

The cannabis withdrawal syndrome

Alan J. Budney^a and John R. Hughes^b

Purpose of review

The demand for treatment for cannabis dependence has grown dramatically. The majority of the people who enter the treatment have difficulty in achieving and maintaining abstinence from cannabis. Understanding the impact of cannabis withdrawal syndrome on quit attempts is of obvious importance. Cannabis, however, has long been considered a 'soft' drug, and many continue to question whether one can truly become dependent on cannabis. Skepticism is typically focused on whether cannabis use can result in 'physiological' dependence or withdrawal, and whether withdrawal is of clinical importance.

Recent findings

The neurobiological basis for cannabis withdrawal has been established via discovery of an endogenous cannabinoid system, identification of cannabinoid receptors, and demonstrations of precipitated withdrawal with cannabinoid receptor antagonists. Laboratory studies have established the reliability, validity, and time course of a cannabis withdrawal syndrome and have begun to explore the effect of various medications on such withdrawal. Reports from clinical samples indicate that the syndrome is common among treatment seekers.

Summary

A clinically important withdrawal syndrome associated with cannabis dependence has been established. Additional research must determine how cannabis withdrawal affects cessation attempts and the best way to treat its symptoms.

Keywords

cannabis, dependence, marijuana, withdrawal

Introduction

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and International Classification of Diseases, Tenth Revision (ICD-10) include a diagnostic category for cannabis dependence, and epidemiological studies indicate that a substantial proportion of cannabis users meet criteria for dependence [1,2]. The number of adults and adolescents enrolled in the treatment for cannabis dependence over the past 10–15 years indicates the clinical and public health importance of this disorder, yet it is only during this time period that treatments specific to cannabis dependence have been discussed and evaluated in the scientific literature [3–5]. A handful of clinical trials targeting cannabis dependence have demonstrated the efficacy of behavior-based treatments with outcomes comparable to that observed with other dependence disorders [3–5]. Although pharmacotherapies are well accepted interventions for substance dependence disorders, only recently have such approaches been contemplated for cannabis dependence [6^{**},7^{*}]. Skepticism regarding the existence and severity of cannabis dependence and withdrawal is the probable explanation for the slow progress in treatment development efforts. Until recently, the scientific community had been reluctant to acknowledge the dependence potential of cannabis because of the lack of evidence for physiological dependence (withdrawal), neurobiological pathways to elucidate the disorder, and self-administration of cannabinoids in animal models [8^{**},9^{*}]. Moreover, the clinical community appeared to hold beliefs that the prevalence of cannabis dependence was low and occurred primarily in the context of polydrug abuse, and consequences of dependence were minimal and as such did not warrant treatment interventions [10]. These notions began to change in the early 1990s with the discovery of the endogenous cannabinoid system and publication of clinical and epidemiological data showing that cannabis dependence was relatively common, had important consequences, and resulted in substantial number of individuals interested in or seeking treatment [1,5].

From the mid-1990s to the early 2000s, basic laboratory research with animals and humans provided clear demonstrations of a withdrawal syndrome associated with cannabis and its primary psychoactive compound Δ -9 tetrahydrocannabinol (THC) [11,12]. Cloning of the cannabinoid CB1 receptor and development of a cannabinoid antagonist (SR141617A) led to a clear demonstration of precipitated withdrawal in mice, rats, and

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^aCenter for Addiction Research (CAR), Department of Psychiatry, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas and ^bDepartment of Psychiatry, College of Medicine, University of Vermont, Burlington, Vermont, USA

Correspondence to Alan J. Budney PhD, Center for Addiction Research (CAR), Department of Psychiatry, College of Medicine, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot 843, Little Rock, AR 72205, USA
Tel: +1 501 686 5207; e-mail: ajbudney@uams.edu

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Abbreviations

DSM Diagnostic and Statistical Manual of Mental Disorders
THC tetrahydrocannabinol

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dogs [8^{••},12]. Controlled inpatient and outpatient laboratory studies with humans demonstrated reliable abstinence symptoms that followed cessation of cannabis smoking or oral THC administration [13–15] and showed that the syndrome has a time course typical of other substance withdrawal syndromes [16,17]. This overview will focus on recent research most relevant to the validation of the cannabis withdrawal syndrome and the determination of its clinical importance.

