# Treatment of Cannabis Use Disorders

# 22

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**Abstract**

Cannabis is being used by approximately 5 % of the world's population, and a subset of regular users develop a cannabis use disorder characterized by tolerance, craving, and a withdrawal syndrome. Correspondingly, there is a demand for cannabis treatment that has risen dramatically in recent years. Yet, similar to other drug treatments, the vast majority of patients seeking treatment for their cannabis use fail to achieve abstinence.

The objective of this chapter is to inform clinicians about characteristic features of cannabis use disorders and update them on the current state of treatment research. Psychosocial treatment remains the primary approach utilized, but relatively poor response rates suggest that medications may be a useful

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adjunct to reduce withdrawal symptoms, enhance treatment retention, and reduce relapse. The strategies tested in developing potential treatment medications include agonist substitution, antagonists, or modulators of non-cannabinoid neurotransmitter systems. Preliminary data from human laboratory and clinical studies suggest that the cannabinoid agonist nabilone, the opioid antagonist naltrexone, and the GABAergic drug gabapentin show promise and warrant further clinical investigation. Overall, results from clinical studies highlight the challenges in treating cannabis use disorders and the need to develop more efficacious therapeutic interventions.

## 22.1 Introduction

Cannabis is being used by approximately 5 % of the world's population, and a subset of regular users develop a cannabis use disorder characterized by tolerance, craving, and a withdrawal syndrome. Correspondingly, there is a demand for cannabis treatment that has risen dramatically in recent years. Yet, similar to other drug treatments, the vast majority of patients seeking treatment for their cannabis use fail to achieve abstinence.

The objective of this chapter is to inform clinicians about characteristic features of cannabis use disorders and update them on the current state of treatment research. Psychosocial treatment remains the primary approach utilized, but relatively poor response rates suggest that medications may be a useful adjunct to reduce withdrawal symptoms, enhance treatment retention, and reduce relapse. The strategies tested in developing potential treatment medications include agonist substitution, antagonists, or modulators of non-cannabinoid neurotransmitter systems. Preliminary data from human laboratory and clinical studies suggest that the cannabinoid agonist nabilone, the opioid antagonist naltrexone, and the GABAergic drug gabapentin show promise and warrant further clinical investigation. Overall, results from clinical studies highlight the challenges in treating cannabis use disorders and the need to develop more efficacious therapeutic interventions.

### 22.1.1 Cannabis Epidemiology and Pharmacology

Cannabis, obtained from the hemp plant *cannabis sativa*, is the most-used illicit drug worldwide, accounting for 75 % of all illicit drug use. Over the last decade, 2.5–5.0 % of the world's population reported using cannabis, with an estimated 119–224 million users worldwide (UNODC 2012). The highest prevalence of cannabis use is currently in Oceania (Australia and New Zealand) at 9.1–14.6 %, followed by North America (10.8 %), Western and Central Europe (7.0 %), and West and Central Africa (5.2–13.5 %). While the prevalence of cannabis use in Asia (1.0–3.4 %) remains lower than the global average, Asia's large population results in the highest absolute number of users worldwide (approximately 26–92 million).

In terms of production, Afghanistan and Morocco remain the largest global cannabis producers, where direct distribution is targeted to neighboring African, east European, and Asian countries. Most developed nations obtain cannabis from indigenously grown (mostly indoor) crops. In fact, the boom in indoor cannabis production in recent years has resulted in highly potent "exotic" strains of cannabis, popular in North America, Europe, Japan, and Oceania (UNODC 2012). Correspondingly, the average potency of confiscated cannabis in the United States tripled from 1992 to 2008. Laboratory studies show that high-potency cannabis is more reinforcing than low-potency cannabis (Chait and Burke 1994), supporting the idea that increased potency may impact the likelihood of developing problematic patterns of use.

Although epidemiological data suggest that only about 5–9 % of individuals who have tried cannabis develop dependence (compared with 15–25 % for cocaine), the widespread prevalence of cannabis use results in a significant number of dependent individuals (Anthony et al. 1994). $\Delta^9$-tetrahydrocannabinol (THC) is the constituent of cannabis critical to the development of dependence. *Cannabis sativa* contains over 60 cannabinoid compounds, but THC is the primary psychoactive component of the plant and defines cannabis potency. THC binds to cannabinoid type-1 ($CB_1$) receptors, which are widely expressed throughout the body and densely populated in neural areas related to cognition, learning and memory, motor coordination, attention, and reward (for a review of neurobiology, see Cooper and Haney 2008).

