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Pharmacological Treatment of Cannabis Dependence

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Abstract

Cannabis is the most frequently used illegal psychoactive substance in the world. There is a significant increase in the number of treatment admissions for cannabis use disorders in the past few years, and the majority of cannabis-dependent individuals who enter treatment have difficulty in achieving and maintaining abstinence. Thus, there is increased need for medications that can be used to treat this population. So far, no medication has been shown broadly and consistently effective; none has been approved by any national regulatory authority. Medications studied have included those that alleviate symptoms of cannabis withdrawal (e.g., dysphoric mood, irritability), those that directly affect endogenous cannabinoid receptor function, and those that have shown efficacy in treatment of other drugs of abuse or psychiatric conditions. Buspirone is the only medication to date that has shown efficacy for cannabis dependence in a controlled clinical trial. Results from controlled human laboratory studies and small open-label clinical trials suggest that dronabinol, the COMT inhibitor entacapone, and lithium may warrant further study. Recent pre-clinical studies suggest the potential of fatty acid amide hydrolase (FAAH) inhibitors such as URB597, endocannabinoid-metabolizing enzymes, and nicotinic alpha7 receptor antagonists such as methyllycaconitine (MLA). Controlled clinical trials are needed to evaluate the clinical efficacy of these medications and to validate the laboratory models being used to study candidate medications.

Keywords

Cannabis; withdrawal; dependence; pharmacotherapy; treatment

CANNABIS USE DISORDERS

Cannabis is the most frequently used illegal substance in the world [1–3]. Cannabis abuse and cannabis dependence are diagnoses recognized in the United States Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM IV) [4] and the WHO International Classification of Diseases, Tenth Revision (ICD-10) [5]. In the United States, the number of individuals with disorders associated with cannabis use is twice that of any other illicit drug [1], with approximately 4 million adults meeting criteria for a life-time diagnosis of cannabis dependence [6]. Relapse rates for cannabis users in treatment are comparable to those found for other drugs of abuse [7–11].

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NEUROPHARMACOLOGICAL MECHANISMS OF CANNABIS DEPENDENCE

Exogenous cannabis (and its primary psychoactive component, Δ-9-tetrahydrocannabinol [THC]) acts on the endogenous cannabinoid (endocannabinoid) system in the brain and other body tissues by binding to two different types of cannabinoid receptors on cell membranes: *CB1* and *CB2* [12]. CB1 receptors are located primarily in pre-synaptic neurons of the CNS and are responsible for the acute psychological and cardiovascular effects of cannabis. CB2 receptors are located largely in the periphery and modulate immune function and inflammatory response.

Endocannabinoids (endogenous ligands at CB receptors) such as anandamide serve as retrograde neuromodulators of synaptic activity. They are released postsynaptically by a variety of stimuli upon demand, travel across the synaptic cleft, and then activate presynaptic CB receptors. A membrane transporter actively takes anandamide into the cell. Anandamide is then broken down by fatty acid amide hydrolase (FAAH) [13–15].

The neuropharmacological mechanism of cannabis dependence may involve interactions of the endocannabinoid system with the dopaminergic and opioid systems. Additionally, CB receptor agonists such as THC act as inhibitors of neurotransmission in acetylcholine, GABA, and glutamatergic pathways. Chronic administration of cannabinoids leads to down-regulation of the CB receptor and receptor function desensitization [16].

THC like other drugs of abuse, releases DA in the mesocortico-limbic regions of animal brains [17–19]. PET brain imaging studies in healthy human volunteers provide inconsistent evidence for this action in humans. One study showed modest THC-induced dopamine release in the ventral striatum and dorsal putamen using [^{11}C] raclopride [20]. Another study found no significant effect of THC on [^{11}C] raclopride binding, although THC markedly increased psychosis-like symptoms [21]. A subsequent study using the same methodology found significant decreases in frontal and temporal lobe [^{11}C] raclopride binding after THC challenges, but no changes in the striatum, which is also part of the dopamine reward pathway [22]. Decreased frontal lobe binding significantly correlated with catechol-O-methyltransferase (COMT) status. Therefore, medications that target the brain dopamine reward system may have a role in the treatment of cannabis dependence, as they may for other drugs of abuse.

