The marijuana withdrawal syndrome: Diagnosis and treatment

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The Marijuana Withdrawal Syndrome: Diagnosis and Treatment

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A subset of marijuana smokers develop a cannabis use disorder and seek treatment for their marijuana use on their own initiative. A less well-known consequence of daily, repeated marijuana use is a withdrawal syndrome, characterized by a time-dependent constellation of symptoms: irritability, anxiety, marijuana craving, decreased quality and quantity of sleep, and decreased food intake. Treatment studies show that rates of continuous abstinence are low (comparable to relapse rates for other abused drugs), and more treatment options are needed. The objective of this review is to update clinicians on the current state of marijuana research and to describe features of marijuana withdrawal to facilitate the diagnosis and treatment of cannabis use disorders.

Introduction

Marijuana is the most frequently used illicit drug worldwide [1], and a subset of marijuana smokers develop patterns of daily use and dependence. Among American high school students, 20% of those who report ever smoking marijuana became daily smokers [2]. Although the likelihood of progressing from occasional marijuana use to daily marijuana use is lower than it is for drugs such as nicotine, cocaine, or heroin [3], the sheer number of individuals who try marijuana guarantees that a substantial number will develop dependence (*eg*, 1.6 million Americans in 2000) [4]. Some marijuana smokers seek treatment for their marijuana use not because they are mandated by the court or because they are concurrently seeking treatment for alcohol or other drug use, but because they report being dissatisfied with their heavy marijuana use and find it difficult to quit on their own [5]. Even those who seek treatment often do not achieve abstinence. Marijuana treatment is characterized by low rates of continuous abstinence, comparable to other abused drugs [see 6,7], thereby showing the importance of developing more marijuana treatment options. There have been few controlled investigations of marijuana treatment, and none were done before 1994. Therefore, one objective of this review is to update clinicians on the current state of marijuana research.

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) characterizes marijuana dependence in part as a persistent desire to use marijuana, unsuccessful efforts to cut down, and tolerance and use despite knowledge of the problems marijuana causes. One component of marijuana dependence currently not included in the DSM-IV-TR criteria is physiologic dependence (*ie*, withdrawal symptoms when use of the drug is abruptly terminated). Abstinence after daily marijuana use often is characterized by a time-dependent constellation of clinically significant symptoms that have been reliably shown across a range of conditions: inpatient laboratory settings in individuals not seeking treatment for their marijuana use, outpatient studies, and clinical treatment trials [see 8••]. Therefore, an additional objective of this review is to describe features of marijuana withdrawal to facilitate the diagnosis and treatment of cannabis dependence.

Evidence of Marijuana Dependence and Withdrawal

Epidemiology

In Australia, 7% of young adults participating in a longitudinal population study (n = 1601) met criteria for cannabis dependence, and the symptoms reported were persistent desire to smoke (91%), unintentional use (84%), and withdrawal symptoms (74%). Many of those interviewed (38%) reported using marijuana to alleviate withdrawal. A low percentage (9%) of those with cannabis dependence also met criteria for alcohol dependence [9], showing that cannabis and alcohol dependence often occur independently.

In the United States, rates of marijuana abuse and dependence have increased. Among individuals who reported smoking marijuana within the past year, rates of marijuana abuse or dependence increased from 30.2% (1991 to 1992) to 35.6% (2001 to 2002), with the largest increases occurring among young black and Hispanic women [10•]. The frequency and quantity of marijuana use did not change in this period, suggesting that increased marijuana potency may have contributed to the rising rates of abuse and dependence. In 1992, marijuana confiscated by the police contained approximately 3.08% Δ9-tetrahy-

drocannabinol (THC), the primary psychoactive ingredient in marijuana. In 2002, confiscated marijuana averaged 5.11% THC [11,12]. Laboratory studies show that high-potency marijuana is more reinforcing than low-potency marijuana [13], supporting the idea that changes in potency may have contributed to a higher incidence of cannabis use disorders.

Laboratory studies

Various controlled studies have shown that most individuals who smoke marijuana repeatedly each day, 6 to 7 days per week, have withdrawal symptoms when use is interrupted. Inpatient data collected in non-treatment–seeking marijuana smokers show that abstinence after daily oral THC (dronabinol) administration [14–16] or daily marijuana smoking [17,18] produced increased ratings of anxiety, depression, irritability, and marijuana craving, decreased quantity and quality of sleep, and decreased food intake as compared with baseline conditions. The amount of marijuana smoked in the laboratory before withdrawal was comparable to or less than what the individuals smoked outside the laboratory. Withdrawal symptoms were alleviated by the resumption of marijuana smoking or by the double-blind administration of oral THC, showing the pharmacologic specificity of marijuana withdrawal [17, 19–21].