### 22.1.2 Cannabis Use Disorders in Humans

Cannabis use disorders are defined as a problematic pattern of cannabis use leading to clinically relevant impairment or distress occurring within a 12-month period as manifested by cannabinoid tolerance and withdrawal; increasing amounts of cannabis use over time; inability to control consumption; craving; and recurrent cannabis use having negative implications on social, professional, and educational life (APA 2013).

Symptoms of cannabis withdrawal commonly appear after 24 h of abstinence, reach their peak around 2–6 days, and remit within 2 weeks, although impaired sleep patterns may persist for longer periods (Budney et al. 2004). According to DSM-V, withdrawal is diagnosed if at least three of the following symptoms develop within a week of abstinence: irritability, anger, or aggression; nervousness or anxiety; sleep difficulty (insomnia, disturbing dreams); decreased appetite or weight loss; restlessness; depressed mood; and at least one of the following physical discomforts – abdominal pain, shakiness/tremors, fever, chills, or headache. Additionally, the following symptoms may be observed a week post abstinence: fatigue, yawning, difficulty in concentration, and rebound periods of increased appetite and hypersomnia following initial bouts of appetite loss and insomnia (APA 2013). Cannabis withdrawal symptoms may cause significant distress and most likely contribute to relapse among those seeking treatment for their cannabis use (Haney et al. 2013a).

## 22.2 Treatment for Cannabis Use Disorders

In recent years, the proportion of people seeking treating for their cannabis use has been steadily increasing. Treatment admissions for cannabis have doubled in the USA in the last decade and tripled in Europe and Australia. Worldwide, it is currently estimated that 25 % of patients presenting for substance use treatment are those with cannabis use disorders (UNODC 2012). The primary approach for treatment is psychosocial, and to date, there is no approved pharmacological treatment to facilitate psychosocial treatment approaches.

### 22.2.1 Psychosocial Treatment

Research on psychosocial treatments for cannabis use disorders has been ongoing for the last 25 years, and results from these studies have demonstrated that outpatient treatment models can reduce cannabis use and promote abstinence compared to control conditions. In both adults and adolescents, modest success rates have been seen with cognitive behavioral therapy (CBT), motivational enhancement therapy (MET), contingency management (CM), and family-based therapies.

CBT focuses on providing skills necessary to achieve abstinence and cope with stressors and high-risk situations (Marlatt and George 1984; Monti et al. 2002). MET is a non-confrontational approach that aims to build motivation to reduce drug use, by addressing ambivalent feelings towards drug use, which may produce a motivation to change behavior (Miller and Rollnick 2002). Evidence from a series of controlled clinical trials for cannabis use disorders in adults suggests that the combination of CBT and MET achieves greater rates of abstinence than delayed treatment (Budney et al. 2007a). MET-CBT was associated with significantly greater long-term abstinence and reduction in frequency of cannabis use than control treatment, and typically achieved 19–29 % abstinence rates in the 12-month follow-up.

In an effort to improve outcome, several studies have examined the efficacy of CM for treating cannabis use disorders. CM, a process of systematically using positive reinforcement to reinforce abstinent behavior, has been shown to significantly enhance treatment retention and increase periods of abstinence for other drugs of abuse (Petry and Simcic 2002). The results from trials examining the efficacy of CM alone or in combination with MET-CBT for adult cannabis use disorders have shown that inclusion of CM significantly increased rates of abstinence. Specifically, inclusion of CM yielded enhanced abstinence rates to 35–37 % at the 12-month follow-up, whereas MET alone had abstinence rates of 5–10 % (Budney et al. 2007a; Litt et al. 2013).