CANNABIS INTOXICATION

Cannabis intoxication is a syndrome recognized in DSM-IV [4] and ICD-10 [5], with both psychological and behavioral (euphoria, relaxation, increased appetite, impaired memory and concentration), and physical (motor incoordination, tachycardia, orthostatic hypotension), manifestations. Intoxication is usually mild and self-limiting, not requiring pharmacological treatment [23]. The most severe effects (anxiety, panic, psychosis) are best treated symptomatically with a benzodiazepine or second-generation (atypical) anti-psychotic medication. No medication is approved specifically for treatment of cannabis intoxication.

Studies with the selective CB1 receptor antagonist/inverse agonist rimonabant suggest that CB1 receptors mediate many of the acute effects of cannabis in humans. In a double-blind, placebo-controlled study of 63 healthy men with a history of cannabis use, single oral doses of rimonabant produced significant dose-dependent blockade of the subjective intoxication and tachycardia caused by smoking an active (2.64% THC) or placebo (double-blind) cannabis cigarette 2 hours later [24] The 90-mg dose produced about 40% reductions in ratings of "high" "stoned" and "drug effect" (on 100-mm visual-analogue scales) and a 60% reduction in heart rate. Rimonabant alone produced no significant physiological or

psychological effects and did not affect peak THC plasma concentration or its time course. This pattern of findings suggests that the observed attenuation of cannabis effects was specifically due to CB1 receptor blockade, and not to reduction in brain THC concentration or counteracting effects of rimonabant.

CB receptor antagonists such as rimonabant might be useful in treating acute cannabis intoxication, in the way that the mu-opioid receptor (mOR) antagonists naloxone and naltrexone are used to treat opiate intoxication. However, such medications are no longer available for clinical use. Rimonant and similar CB1 receptor antagonists were withdrawn from clinical development and use because of psychiatric side-effects associated with their long-term use [25].

THE CANNABIS WITHDRAWAL SYNDROME

Both human laboratory and clinical outpatient studies have established the reliability, validity and time course of the cannabis withdrawal syndrome [26, 27] and the cannabis withdrawal syndrome has been proposed for inclusion in DSM-V [28]. Some US studies suggest that about half of patients in treatment have reported symptoms of the cannabis withdrawal syndrome [23, 29–33]. The main symptoms of cannabis withdrawal are anxiety, irritability, depressed mood, restlessness, disturbed sleep, G-I symptoms, and decreased appetite. Most symptoms begin during the first week of abstinence and resolve after a few weeks.

TREATMENT OF CANNABIS WITHDRAWAL SYNDROME

Because symptoms of cannabis withdrawal may serve as negative reinforcement for relapse to cannabis use in individuals trying to abstain [27, 34], pharmacological treatment aimed at alleviating cannabis withdrawal might prevent relapse and reduce dependence.

Several studies have tested the effects of medications on cannabis withdrawal [35–37]. These medications are either CB receptor agonists that directly suppress the withdrawal syndrome (analogous to using an opiate to suppress heroin withdrawal) or are designed to indirectly alleviate symptoms of cannabis withdrawal (e.g. dysphoric mood, irritability) by influencing the brain circuits that mediate these symptoms. No medication has regulatory approval for the treatment of cannabis withdrawal. The CB receptor agonist THC has shown efficacy in several human laboratory studies and open-label case series. See Table 1 for description of all pharmacological treatment trials for cannabis dependence.

Most published studies have been human laboratory studies of short duration (typically 3–4 days), using an inpatient human laboratory model developed at Columbia University (New York, US) [35]. Participants were non-treatment-seeking volunteers who smoked cannabis many times a day. They smoked cannabis (active or placebo) and received oral medication (active or placebo) each day under double-blind conditions. The protocols used a within-subjects crossover design so that each participant received each active and placebo combination of cannabis and medication [38].

The early laboratory studies evaluated divalproex, an anticonvulsant which is used clinically as a mood stabilizer and to treat epilepsy and migraine headaches [39] buproprion, which is used clinically as an antidepressant and for smoking cessation; and nefazodone, an antidepressant that blocks post-synaptic 5HT-2a receptors and inhibits pre-synaptic 5HT and NE reuptake [40]. Bupropion is thought to exert its clinical effects by inhibiting reuptake of norepinephrine (NE) and dopamine (DA) and possibly by acting as a nicotine receptor antagonist [41]. Single doses of bupropion sustained-release (300 mg/day for 17 days) and divalproex (1500 mg/day for 29 days) actually worsened, rather than improved, some

withdrawal symptoms and had no positive effects [42, 43]. A single dose of nefazodone (450 mg/day) decreased some, but not the majority, of cannabis withdrawal symptoms [44].