Data collected from outpatients, for whom marijuana and the cues associated with marijuana are present, are comparable to the inpatient data. Again, withdrawal from marijuana was associated with anxiety, irritability, marijuana craving, and decreased mood and appetite. These symptoms typically begin after at least 24 hours of abstinence, peak on days 2 to 6, and remit within 2 weeks [21–23]. Withdrawal also has been associated with increased aggressive behavior as assessed in a laboratory model [24] and by ratings from collateral observers [21]. These data reflect individuals who were not seeking treatment for their marijuana use, and therefore are not skewed toward those who find their marijuana use problematic enough to motivate treatment.

Given the consistent data collected within recent years, few would currently debate the existence of a marijuana withdrawal syndrome. Yet, the critical questions are whether most daily marijuana smokers experience withdrawal, and if so, is it clinically significant. In terms of significance, the severity of marijuana withdrawal symptoms is comparable to nicotine withdrawal [22], and nicotine withdrawal clearly plays a role in maintaining cigarette smoking. Nicotine deprivation has been shown to lead to smoking to reverse the effects of withdrawal [25], and for heavy cigarette smokers attempting to quit, the best predictor of relapse was negative affect occasioned by abstinence [26••]. In terms of the rate of occurrence, when a range of controlled studies are compared, the percentage of abstinent marijuana smokers who report withdrawal symptoms is greater than 50% [8••].

As a personal observation, it is worth noting that a subset of marijuana smokers do not attribute their negative mood to the absence of marijuana. For example, in inpatient studies it is not uncommon for participants to withdraw from the study on the second or third day of marijuana withdrawal. They describe feeling anxious, irritable, and unable to eat or sleep, but will attribute these symptoms to the discomforts of the inpatient setting or to personal concerns outside of the study (concerns that were not overwhelming when active marijuana was available). We trace this resistance to two factors. First, a marijuana withdrawal syndrome is not a well-known phenomenon. It only occurs in heavy marijuana smokers; symptoms are primarily mood related and they take 1 to 2 days to manifest. Second, attitudes toward marijuana are politically charged. Many marijuana smokers, perhaps particularly those not seeking treatment, are defensive of marijuana use, even in a nonjudgmental environment. Without prompting, they are emphatic that they are different from other drug users (*eg*, they are not "crackheads"), and that they do not steal or sell their possessions to buy marijuana. Therefore, self-awareness or acceptance of withdrawal is not universal among marijuana smokers, and there may be resistance to the concept for fear it will imply a commonality with those who use other illegal drugs.

Clinical studies

Clinical studies show that marijuana smokers will seek treatment for their marijuana use on their own initiative (as opposed to being court-mandated). There is a large response when treatment that is specific for marijuana is offered (*eg*, 400 potential clients in 3 months) [6]. Patients report difficulty finding treatment through current drug abuse treatment, which is largely targeted to users of heroin, cocaine, or alcohol [5,27].

Adolescents [28] and adults [7,29–33] who seek treatment for their marijuana use report a similar set of mood and behavioral withdrawal symptoms as those not seeking treatment. Specifically, treatment-seekers report substantial distress about their marijuana use, but repeatedly fail in their attempts to quit. Withdrawal symptoms are among the most prevalent consequences of marijuana abstinence among treatment seekers, with 85% reporting increased irritability, aggressive behavior, depression, nervousness, and craving, and approximately 65% reporting using marijuana to alleviate symptoms [7,30].

Failure to maintain abstinence is borne out by studies showing that marijuana treatment-seekers have rates of relapse comparable to those found for other drugs of abuse. Among those who attained 2 weeks of abstinence in a study described below [7], 71% lapsed (used marijuana at least once) within 6 months, and 71% of those who lapsed, relapsed (used marijuana at least four times in 7 days) [34].

There have been five marijuana treatment studies published, and the first was published in 1994 [5,31–33,35].

Patients in all of the studies reported smoking marijuana repeatedly throughout the day on a daily (or near daily) basis, and doing so for many years. Most (90%) had repeatedly tried and failed to quit smoking marijuana. Two studies collected data on withdrawal symptoms and reported that approximately 80% of patients had experienced withdrawal symptoms, and 61% to 96% reported using marijuana to relieve these symptoms [5,33].

