clinical Trials

At this time, there is only one published controlled clinical trial in which a medication was tested for efficacy in participants presenting for treatment where cannabis dependence was the primary problem [66]. In this double blind trial, 25 participants were randomized to receive divalproex (500 to 2000 mg/day; mean 1673 mg/day) or placebo for 6 weeks, and were then crossed over to the opposite medication condition. Participants also received weekly relapse prevention counseling throughout the study. Cannabis use was assessed via self-report and quantitative urine testing. An overall reduction of cannabis use was reported, but few urine drug screens were free of cannabis suggesting that sustained abstinence was not achieved. There was no effect of divalproex compared with placebo on any cannabis use measures. Adverse events related to divalproex were common, resulted in discontinuation for 3 participants, and overall medication compliance was poor.

One other controlled clinical trial has been published in which cannabis use was measured following administration of medication, but in this study participants represented a sub-group of participants in a larger trial for the treatment of alcoholism and depression primary to their cannabis dependence [67]. Following a brief inpatient detoxification, participants were randomly assigned to receive 20-40 mg/day of fluoxetine (an SSRI used to treat depression) or placebo for 12 weeks (n = 11 per group). Compared with placebo, those who received fluoxetine reported using less cannabis, using cannabis on fewer days, drinking less alcohol, and greater decrease in ratings of depression. No objective measures of substance use were obtained to verify the self-reports in this study, and it is unclear whether the decrease in cannabis use was mediated by reductions in alcohol use or depression.

Conclusion

Efforts to identify medications that can improve treatment outcomes for cannabis use disorders have increased considerably in recent years, but still lag far behind the medications development efforts for treating dependence on other drugs (e.g. alcohol, cocaine, opiates). Most of the current research is limited to laboratory models and small open-label trials with only one published controlled clinical trial (compared with dozens or hundreds of controlled pharmacotherapy trials for treating dependence on alcohol, cocaine, nicotine, and opiates). The laboratory studies described above all employed cannabis users who were not trying to reduce or quit their cannabis use. Although it is possible that this limits the generality of these studies [68], it is important to point out that for drugs such as cocaine and heroin, the validity of human laboratory studies of self-administration for predicting medication efficacy in the clinic is better than most other models, including open-label clinical studies, which are often characterized by a high number of false positives [69]. That said, controlled clinical trials for cannabis dependence are clearly needed, not only to determine the efficacy of candidate medications, but also to evaluate the predictive validity of the laboratory models being used.

At this point several medications studied appear to warrant further investigation. Dronabinol has been the most extensively studied and appears to be the strongest candidate medication to date. Studies have indicated several clinically important effects of dronabinol (reduction of withdrawal and effects of smoked cannabis, and relapse prevention when combined with lofexidine, divalproex, or venlafaxine). Moreover, agonist medications have demonstrated efficacy in the treatment of tobacco and opioid dependence. Replication in controlled clinical trials is needed (two placebo-controlled trials are currently being conducted in patients specifically seeking treatment for their marijuana use). Further, while extant research and clinical use does not indicate great risk with regards to safety or abuse liability/diversion of dronabinol [70], the population seeking treatment for cannabis dependence (many adolescents, extensive drug use histories, and preference for cannabinoid self-administration) may present unique safety and abuse liability/diversion concerns not yet encountered. Thus, additional research will be needed to assess the safety and abuse liability/diversion of dronabinol in addiction treatment settings.

The cannabinoid antagonist rimonabant reduced the effects of smoked cannabis in two studies, but a reduction of subjective drug effects was not consistently observed. Additional research is needed to investigate the dose-effects of this antagonism and whether it translates to clinically meaningful behavior change (reduced use or relapse prevention). Also to consider for rimonabant are the concerns that antagonist medications usually require a period of abstinence prior to use (to avoid precipitated withdrawal), medication compliance with antagonists is generally poor, and rimonabant has been associated with an increased risk for adverse psychiatric side effects in clinical trials for other medical indications [71,72].

That administration of fluoxetine was associated with reduced cannabis use among depressed alcoholics suggests therapeutic potential. Replication of this effect is needed in either laboratory or clinical studies in which cannabis is the primary drug of abuse among participants. Initial studies of buspirone, lithium, lofexedine, and quetiapine have also indicated promise, but the research completed to date is limited by small sample sizes and lack of placebo control conditions in the open-label studies. The occurrence of side effects may also be limiting in the use of these medications.