So far, the only medication successful in suppression of withdrawal symptoms in the laboratory was a single dose of 10mg/day oral synthetic THC (dronabinol) [44]. Oral THC was also more effective than placebo in an outpatient study in which oral THC was given to 8 adult, daily cannabis users who were not seeking treatment in a 40-day, within-subject design study [44]. Participants received daily doses of placebo, 30 mg (10 mg/tid), or 90 mg (30 mg/tid) oral THC during three 5-day periods of abstinence from cannabis use, separated by 7–9-day periods of cannabis smoking as usual. Comparison of measures of withdrawal symptoms across conditions indicated a dose-dependent reduction of withdrawal discomfort by THC. Minimal adverse effects were associated with either THC dose. This demonstration of dose-response effect replicates and extends prior findings of the pharmacological specificity of the cannabis withdrawal syndrome [43].

More recently, the Columbia group has evaluated medications in a more complicated human laboratory design that models both withdrawal and relapse. Regular cannabis users were maintained on each medication condition for 7 inpatient days. Each medication phase was separated by an outpatient washout phase. During the first three inpatient days, placebo cannabis was available for self-administration (withdrawal). For the next 4 days, active cannabis was available for self-administration. Participants paid for self-administered cannabis using study earnings.

The first such study evaluated lofexidine, an agonist at the alpha2-adrenergic receptor that is used to treat opiate withdrawal [46]. Lofexidine was tested both alone and in combination with THC [47]. Eight non-treatment-seeking male regular cannabis users were maintained on each of four medication conditions double-blind: placebo, THC (60 mg/day), lofexidine (2.4 mg/day), and THC (60 mg/day) combined with lofexidine (2.4 mg/day). THC reversed the anorexia and weight loss associated with cannabis withdrawal, and decreased some withdrawal symptoms, but increased sleep onset latency, and did not decrease the resumption of cannabis use when active cannabis was available. Lofexidine, which was sedating, worsened withdrawal-related anorexia and did not robustly attenuate mood symptoms associated with withdrawal, but improved sleep and decreased cannabis relapse. The combination of lofexidine and THC produced the most robust improvements in sleep and decreased cannabis withdrawal, craving, and relapse in daily cannabis smokers relative to either medication alone.

The second such study evaluated baclofen, a GABA B receptor agonist and antispasmodic medication that reduces mood symptoms in heroin withdrawal [48], and mirtazapine, an antidepressant that enhances noradrenergic and serotonergic transmission and decreases withdrawal symptoms in alcohol-dependent patients [49], especially agitation and insomnia [50]. In this study, separate groups received baclofen (60, 90 mg/day) for 16 days (n=10) or mirtazapine (30 mg/day) for 14 days (n=11) [51] Medication administration began when subjects were outpatients prior to each 8-day inpatient phase. On the first inpatient day of each medication condition, participants smoked active cannabis (baclofen group : 3.3% THC; mirtazapine: 6.2% THC). For the next 3 days, participants could self-administer placebo cannabis (withdrawal phase), followed by 4 days in which they could self-administer active cannabis (relapse phase). During active cannabis smoking, baclofen dose-dependently decreased craving for tobacco and cannabis, but had little effect on mood during abstinence and did not decrease relapse. Mirtazapine improved sleep during abstinence, and robustly increased food intake, but had no effect on withdrawal symptoms and did not decrease cannabis relapse. Overall, this human laboratory study did not find

evidence to suggest that either baclofen or mirtazapine show promise for the treatment of cannabis withdrawal.

TREATMENT OF CANNABIS DEPENDENCE

3.1. Agonist Approach

One strategy to treat drug dependence is long-term treatment with the same agonist drug or with a cross-tolerant drug to suppress withdrawal and drug craving. This approach is successfully used in the treatment of tobacco (nicotine) dependence (nicotine itself) and opiate dependence (methadone, buprenorphine). It is being studied for treatment of cannabis dependence using synthetic THC which is legally marketed in many countries as an oral medication for appetite stimulation and suppression of nausea and vomiting due to chemotherapy. Questions of medication abuse and diversion must be addressed, as with opiate agonist substitution treatment.

Use of oral synthetic THC in outpatients was reported in a study that showed the potential benefit, as well as questions that arise from the use of this medication in cannabis-abusing populations [52]. Controlled clinical trials of oral THC are currently underway (www.clinicaltrials.gov).