By contrast, CM was not quite as efficacious for adolescent or young adults mandated to drug treatment. A study by Carroll and colleagues (2012) showed that the combination of CM and CBT was ineffective in improving treatment outcome for cannabis use disorders in young adults involved with the criminal justice system compared to CBT alone. In adolescents (12–18 years) presenting for publically funded treatment programs, a variety of treatment approaches,

alone and in combination (e.g., CBT, MET, CM, family therapy), yielded about 25 % abstinence rates 1 year later regardless of treatment condition (Dennis et al. 2004). These data suggest that maintaining cannabis abstinence may be more difficult in this population relative to adults.

Taken together, psychosocial approaches improve outcomes for people with cannabis use disorders relative to no treatment; however, relapse rates remain high (about 70 %), consistent with abstinence rates for other drugs of abuse. There is clearly a need to increase treatment outcomes by improving the efficacy of currently available treatment options. The development of medications to supplement psychosocial approaches may result in better treatment retention, alleviation of withdrawal symptoms, and a reduction in cannabis use.

### 22.2.2 Pharmacotherapy

A variety of medications have been investigated for their potential to improve marijuana treatment outcome. Most of the current research is limited to human laboratory models and small open-label or placebo-controlled clinical trials. A variety of human laboratory studies have been conducted to directly assess the effect of medications on different aspects of cannabis abuse (e.g., intoxication, withdrawal, self-administration) in a controlled, medically supervised environment. These studies provide useful information regarding safety and tolerability of medications combined with cannabis as well as provide clinically relevant outcomes to guide the selection of medications to test in expensive and time-consuming clinical trials. In terms of clinical studies, there are a handful of published case reports, open-label treatment studies, and randomized controlled trials assessing the effects of medications for cannabis use disorders. Medications investigated in the these models include cannabinoid substitutes such as dronabinol and nabilone and non-cannabinoid agents, which were selected to treat specific aspects of cannabis withdrawal symptoms or to blunt positive effects of cannabis.

#### 22.2.2.1 Blocking Cannabinoid Intoxication: The Antagonist Approach

One strategy for developing pharmacological treatments for cannabis addiction is to reduce the positive subjective and reinforcing effects of the drug. The $CB_1$ receptor antagonist, rimonabant, was found to block many behavioral effects of cannabinoids in animals (Compton et al. 1996). In humans, an initial laboratory study found that acute doses of rimonabant dose-dependently blocked the effects of smoked cannabis. Compared to placebo, the highest rimonabant dose tested (90 mg) reduced positive subjective effects and cardiovascular effects of cannabis by around 40 % and 60 %, respectively (Huestis et al. 2001). A follow-up study assessed the effects of daily rimonabant (40 mg) administration over 15 days on responses to smoked cannabis (Huestis et al. 2007). Rimonabant (40 mg) significantly reduced the cardiovascular effects of cannabis on both days 8 and 15 of daily administration relative to placebo. Rimonabant maintenance also reduced cannabis' positive subjective effects on day 8 but not 15. Further, a single dose of

90-mg rimonabant reduced cannabis-induced heart rate increases but did not blunt the positive subjective effects of cannabis, thereby failing to replicate the earlier study. Unfortunately, rimonabant was found to increase the risk of adverse psychiatric reactions (depression, suicidality) in a clinical trial for obesity, so the medication has been removed from the market and further testing is not possible.

An alternative approach to medications directly blocking the cannabinoid receptor is to target neurotransmitter systems that have been implicated in the effects of cannabis. For example, preclinical studies have demonstrated a functional interaction between endogenous opioids and cannabinoids. Opioid antagonists such as naloxone and naltrexone have been shown to attenuate the reinforcing and rewarding effects of cannabinoid agonists in rodents and nonhuman primates. Conversely, in daily cannabis smokers, acute administration of a range of acute naltrexone doses (12–100 mg) enhanced the subjective and cardiovascular effects of cannabis (3.27 % THC) compared to placebo capsules (Cooper and Haney 2010). Yet, repeated naltrexone administration (50 mg), for 2 weeks or longer, appears to blunt positive subjective and reinforcing effects of smoked cannabis (Haney et al. in preparation). Taken together, these results suggest that clinical studies testing maintenance on naltrexone as an adjunct therapy in the management of cannabis use disorders may be warranted.