The objective of these studies was to compare the efficacy of different treatment approaches in decreasing marijuana use, such as cognitive-behavioral therapy (CBT), motivational enhancement therapy (MET), and contingency management, in which vouchers exchangeable for retail goods are used to reinforce volunteers for urine consistently clear of marijuana metabolites. Treatment approaches were compared with each other or with a delayed-treatment control group. In the first study (n = 212), the effects of CBT (10 sessions) did not differ from social support (10 sessions) [32]. In a second study (n = 291), CBT (14 sessions) also did not differ from MET (two sessions). At the 4-month follow-up, patients in both active treatment conditions reported decreased dependence symptoms, fewer marijuana-related problems, and less self-reported marijuana use as compared with the control group, although there was no urine verification of abstinence [33].

Another study (n = 60) compared three conditions: MET (two sessions), CBT plus MET (14 sessions), and CBT/MET/contingency management (14 sessions) [31]. The approach most effective in promoting continuous abstinence by the study end was the combination of the three treatments: 35% in the CBT/MET/contingency management group were abstinent, compared with 10% in the CBT plus MET group, and 5% in the MET group. More research on the effect of vouchers alone is needed in addition to data on abstinence rates after the termination of voucher incentives.

A study done in Australia (n = 229) compared MET plus CBT (one session) and MET plus CBT (six sessions) to a delayed-treatment control group. Both active treatments were reportedly better than the control condition, but rates of continuous abstinence were low (4% to 15%) at 6-month follow-up compared with 0% abstinence in the control group [35].

In all of the clinical studies described, the patients were primarily white men, thereby limiting the generalizability of the findings. A large randomized clinical trial (n = 450) was recently done to test marijuana treatment in demographically distinct communities [5]. This study compared MET (two sessions) and MET/CBT/case management (nine sessions) to a delayed-treatment control contdition. In addition to the 450 subjects enrolled in the above study, more than 1200 individuals inquired about marijuana treatment, and an additional 363 individuals were screened but declined enrollment [36]. This shows that large numbers of individuals seek treatment for their marijuana use. More than 69% of those who were screened showed no evidence of alcohol or other drug dependence [37]. At the 4-month follow-up visit, rates of continuous abstinence were 22% for the nine-session condition, 9% for the two-session condition, and 4% for the control condition, although these data were not verified by urine toxicology.

The authors of this study pointed out that the "constellation of concerns that bring marijuana users to treatment may not manifest themselves in major socioeconomic or psychosocial problems. Instead it may be a more subtle dissatisfaction with multiple areas of functioning, and concerns about future health problems that motivate the desire to quit or reduce use." [5]. That marijuana dependence is not associated with major disruptions to daily routine may explain why marijuana treatment seekers seem less motivated to change and less confident in their ability to abstain from drug use than cocaine-dependent and alcohol-dependent patients [7]. Given the negative mood and behavioral symptoms associated with marijuana abstinence after daily marijuana exposure, it seems likely that the onset of abstinence symptoms partly maintains chronic marijuana use (*ie*, similar to nicotine, people continue to smoke marijuana each day because abruptly stopping is associated with negative mood). It may be that individuals who have a history of using drugs such as marijuana to modulate mood are particularly sensitive to these effects. Although not as dramatic as the opioid or alcohol withdrawal syndrome, this pattern of emotional withdrawal symptoms is likely to be highly significant to individual marijuana users.

One factor often excluded in the above studies is psychiatric comorbidity, despite the high frequency of comorbidity and marijuana dependence [see 38,39]. Among substance-abusing adolescents with conduct disorders, 79% met criteria for marijuana dependence, and 67% reported having marijuana withdrawal symptoms, such as anxiety, restlessness, or irritability [40]. Longitudinal studies suggest an inverse relationship between marijuana use and prescription medications, suggesting that some heavy marijuana users smoke marijuana in part to self-medicate, and when they stop using marijuana, they start taking medication [41]. One example of self-medication occurred in an inpatient study of marijuana withdrawal [42]. A research participant who denied any psychiatric history in several clinical interviews became verbally aggressive on the third day of marijuana withdrawal, articulating threats of violence toward study staff. He was immediately terminated from further participation. During debriefing he reported having bipolar disorder and using marijuana to manage his symptoms. Withdrawal from marijuana seems to have unmasked these symptoms.

To characterize withdrawal per se (rather than unmasking an underlying psychiatric disorder), most studies of marijuana withdrawal or treatment have excluded those with current Axis I diagnoses and those taking psychotropic medications, perhaps resulting in a conservative esti-

mate of the magnitude of marijuana withdrawal in general. Psychiatric diagnoses are associated with more severe marijuana withdrawal symptomatology [30], and those who drop out or who are discontinued from research may experience the most severe withdrawal.