3.2. Antagonist Approach

The antagonist approach uses long-term treatment with a CB1 antagonist to prevent patients from experiencing the pleasurable reinforcing effects of cannabis use, resulting in extinction of drug-seeking and drug-taking behavior. This approach has been used successfully with the mOR antagonist naltrexone in the treatment of opiate dependence [53]. It could be implemented should a CB1 receptor antagonist again become available for human use.

A recent randomized, double blind, parallel group study investigated whether subacute (2-week) treatment with the CB1 receptor antagonist rimonabant (40 mg daily) attenuated the effects of smoked cannabis in 42 healthy men with a history of cannabis use [54]. The repeated daily rimonabant doses attenuated the acute cardiovascular effects of a cannabis cigarette (2.78% THC) to a similar degree as a single 90-mg dose; repeated 40-mg doses attenuated subjective effects after 8 but not 15 days (possibly because of smaller sample size and lower statistical power at day 15). Rimonabant did not significantly affect THC pharmacokinetics, suggesting that the observed effects were due to receptor blockade and not reduced THC levels in the brain.

3.3. Other Approaches

Alternative pharmacotherapy approaches may arise from improved understanding of the neuropharmacology of cannabis use disorders, including the recognition that (i) frequent cannabis use may cause an adaptive down-regulation of brain endocannabinoid signaling, and (ii) genetic traits that favor hyperactivity of the endocannabinoid system in humans may decrease susceptibility to cannabis dependence [55]. These findings suggest that pharmacological agents that elevate brain levels of the endocannabinoid neurotransmitters anandamide and 2-arachidonoylglycerol (2-AG) might alleviate cannabis withdrawal and dependence. One such agent, the FAAH inhibitor URB597, selectively increased anandamide levels in the brain of rodents and primates. Preclinical studies showed that URB597 produced analgesic, anxiolytic-like, and antidepressant-like effects in rodents, which were not accompanied by overt signs of abuse liability. This evidence suggests that FAAH inhibitors such as URB597 might offer a possible therapeutic avenue for the treatment of cannabis withdrawal [55].

3.3.a. Opiate Antagonist Naltrexone—Because animal studies show that mOR antagonists block effects of THC, several human laboratory studies have investigated whether the mOR antagonist naltrexone 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 THC [56, 57] or smoked cannabis [58]. However, a lower, more mOR-selective dose of naltrexone (12 mg) decreased the intoxicating effects of 20 mg, but not 40 mg, of THC [59]. A recent placebo-controlled study in 29 heavy cannabis smokers found that opioid-receptor blockade by naltrexone (12, 25, 50, or 100 mg daily) enhanced the subjective and cardiovascular effects of cannabis [60]. This pattern of human experimental findings is not completely consistent, but suggests that clinically used doses of naltrexone would not be effective as treatment for cannabis dependence, and might actually increase the abuse liability of cannabis.

3.3.b. Dopamine Agents

Catechol-O-Methyl Transferase (COMT) Inhibitor-- Entacapone: Dopamine (DA) is a major neurotransmitter in the brain's meso-cortico-limbic reward pathway, believed to be a common pathway involved in drug-seeking for all drugs of abuse [61–63] DA deficiency in this reward pathway plays a major role in drug compulsion and craving [64]. Catechol-O-methyl transferase (COMT) is an enzyme that inactivates catecholamine neurotransmitters and plays a pivotal role in regulating homeostatic levels of DA neurotransmitter in the inter-synaptic cleft. COMT inhibitors would increase synaptic DA activity, perhaps counteracting the DA deficiency considered to play a role in drug compulsion and craving. The gene for COMT is located on chromosome 22q11.21 There is some evidence that carriers of the valine158 allele of the COMT gene, who should have increased brain dopamine turnover, are at increased risk for psychotic symptoms and development of schizophrenia if they use cannabis by the age of 18 [65]. However, these findings were not replicated in a later study [66].

As mentioned earlier, THC, like other drugs of abuse, releases DA in the meso-cortico-limbic regions of animal brains. PET brain imaging studies in healthy volunteers so far seems to suggest that THC administration results in modest dopamine release in some human brain regions, but the role of this action in the rewarding effects of THC remains unclear. Therefore, the place in treatment of medications that target the brain dopamine reward system also remains unclear.