#### 22.2.2.2 Alleviating Cannabinoid Withdrawal and Preventing Relapse

A variety of potential medications have been investigated for their ability to ameliorate cannabis abstinence symptoms and prevent relapse. Most promising findings are from studies employing a cannabinoid receptor agonist, such as dronabinol or nabilone. The first study using this approach reported that dronabinol (10 mg, five times/day for 6 days) significantly decreased symptoms of cannabinoid withdrawal, such as craving, anxiety, chills, misery, troubled sleep, and decreased food intake, while producing no evidence of abuse liability (Haney et al. 2004); this pattern of effects was subsequently replicated (Budney et al. 2007b). In a follow-up study, dronabinol was administered at a higher dose (20 mg, three times/day for 8 days). The study also incorporated a laboratory measure of relapse, which is operationally defined as cannabis self-administration, at a cost, after a period of abstinence. Dronabinol at this dose decreased symptoms of cannabis withdrawal, such as restlessness, anorexia, and chills, and produced mild intoxication, but did not decrease relapse to cannabis (Haney et al. 2008). In the same study, a combination of oral dronabinol (60 mg/day) and lofexidine (2.4 mg/day), an $\alpha_2$-adrenergic receptor agonist shown to improve opioid withdrawal symptoms, was evaluated. Lofexidine was tested because preclinical studies showed that clonidine, another adrenergic receptor agonist, reduced cannabinoid withdrawal symptoms in rodents, presumably by reversing enhanced noradrenergic signaling during withdrawal. Lofexidine alone did not robustly attenuate mood symptoms of withdrawal but improved sleep and decreased cannabis relapse. Yet the combination of lofexidine and dronabinol produced the most robust improvements in sleep, withdrawal, craving, and relapse relative to placebo (Haney et al. 2008).

In terms of clinical data, there are two case reports testing long-term cannabis smokers with dronabinol in concert with other medications (Levin and Kleber 2008). One patient was medicated for 6 months with dronabinol (40 mg/day) and divalproex (250 mg/day), a mood stabilizer that reduces irritability and mood swings in bipolar disorder and during alcohol withdrawal. A second patient was maintained on dronabinol (10–15 mg/day) while also receiving venlafaxine (25 mg/day) for depression and modafinil (100 mg PRN) to counter the energy decreases experienced with dronabinol. In both cases, patients achieved and maintained abstinence.

A randomized, placebo-controlled, double-blind, 12-week trial was then conducted (Levin et al. 2011). Participants ($n = 156$) were randomized to either dronabinol (40 mg/day) or placebo following a 1-week placebo lead-in phase; both groups received weekly MET and CBT therapy. All participants reduced cannabis use over time irrespective of treatment, and there was no significant difference between treatment groups in the proportion of participants who achieved 2 weeks of abstinence at the end of the medication phase. However, the dronabinol group had higher treatment retention (77 %) compared to placebo (61 %), and consistent with laboratory studies, withdrawal symptoms were significantly lower in the dronabinol group than placebo.

Given that both the human laboratory and the clinic found that dronabinol decreased withdrawal but did not alter cannabis use, the next study tested nabilone: a cannabinoid agonist with better bioavailability, less individual variability in drug response, and a more predictable dose–response function than dronabinol (Bedi et al. 2012). Nabilone (6, 8 mg/day, for 8 days) significantly reversed withdrawal-induced irritability and disruptions in sleep and food intake (Haney et al. 2013b). Importantly, nabilone maintenance also decreased a laboratory measure of cannabis relapse. These findings are the most promising human laboratory evidence to date, where a single medication improved both cannabis withdrawal symptoms and prevented relapse and suggest that nabilone is a promising candidate for investigation in a clinical trial for cannabis treatment.

In terms of other cannabinoids, a case report presented the effects of cannabidiol, a non-psychoactive cannabinoid constituent of cannabis, on withdrawal symptoms following abrupt cessation of cannabis use in a chronic, heavy cannabis smoker (Crippa et al. 2013). Following maintenance on cannabidiol (300–600 mg/day) for 11 days, the patient demonstrated no self-reported abstinence symptoms. Controlled testing of cannabidiol is needed.

Various non-cannabinoid medications have also been evaluated in controlled inpatient studies for the treatment of cannabis withdrawal, largely with negative results. For example, bupropion, an indirect noradrenergic and dopaminergic agent used for tobacco cessation (150–300 mg/day for 28 days) was found to worsen ratings of irritability, restlessness, depression, and troubled sleep during cannabis withdrawal compared to placebo (Haney et al. 2001).