The optimal type of treatment, duration, and intensity still is unclear, but it seems that longer treatment regimens are superior to shorter regimens, and adding voucher-based incentives to cognitive or motivational techniques may improve treatment compliance during study participation because this is the case for treatment of other drug dependencies. There is clearly a demand for marijuana treatment and more research on the most effective treatment approaches is needed.

Pharmacologic Treatment

Laboratory studies

We hypothesize that one reason marijuana relapse rates are high in the initial weeks of treatment is withdrawal symptoms. A comparable relationship between nicotine deprivation and tobacco smoking has been shown, and pharmacologic aids that reduce withdrawal and craving are central to tobacco smoking cessation treatment [see 43]. Therefore, one approach to expanding treatment options for marijuana smokers is to decrease symptoms of withdrawal with medication. The first medication tested in a human laboratory model of marijuana withdrawal was sustained-release bupropion (0, 300 mg/d). Bupropion has been shown to dose-dependently maintain nicotine abstinence, presumably by reducing the negative mood symptoms associated with nicotine withdrawal [44,43], and certain mood symptoms of nicotine withdrawal are similar to cannabinoid withdrawal (*eg*, irritability, depression, and anxiety) [14,17,45].

Non-treatment-seeking marijuana smokers, who averaged six marijuana cigarettes per day, 6 days per week (but who were not dependent on any other drugs, except perhaps nicotine) were recruited. Participants were instructed that the study investigated how medications influence the effects of marijuana, and that the strength of both the medication and marijuana might change at any time; they were not aware that the study focus was marijuana withdrawal. Participants (n = 10) were first maintained outpatient on placebo or active bupropion for 11 days. After steady state was attained, participants moved into the laboratory for 17 days, where they continued taking the same dose of bupropion. They lived in a residential laboratory in groups of two to four, in which mood, physical symptoms, psychomotor task performance, food intake, and social behavior were measured throughout the day, and subjective sleep ratings were measured each morning. For the first 4 inpatient study days, a controlled amount of active marijuana (2.8% THC) was smoked at regular intervals five times per day to standardize recent marijuana exposure. For the remaining 12 inpatient study days, participants smoked placebo marijuana at the same daily intervals (*ie*, withdrawal). After the first inpatient phase, participants were switched to the alternate dose of bupropion, and a second outpatient and inpatient phase was repeated paralleling the first.

Maintenance on bupropion did not alter the acute effects of active marijuana compared with placebo: food intake and ratings such as "High" and "Good Drug Effect" were increased substantially regardless of whether participants were maintained on active or placebo bupropion. During withdrawal from active marijuana, bupropion substantially worsened mood compared to placebo maintenance. Relative to placebo, bupropion significantly increased ratings of "Depressed" and "Irritable" during withdrawal. Bupropion also significantly increased ratings of stomach pain, and decreased food intake and subjective sleep ratings during marijuana withdrawal [46]. These data do not support the use of bupropion to treat marijuana withdrawal.

In hindsight, we recognize that a medication with stimulant side-effects, such as bupropion, may be ill-advised to treat irritability, disrupted sleep, and decreased food intake. Additionally, anxiety is an essential feature of marijuana withdrawal, and bupropion has no anxiolytic effects. Therefore, nefazodone, an antidepressant that effectively treats anxiety, depression, and agitation, and has sedative side-effects was assessed. The design for this study was comparable to the bupropion study: regular marijuana smokers (n = 7), who averaged six marijuana cigarettes per day, 6 days per week, were first maintained outpatient on placebo or active nefazodone (450 mg/d) for 9 days. After a steady state was attained, participants moved into the laboratory for 17 days, where they smoked active marijuana repeatedly and then were switched to placebo marijuana to assess withdrawal. Participants then were crossed over to the alternate nefazodone dose and the outpatient and inpatient study phases were repeated.

Nefazodone had no direct effects in combination with active marijuana. During withdrawal, nefazodone significantly decreased ratings of "Anxiety" and muscle pain compared with placebo, but the effects of nefazodone were limited to this subset of symptoms. Other essential features of marijuana withdrawal, such as irritability, edginess, and decreased food intake were unaltered by nefazodone. Therefore, maintenance on a moderate dose of nefazodone decreased certain symptoms of marijuana withdrawal, but did not improve mood overall [42]. Higher nefazodone doses may be more effective, but additional study is limited by recent United States Food and Drug Administration warnings of hepatotoxicity. However, other anti-anxiety medications may be useful.