Entacapone is a COMT inhibitor approved for the treatment of Parkinson's disease, in a recent study entacapone (up to 2000 mg/day) was given to 36 patients with cannabis dependence (DSM-IV) in an open-label trial for 12 weeks, continued for 12 months in interested individuals. Entacapone both short-term and long-term significantly decreased craving for cannabis in 52.7% of the patients, but no information was reported on patients' cannabis use. Entacapone was well tolerated and there was no serious adverse event [67].

3.3.c. Glutamate- N-acetylcysteine (NAC)—The neurotransmitter glutamate has emerged as a potential target in the treatment of addictions, such as cocaine, nicotine, and cannabis dependence. In animal studies, *N*-acetylcysteine (NAC) reverses drug-induced down-regulation of the cystine-glutamate exchanger, which restores normal regulation of glutamate release, reducing compulsive drug-seeking behaviors [68]. Consistent with this evidence, preliminary studies have demonstrated significant reductions in cocaine craving [69] and cigarette use [70] during NAC treatment.

A recent open-label study gave NAC (1,200 mg) twice daily for 4 weeks to 24 cannabis-dependent males and females who were interested in reducing their cannabis use [71]. Treatment with NAC was well tolerated and associated with significant decreases in self-

report measures of cannabis use and craving, but no change in semi-quantitative urine cannabinoid levels.

3.3.d. Norepinephrine Reuptake Inhibitor- Atomoxetine—Cannabis users demonstrate time and dose-dependent impairments in attention, memory, executive function and response inhibition that resemble deficits in patients with attention deficit hyperactivity disorder (ADHD) and share morbidity with this disorder [72]. A recent study [73] evaluated atomoxetine, an ADHD medication with low abuse potential, in an 11-week open-label study of thirteen treatment-seeking, cannabis-dependent patients (25, 40, 80mg/day). For the eight participants who completed the study, there was a trend towards reduction in cannabis use and increase in percent days of abstinence. The majority of patients experienced gastrointestinal adverse events.

A more recent double-blind, placebo-controlled 12-week study of atomoxetine (25–100 mg/day escalating doses) in 38 cannabis-dependent outpatients with concurrent ADHD found no significant change in cannabis use, although there was some improvement in ADHD symptoms [74].

3.3.e. Anxiolytic- Buspirone—Buspirone shares some of the properties of the benzodiazepines and the neuroleptics; it is a 5-HT ($_{1A}$) receptor agonist [75] and a D_2 receptor antagonist [76]. A preliminary 12-week, open-label study in 10 cannabis-dependent men found that buspirone (maximum 60 mg per day) in a 12-week open-label trial significantly reduced frequency and duration of cannabis craving and use and reduced irritability and depression [77]. A following 12-week controlled clinical trial compared buspirone (maximum 60mg/day) vs. placebo, together with motivational interviewing, in 23 cannabis-dependent participants [78]. Among the 24 participants who completed the trial, those randomized to buspirone had a greater percentage of cannabis-negative urine samples (95% CI:7–63%, $p<0.05$) and a trend towards achieving the first cannabis-negative urine sample sooner than those participants treated with placebo. These findings support the promise of buspirone as a treatment for cannabis dependence.

3.3.f. Mood Stabilizers—Lithium is a mood stabilizer used primarily in the treatment of bipolar disorder (depression and mania), both acutely and chronically. A preclinical study showing that lithium attenuated cannabis withdrawal in rats [79] prompted two small open-label clinical studies. In the first study, lithium (600 to 900 mg/day), administered to 9 adults for 6 days, reduced withdrawal symptoms in 4 of the 9 participants [80]. 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 [81]. Twelve participants completed the 7-day inpatient detoxification. Self-reported cannabis abstinence at post-treatment follow-up sessions was 64% (Day 10), 65% (Day 24), and 41% (Day 90). Participants self-reported cannabis abstinence on 88% of days post-treatment. Five participants reported continuous abstinence that was corroborated with urine toxicology tests on Day 90. These results provide limited support for a double-blind trial of lithium as treatment for cannabis dependence.

A small 6-week controlled clinical trial in 25 cannabis-dependent outpatients also receiving weekly relapse prevention psychotherapy found that divalproex (1500–2000 mg daily, to achieve plasma concentrations of 50–120 ng/mL) did not reduce cannabis use more than placebo and was poorly tolerated by participants [82].