Since bupropion has stimulant properties that may have exacerbated abstinence-associated agitation and insomnia, subsequent human laboratory studies assessed the effects of medications with sedative properties on cannabis withdrawal and

relapse. Nefazodone and mirtazapine are both antidepressants that enhance noradrenergic and serotonergic activity. During cannabis withdrawal, nefazodone maintenance (450 mg/day for 26 days) decreased certain cannabis withdrawal symptoms (anxiety, muscle pain) but did not alleviate irritability, misery, or troubled sleep (Haney et al. 2003). Mirtazapine (30 mg/day for 14 days), on the other hand, robustly reversed sleep disruption and appetite loss during cannabis withdrawal, but did not improve participants' mood and did not decrease relapse (Haney et al. 2010).

Consistent with the laboratory data, clinical trials with bupropion and nefazodone were also negative. Bupropion (300 mg/day) and nefazodone (600 mg/day) were each compared to placebo in treatment-seeking, cannabis-dependent individuals (Carpenter et al. 2009). Patients ($n = 106$) were randomized to one of the study medications or placebo in this 13-week trial, with 1 week of placebo lead-in, 10 weeks of study medication, and 2 weeks of lead-out. All patients completed weekly sessions with a psychosocial intervention, and around half of the patients completed the 10-week medication phase. Both cannabis use and withdrawal symptoms decreased over time, and there was no effect of bupropion or nefazodone relative to placebo. Results of this clinical trial are, therefore, consistent with the conclusions of laboratory studies.

Venlafaxine and fluoxetine, both antidepressants, have been investigated for their utility in treating cannabis use disorders in those with comorbid depression. A randomized double-blind placebo-controlled trial with depressed cannabis-dependent adolescents ($n = 70$) found no advantage for fluoxetine (10–20 mg/day for 12 weeks) over placebo on either depression or cannabis use outcomes (Cornelius et al. 2010). A subsequent trial in adult patients ($n = 103$) found that extended-release venlafaxine ($\leq$375 mg/day for 12 weeks) was not effective relative to placebo in reducing depression and could potentially increase cannabis use in this population (Levin et al. 2013). Overall, neither laboratory nor clinical studies provide compelling evidence for the utility of antidepressants to treat cannabis use disorders.

Given that anxiety can be a symptom of cannabis withdrawal, the non-benzodiazepine, antianxiety medication, buspirone, was tested in a randomized, controlled clinical trial for cannabis use disorders (McRae-Clark et al. 2009). Cannabis-dependent patients were randomized to buspirone (60 mg/day) or placebo for 12 weeks in conjunction with a psychological intervention (two or three sessions of motivational interviewing during the first 4 weeks). The study reported a high dropout rate (50 %) and no direct effect of buspirone on self-reported anxiety, withdrawal symptoms, or craving. However, exploratory analyses suggested that decreased anxiety over the study predicted cannabis abstinence, indicating that anxiety symptoms may be a useful treatment target.

Divalproex has been investigated in the laboratory and the clinic for its mood-stabilizing properties. Although divalproex (1,500 mg/day for 29 days) decreased cannabis craving during abstinence, the medication worsened ratings of anxiety, irritability, fatigue, and cognitive performance relative to placebo (Haney et al. 2004). Similarly, a double-blind, placebo-controlled pilot study tested

divalproex (250–2,000 mg/day; adjusted to individual response) in combination with CBT for adults ($n = 25$) (Levin et al. 2004). Patients were randomized to either divalproex or placebo for an initial 6-week period after 2 weeks of placebo lead-in. In the 19 patients who completed at least the initial 8 weeks, self-reported irritability, cannabis craving, and cannabis use decreased over time. There was, however, an increased incidence of divalproex-related adverse reactions (fatigue, headaches, drowsiness, and nausea) and poor patient compliance during the trial. These negative results are consistent with the laboratory findings and do not support the clinical utility of divalproex.