The next approach was to determine if either a cannabinoid agonist, oral THC, or a mood stabilizer (divalproex) would attenuate marijuana withdrawal [19]. The rationale for using a cannabinoid agonist to treat marijuana withdrawal is comparable to using methadone to treat opioid detoxification, or nicotine replacement for tobacco cessation. Regular marijuana smokers were admitted for two inpatient

phases on two occasions: during one inpatient phase, placebo THC was administered during marijuana abstinence, and in another phase, oral THC was administered (50 mg/d in five divided doses) during marijuana abstinence. The recommended THC dose for appetite stimulation (2.5 mg twice a day [47]) is considerably lower than the dose tested in this study, but this recommendation is based on data from non-marijuana smokers. Current marijuana smokers are tolerant to the effects of oral THC, and require higher doses for any effect to be seen [14,18,19,48].

Compared to placebo, oral THC administered during marijuana abstinence significantly decreased ratings of anxiety, misery, chills, and self-reported sleep disturbance, and reversed the anorexia and weight loss associated with marijuana withdrawal. Oral THC also decreased marijuana craving during abstinence, and improved withdrawal-related decrements in psychomotor task performance. This attenuation of withdrawal symptoms occurred even though participants were unable to distinguish oral THC capsules from placebo: oral THC attenuated symptoms of withdrawal at doses that produced no intoxicating effects. The mechanism of action of oral THC is to decrease marijuana's negative reinforcing effects (withdrawal). It does not alter the positive reinforcing effects of marijuana (*ie*, marijuana self-administration in individuals not in withdrawal) [18]. Therefore, oral THC may only be an effective treatment medication in abstinent marijuana smokers.

Oral THC is not currently envisioned as a long-term maintenance medication. The objective is to decrease withdrawal symptoms in the initial weeks of abstinence, rather than use oral THC as a relapse prevention medication. An approach that has been used with clinical success in a small number of patients is to use oral THC for a finite period to decrease withdrawal and craving (Herbert Kleber, personal communication). After the patient has gone several weeks without smoking marijuana, the dose of oral THC then is tapered. Typically, patients will take oral THC (10 mg three or four times a day) for several weeks before titration. Marijuana smokers will vary in their degree of tolerance to the effect of oral THC; therefore, clinicians will need to individualize the treatment regimen, maximizing the decrease in withdrawal while minimizing intoxication. A placebo-controlled clinical trial with oral THC in marijuana-dependent treatment seekers has recently been initiated, and will provide important data on clinically effective doses and procedures (Frances Levin, personal communication).

Regarding divalproex, the rationale for testing this medication was that it has been used to treat irritability, mood lability, and temper outbursts [49], which are symptoms of marijuana withdrawal. Divalproex also has been shown to decrease irritability in alcoholic patients [50], and has been used to treat alcohol and benzodiazepine withdrawal symptoms, including anxiety, insomnia, and nausea [51]. For this study, marijuana smokers were first maintained outpatient on placebo or active divalproex (1500 mg/d). After a steady state was attained, participants moved into the laboratory where they continued to take the same dose of divalproex during active and placebo marijuana conditions. Participants then crossed over to the alternate divalproex dose and the outpatient and inpatient study phases were repeated.

In contrast to THC, divalproex worsened mood ratings of irritability, edginess, anxiety, and worsened the subjective impression of sleep. Divalproex also produced a marked impairment of cognitive task performance, whether participants were smoking active or placebo marijuana. Divalproex also increased food intake and body weight [19].

Clinical studies

Divalproex also was tested in the only placebo-controlled clinical study testing a medication for marijuana dependence [52]. A 12-week, double-blind pilot study (n = 25), comparing placebo to divalproex (average dose, 1673 mg/d) found that it did not alter marijuana use, measured by self-report and urine toxicology. Few patients in this trial maintained abstinence from marijuana regardless of medication dose. Compliance in taking the medication was poor, suggesting that it was not well tolerated. These data are consistent with the increased irritability, sleepiness, and anxiety associated with divalproex maintenance in the laboratory [19].

Conclusions

Marijuana withdrawal is gaining recognition as a clinically significant component to marijuana dependence. The treatment trials to date have failed to produce long-term marijuana abstinence, and relapse rates observed for marijuana are comparable to those observed for other drugs, indicating that marijuana dependence is not easily overcome. Although the DSM-IV-TR does not include a withdrawal syndrome as part of the marijuana dependence disorder, Budney *et al*. [8••] present a compelling case for its inclusion, based on the consistent, clinically significant constellation of marijuana withdrawal symptoms observed in most of those studied. Given the vast numbers of daily marijuana smokers, the mounting evidence that abstinence after daily marijuana use is associated with withdrawal symptoms, and the difficulty treatment-seekers have in maintaining abstinence, it is clear that more behavioral and pharmacologic treatment options for marijuana-dependent individuals are needed.

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