3.3.g. Anti-Depressants—A 13-week controlled clinical trial comparing nefazodone (300mg/day), bupropion-sustained release (150mg/day), or placebo, plus weekly, individual

coping skills therapy in 106 cannabis-dependent outpatients found no significant medication effects on cannabis use or cannabis withdrawal symptoms [83]. These results suggest that nefazodone and bupropion-sustained release are not effective in treating cannabis dependence.

TREATMENT OF PATIENTS WITH COMORBID CANNABIS DEPENDENCE AND DEPRESSION

Cannabis users frequently have co-morbid mood symptoms, especially depression [84, 85]. The prevalence of depression in this population suggested that anti-depressant medication might promote abstinence in this population.

Two studies evaluated the selective serotonin reuptake inhibitor (SSRI) anti-depressant medication fluoxetine in this population. A post hoc analysis of 13 cannabis-using patients among a larger sample of alcohol-abusing, depressed adolescents treated with fluoxetine (20–40 mg daily) showed reduction in cannabis and alcohol dependence and depressive symptoms [86]. Five-year follow-up of 10 patients showed that cannabis and alcohol dependence were reduced and academic ability improved, but clinical depression remained problematic. A later 12-week, controlled clinical trial in 70 adolescents and young adults with comorbid major depression and cannabis use disorder found fluoxetine (20 mg daily) no better than placebo in treating either the depressive symptoms or the cannabis- related symptoms [87]. The lack of a significant between-group difference in symptoms may reflect limited medication efficacy, a ceiling effect because of the efficacy of the concurrent psychosocial treatment (cognitive behavioral/motivational enhancement psychotherapy), or low statistical power from small sample size.

4. NEW PRE-CLINICAL DEVELOPMENTS

Several recent studies in animals have used compounds that affect the endocannabinoid system and offer promising leads for future therapeutic agents. First, the benzoflavone moiety from methanol extracts of passiflora incarnate Linneaus reversed the effects of THC in mice [88]. Second, nicotinic alpha7 receptor antagonists such as methyllycaconitine (MLA) antagonized the discriminative effects of cannabinoids at doses that did not produce depressant or toxic effects [89]. Finally, inhibitors of endocannabinoid- metabolizing enzymes reduced rimonabant-induced precipitated withdrawal responses in THC- dependent mice [90]. These results suggest several potential therapeutic agents that warrant further study.

SUMMARY

Results from controlled human laboratory studies suggest that CB1 receptor antagonists, should they again become available for clinical use, might be effective treatment for cannabis intoxication and that oral THC (perhaps combined with an α-adrenergic agonist such as lofexidine) might be effective treatment for cannabis withdrawal. For the treatment of cannabis dependence, there is little data to guide the clinician, as few controlled clinical trials have been conducted. Only buspirone has shown efficacy in such a trial, while atomoxetine, bupropion, divalproex, and nefazadone have not. A few small open-label clinical trials suggest that the COMT inhibitor entacapone, dronabinol, and lithium may warrant further study, although this recommendation is tempered by the weakness of evidence from open-label studies. In contrast, available evidence from human laboratory studies suggests that the mu-opioid receptor antagonist naltrexone may increase the abuse liability of cannabis and therefore should not be used for treatment. Recent pre-clinical studies suggest the potential of FAAH inhibitors such as URB597 for the treatment of cannabis withdrawal and of endocannabinoid-metabolizing enzymes andnicotinic alpha7

receptor antagonists such as methyllycaconitine (MLA) for treatment of cannabis dependence.

In response to the continuing public health problem that they pose, the National Institute on Drug Abuse launched in 2004 a research program to develop medications for treating cannabis use disorders (CUDs) [16] which hopefully will bear fruit in the future.