Lithium, another mood stabilizer, has also been tested for the treatment of cannabis withdrawal. A small ($n = 9$), open-label, inpatient laboratory study administering lithium (600–900 mg/day for 6 days) reported a reduction in withdrawal signs in 50 % of the participants (Bowen et al. 2005). A second open-label trial maintained cannabis-dependent patients on lithium (1,000 mg/day) in an inpatient setting for 7 days (Winstock et al. 2009). Lithium was generally well tolerated in this short-term inpatient protocol. Although rates of reported withdrawal symptoms were lower and follow-up reports of abstinence higher than in some previous studies, the safety of outpatient lithium administration is a potential concern.

The hormone, oxytocin, is another potential treatment approach, as it has been shown in several preclinical models to reduce drug reinforcement and anxiety-like behavior. A trial is currently under way examining the effects of intranasal oxytocin following preliminary laboratory findings that acute administration of oxytocin (40 IU) alleviated stress-induced reactivity and craving in eight cannabis users (McRae-Clark et al. 2013). This data is supported by findings that oxytocin mediates lithium's effects on cannabis withdrawal.

A case study with the atypical antipsychotic, quetiapine, given to cannabis users with schizophrenia or bipolar disorder reported reduced cannabis use over the course of treatment (Potvin et al. 2004). Quetiapine is a 5-$HT_{2A}$ and $D_2$ antagonist, a partial agonist at the 5-$HT_{1A}$ receptor, and inhibits the norepinephrine transporter. An inpatient laboratory study evaluating the effects of quetiapine reported that although maintenance (200 mg/day for 15 days) improved sleep quality, increased caloric intake and decreased weight loss during cannabis withdrawal compared with placebo, quetiapine increased cannabis craving and self-administration. These data do not support quetiapine's potential for the treatment for cannabis use disorders (Cooper et al. 2012).

The clinical utility of atomoxetine (a norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder, ADHD) to treat cannabis withdrawal has been investigated in a small open-label study. Atomoxetine (20–80 mg daily for 11 weeks) demonstrated a trend to reduce cannabis use in cannabis-dependent individuals (Tirado et al. 2008). However, the medication produced adverse effects in the majority of patients (nausea, vomiting, dyspepsia, loose stools). A subsequent placebo-controlled trial evaluated the effects of atomoxetine on symptoms of ADHD and cannabis use in cannabis-dependent adults (McRae-Clark et al. 2010). In conjunction with MET, participants received

either atomoxetine ($n = 19$) or placebo ($n = 19$) for 12 weeks. Participants randomized to atomoxetine had greater improvement in ADHD on the Clinical Global Impression-Improvement scale than those treated with placebo, yet there were no significant effects of atomoxetine on self-rated ADHD symptoms or cannabis use outcomes. These results suggest that atomoxetine may improve some ADHD symptoms but does not reduce cannabis use in this population.

A small open-label, 12-week pilot study investigated the effects of the entacapone, an inhibitor of catecholaminergic catabolism, in patients meeting criteria for a cannabis use disorder ($n = 36$). Entacapone (up to 2,000 mg/day, daily and PRN), as acute or maintenance treatment, significantly decreased craving for cannabis in over half of the patients; controlled studies are needed to confirm these findings (Shafa et al. 2009).

A recent open-label treatment study in adolescents tested the antioxidant N-acetylcysteine (NAC), shown in animal studies to reverse alterations to the glutamate system associated with repeated self-administration of a range of addictive drugs. Patients ($n = 24$) received NAC daily (2,400 mg/day) over a 4-week period with no other intervention (Gray et al. 2010). The medication produced some mild-to-moderate side effects but was generally well tolerated. Self-reported cannabis use as well as cannabis craving decreased during treatment with NAC. In a subsequent 8-week double-blind, randomized, placebo-controlled trial, treatment-seeking cannabis-dependent adolescents (ages 15–21 years; $n = 116$) received NAC (1,200 mg) or placebo twice daily as well as CM and brief cessation counseling weekly (Gray et al. 2012). Participants receiving NAC had more than twice the odds of having negative urine cannabinoid results during treatment, compared with those receiving placebo. Exploratory secondary abstinence outcomes (assessing time to first negative urine cannabinoid test and end-of-treatment abstinence) favored NAC but were not statistically significant.