In conclusion, the need for identifying medications to improve treatment outcomes for cannabis dependence is clear. Medications should be used in conjunction with evidence-based psychosocial treatments to maximize clinical benefit, and some combination of multiple medications may be needed to achieve sustained abstinence in more severe cases [64]. At this time, while it does not appear that we are close to the broad use of pharmacotherapies for cannabis dependence, several promising candidate medications have been identified. Continued research studies, particularly controlled clinical trials, are obviously needed for the medications that have demonstrated promise to date. Moreover, there are a number of compounds (e.g. second generation cannabinoid antagonists, FAAH inhibitors) for which preclinical data indicate potential for treating cannabis-use disorders once approved for research in humans. It will be important for scientists and clinicians to continue to investigate these and other medications that could reasonably be considered to have therapeutic potential for treating cannabis use disorders.

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Summary of medications tested for therapeutic benefit in cannabis users.

Medication Tested	Current Indication	Mechanism of Action	Published articles	Outcome
atomoxetine	ADHD	norepinephrine reuptake inhibitor	Tirado et al., 2008	No effect on cannabis use, concerning side effects (GI)
buproprion	depression, smoking cessation	norepinephrine and dopamine reuptake inhibitor	Haney et al., 2001	Reduced effects of smoked cannabis, but exacerbated cannabis withdrawal symptoms
buspirone	anxiety	serotonin $5HT_{1A}$ receptor partial agonist	McRae et al., 2006	Reduced cannabis use, craving, and irritability, but only 2 of 10 participants completed 12-week trial
clonidine	hypertension, opiate dependence	α_2 adrenergic agonist	Cone et al., 1988	Reduced tachycardia, but not subjective effects
divalproex	bipolar disorder, epilepsy, migraines	unknown	Haney et al., 2004 Levin et al., 2004	No effect on cannabis use; increased withdrawal and effects of smoked cannabis
dronabinol	nausea/vomiting, excessive weight loss associated with AIDS wasting	cannabinoid CB1 receptor agonist	Budney et al., 2007 Haney et al., 2004, 2007 Hart et al., 2002 Levin & Kleber, 2008	Reduced cannabis withdrawal and subjective effects of smoked cannabis, but had no effect on reinforcement of cannabis and did not prevent relapse in laboratory studies, aided long-term cannabis cessation in 2 case studies
fluoxetine	depression, OCD, eating disorders, panic disorder	selective serotonin reuptake inhibitor	Cornelius et al., 1999	Reduced self-reported cannabis use among a treatment sample of depressed alcoholics
lithium	bipolar disorder	unknown	Bowen, 2005 Winstock et al., 2008	2 open-label studies suggest reduced

Medication Tested	Current Indication	Mechanism of Action	Published articles	Outcome
				withdrawal and cannabis use
lofexedine	opiate dependence	α_2 adrenergic agonist	Haney et al., 2007	Reduced withdrawal and relapse alone and in combination with dronabinol
naltrexone	alcohol and opiate dependence	mu-opioid receptor antagonist	Greenwald & Stitzer, 2000 Haney et al., 2003. 2007 Wachtel & de Wit, 2000	Low dose (12 mg) decreased subjective effects of 20 mg, but not 40mg oral THC; high doses (≥50 mg) increased or had no effect on the subjective effects of oral THC or smoked cannabis.
nefazodone	depression	norepinephrine and serotonin reuptake inhibitor, $5HT_2$ receptor antagonist	Haney et al., 2003	Reduced select withdrawal effects but had no effect on total withdrawal severity or the subjective effects of smoked cannabis
quetiapine	schizophrenia and bipolar disorder	Antagonism of $5HT_2$ D_2 α_1 α_2 and H_1 receptors	Potvin, 2004	Reduced cannabis use in small sample with schizophrenia or bipolar disorder
rimonabant	obesity	cannabinoid CB1 receptor antagonist	Huestis et al., 2001, 2007	Mixed results in ability to attenuate subjective effects of smoked cannabis