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Table 1

Pharmacological Trials for Cannabis Dependence

1. Anti-Depressants					
Study	**Drug**	**N**	**Dose**	**Design**	**Results**
Haney *et al.*, (2001)	Bupropion	(10)	300mg	Randomized Double-blind Placebo-controlled Cross-over	Worsened withdrawal
Haney *et al.*, (2003a)	Nefazodone	(7)	450mg	Randomized Double-blind Placebo-controlled Cross-over	Improved anxiety
*Cornelius *et al.*, (2005)	Fluoxetine	(22)	20–40mg	Randomized Double-blind Placebo-controlled Cross-over	Reduced cannabis use
Haney *et al.*, (2008)	Lofexidine+ THC	(8)	2.4mg 60mg	Placebo-controlled	Reduced withdrawal
*Carpenter *et al.*, (2009)	Nefazodone Bupropion	(106)	300mg 150mg	Randomized Double-blind Placebo-controlled Cross-over	No effect
Haney *et al.*, (2010)	Baclofen Or Mirtazapine	(11)	30, 60, 90 mg 30mg	Randomized Double-blind Placebo-controlled Cross-over	No effect
*Cornelius *et al.*, (2010)	Fluoxetine	(70)	20 mg	Randomized Double-blind Placebo-controlled Cross-over	No effect
2. Cannabis Agents **Cannabis Agonists**					
Study	**Drug**	**N**	**Dose**	**Design**	**Results**
Haney *et al.*, (2004)	Oral THC	(11)	10mg	Randomized Double-blind Placebo-controlled cross-over	Reduced withdrawal
Budney *et al.*, (2007)	Oral THC	(8)	30, 90 mg	Randomized Double-blind Placebo-controlled Cross-over	Reduced withdrawal
Levin and Kleber (2008)	Dronabinol	(2)	10–50mg	Case studies	Mixed results
Cannabis Antagonists					
Study	**Drug**	**N**	**Dose**	**Design**	**Results**
Huestis *et al.*, (2001)	SR141716	(63)	(1, 3,10, 30, 90 mg)	Randomized Double-blind Placebo- controlled Cross-over	Attenuated effects of cannabis
Huestis *et al.*, (2007)	Rimonabant	(42)	90mg	Double blind parallel groups	Attenuated effects of cannabis
3. Other Agents **Opiate Antagonists**					
Study	**Drug**	**N**	**Dose**	**Design**	**Results**
Wachtel and de Wit (2000)	Naltrexone	(14)	50mg	Double blind Placeb-controlled Cross-over	Failed to attenuate dronabinol
Haney *et al.*, (2003b)	Naltrexone	(9,23)	50mg	Double blind Placebo-controlled Cross-over	Enhanced subjective effects of THC
Haney *et al.*, (2007)	Naltrexone	(21)	12mg	Double blind Placebo-controlled Cross-over	Mixed results
Cooper and Haney, (2010)	Naltrexone	(29)	(12, 25, 50, or 100 mg)	Double blind Placebo-controlled Cross-over	Enhanced subjective effects of cannabis
Greenwald & Stitzer (2000)	Naltrexone	(5)	(50, or 200 mg)	Double-blind Placebo-controlledCross-over	No effect
Dopamine Agents					

1. Anti-Depressants					
Study	**Drug**	**N**	**Dose**	**Design**	**Results**
Study	**Drug**	**N**	**Dose**	**Design**	**Results**
Shafa (2009)	Entacapone	(36)	200mg	Open label	Reduced craving
Glutamate					
Study	**Drug**	**N**	**Dose**	**Design**	**Results**
Gray *et al.*, (2010)	N-acetylcysteine	(24)	1200mg	Open label	Reduced self-reported use, but not urine cannabinoid levels
Norepinephrine Reuptake Inhibitor					
Study	**Drug**	**N**	**Dose**	**Design**	**Results**
*Tirado *et al.*, (2008)	Atomoxetine	(13)	25–80mg	Open label	Reduction in cannabis use but adverse events
*McRae-Clark *et al.*, (2010)	Atomoxetine	(36)	25–80 mg	Double-blind Placebo-controlled	No effect
Anxiolytic					
Study	**Drug**	**N**	**Dose**	**Design**	**Results**
*McRae *et al.*, (2006)	Buspirone	(10)	Up to 60mg	Open label	Reduced craving and irritability
*McRae *et al.*, (2009)	Buspirone	(50)	Up to 60 mg	Double-blind, Placebo-controlled	Reduced cannabis use
Mood Stabilizers					
Bowen *et al.*, (2005)	**Lithium**	**(9)**	**600–900 mg**	**Open label**	**Reduced withdrawal**
Winstock *et al.*, (2009)	Lithium	(12)	500mg	Open label	Reduced cannabis use
Haney *et al.*, (2004)	Divalproex	(7)	1500mg	Randomized Double-blind Placebo-controlled Cross-over	Worsened withdrawal
*Levin *et al.*, (2004)	Divalproex	(25)	1500–2000mg	Randomized Double-blind Placebo- controlled Cross-over	No effect

*Indicates Clinical Trial