A recent inpatient laboratory study assessing the effects of baclofen, an antispasmodic agent that increases gamma-aminobutyric acid (GABA) signaling, failed to engender any clinical benefits for cannabis withdrawal (Haney et al. 2010). Baclofen (60, 90 mg/day) had few positive effects on mood or behavior, reduced cognitive performance across conditions, and did not reduce cannabis relapse. A case series assessed the effects of baclofen (40 mg/day) in six patients with both cannabis and nicotine dependence (Nanjayya et al. 2010). Common side effects were sedation and lethargy, consistent with the cognitive impairment demonstrated in the laboratory trial. The authors report that the medication was well tolerated and that withdrawal symptoms decreased in patients who maintained abstinence for between 1 and 13 months. However, the negative results of the controlled laboratory study do not support baclofen's potential to treat cannabis use disorders, despite this case findings.

Finally, a recent pilot clinical trial investigated the effects of the GABAergic agonist, gabapentin, for cannabis use disorders (Mason et al. 2012). Patients ($n = 50$) received either gabapentin (up to 1,200 mg/day) or placebo for 12 weeks in addition to manual-guided, abstinence-oriented individual counseling. Relative to placebo, gabapentin significantly reduced cannabis use and decreased

withdrawal symptoms. Gabapentin was also associated with significantly greater improvement in overall performance on tests of executive function.

In summary, a variety of cannabinoid and non-cannabinoid agents have been tested in the laboratory and clinic for their potential to reduce cannabis intoxication, withdrawal, and cannabis use. Most of these medications did not significantly reduce the wide spectrum of cannabis withdrawal symptoms, and some actually worsened them, but several medications showed promise in the human laboratory and in the clinic.

## 22.3 Conclusion

Prolonged cannabis use can lead to a clinically significant substance use disorder. Over the past 20 years, there has been a steady increase in studies focusing on both psychosocial approaches and medications development for cannabis use disorders. Most psychosocial treatment studies are better than control conditions but nonetheless produce low rates of long-term abstinence. Thus, as with drugs such as nicotine, alcohol, and opioids, adjunct pharmacotherapy is worth exploring to maximize treatment outcome. Among the cannabinoid and non-cannabinoid agents investigated, several appear to have therapeutic potential.

Cannabinoid agonists like dronabinol reduced withdrawal symptoms and improved treatment retention but failed to alter cannabis use in either the laboratory or the clinic. Yet another cannabinoid agonist, nabilone, reduced both laboratory measures of withdrawal and relapse. The advantages of nabilone over dronabinol include higher bioavailability as well as a longer duration of action, both of which are essential features of a potential treatment medication. Thus, its efficacy needs to be further explored in the clinic. Two medications shown to improve alcohol treatment outcome, gabapentin and naltrexone, also show promise. Further clinical studies confirming these promising findings are needed.

In terms of future directions, the inhibition of endocannabinoid catabolic enzymes, fatty acid amide hydrolase (FAAH), and monoacylglycerol lipase reduces cannabinoid withdrawal in animal models of cannabinoid dependence. Unlike cannabinoid substitutes, FAAH inhibitors do not appear to possess abuse liability (for a full review, see Panlilio et al. 2013). There is currently a study under way at Yale University measuring the efficacy of FAAH inhibitors for reducing withdrawal in cannabis-dependent individuals.

The impact of risk factors (both environmental and genetic) that lead to heavy drug use and the factors that make achieving abstinence challenging need to be better understood in order to optimize treatment approaches. Additionally, over 50 % of patients with cannabis use disorders also abuse other drugs such as nicotine and alcohol and have comorbid psychiatric disorders, but most treatment trials select for psychiatrically healthy cannabis users without dependence on other substances. Indeed, a recent laboratory study has shown that cigarette smoking is an important predictor of cannabis relapse in the laboratory and can influence the efficacy of medications used for treating cannabis use disorders (Haney et al. 2013a). In summary, with the growing treatment demand and increasing awareness about the risks of

cannabis abuse, research into treatment of cannabis use disorders is rapidly expanding. Existing evidence suggests that combining psychosocial treatment with a complementary medication is likely to reduce aversive cannabis withdrawal symptoms, prevent relapse, and improve treatment outcome.

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