Validity of the syndrome

In 2004, Budney and colleagues [18^{••}] published a review of the scientific literature concluding that research using diverse methodologies had produced convergent evidence of a valid cannabis withdrawal syndrome. Early inpatient studies in the 1970s and 1980s designed primarily to explore the direct effects of cannabis had reported abstinence symptoms following cessation of cannabis smoking or oral THC administration [19], but these findings were largely ignored. More recent experimental laboratory studies conducted with participants who volunteered in response to newspaper advertisements were designed specifically to test for cannabis withdrawal. These studies provided consistent findings indicating that a reliable set of symptoms occurred following cessation of cannabis use or oral THC administration. Two of these studies collected withdrawal data from heavy/daily cannabis smokers during lengthy periods of voluntary abstinence in outpatient settings, providing an indication of the magnitude and time course of the syndrome. Kouri and Pope [17] compared 30 daily cannabis smokers with former cannabis smokers and nonusers during a 28-day period of verified abstinence. Current cannabis users reported greater levels of anxiety, irritability, negative mood, physical symptoms, and decreased appetite during the abstinence period than those of the two comparison groups. Hamilton Depression and Anxiety scores were also greater than comparison group scores on day 1 and day 7 of abstinence, but not on day 28. Most symptoms had their onset during the first day of abstinence and returned to baseline within 2 weeks. A study from our laboratory [16] assessed 18 daily cannabis users during a 5-day baseline smoking-as-usual period and a 45-day cannabis abstinence period and compared the findings with a group of ex-cannabis smokers. The effects and symptoms observed during the abstinence period were almost identical to that observed by Kouri and Pope [17] and included anger and aggression, decreased appetite, irritability, nervousness, restlessness, shakiness, sleeping difficulty, stomach pain, strange dreams, sweating, and weight loss. Onset of most symptoms occurred primarily on the first day of abstinence, and peak effects were observed between day 2 and day 6. Most effects returned to baseline levels and to levels observed in the ex-user comparison group by the end of second week of

abstinence. In addition, collateral observers who lived with the participants confirmed reports of aggression, irritability, restlessness, and sleeping difficulty during the abstinence period.

The results of human laboratory studies on cannabis withdrawal have provided consistent findings showing clear cannabis abstinence effects. Generalizability, however, is somewhat limited because this research has included only heavy/daily cannabis users. The extent of withdrawal, if any, that occurs in light or nondaily users is unclear. Moreover, these studies excluded treatment seekers, those with significant psychiatric disorder, and those who used other substances or abused alcohol. Such excluded participants would probably experience more severe withdrawal symptoms [20], suggesting that observations from these laboratory studies underestimate the discomfort, especially among those who seek treatment in a drug abuse, psychiatric, or medical setting.

Budney and colleagues [21,22[•]] have published two studies on cannabis withdrawal among adults and adolescents enrolled in outpatient treatment for cannabis dependence. Both adults ($n = 54$) and adolescents ($n = 72$) reported symptom profiles remarkably consistent with those observed in the laboratory studies providing convergent validity for the syndrome. Over 67% of the adults in treatment reported experiencing four or more withdrawal symptoms of at least moderate severity. The most frequently reported symptoms were cravings, irritability, nervousness, depressed mood, restlessness, sleeping difficulty, and anger [21]. Among the adolescents in outpatient treatment with shorter histories and less frequent use of cannabis than the adults, over 33% reported four or more cannabis withdrawal symptoms of at least moderate severity [22[•]]. Crowley and colleagues [23,24] have reported similar findings with adolescents in residential treatment.

Clinical and general population epidemiological studies further validate the experience of cannabis withdrawal among adults and youth and suggest that it is relatively common. Structured survey studies [2,25–29] from the United States and Australia indicate that among persons who have used cannabis regularly during some period of their lifetime, up to a third report having experienced cannabis withdrawal. Among adults and adolescents enrolled in treatment studies [23,24,30–32], 50–95% reported cannabis withdrawal during the past year. The consistency of these survey findings strongly suggests that cannabis withdrawal occurs among a substantial subset of regular cannabis users who quit, and most likely, the prevalence and severity of such withdrawal is greater among heavier users and particularly among those seeking treatment for cannabis dependence.

Table 1 Cannabis withdrawal syndrome

| |
|---|
| Most common symptoms |
| Anger, aggression, irritability |
| Anxiety/nervousness |
| Decreased appetite or weight loss |
| Restlessness |
| Sleep difficulties including strange dreams |
| Less common symptoms |
| Chills |
| Depressed mood |
| Stomach pain/physical discomfort |
| Shakiness |
| Sweating |

Reproduced from [18**].

In summary, on the basis of the above findings, we have proposed the following as a set of core symptoms of cannabis withdrawal: anxiety/nervousness, decreased appetite/weight loss, restlessness, sleep difficulties including strange dreams, chills, depressed mood, stomach pains/physical discomfort, shakiness, and sweating (Table 1).

Pharmacological specificity

Demonstration of pharmacological specificity is probably the most important criterion for demonstrating that an abstinence syndrome upon cessation of a substance is indeed a *true* drug withdrawal syndrome [20]. That is, symptom expression is due to deprivation of a specific substance (i.e., THC in the case of cannabis), and symptoms abate with re-administration of the substance. Several converging lines of research have provided strong evidence for such specificity with cannabis. In non-humans, precipitated withdrawal using a CB1 receptor antagonist and the absence of precipitated withdrawal in CB1 receptor knockout mice suggest pharmacological specificity [12,33,34,35*]. In humans, smoked cannabis or oral THC appears to relieve withdrawal symptoms observed during periods of abstinence from cannabis or oral THC [13,15,36]. Smoking placebo cannabis cigarettes (THC removed) does not abate this withdrawal. Furthermore, cessation of oral THC produces abstinence effects similar to those observed following cessation of smoked cannabis [14,36,37]. In one of the most clinically relevant studies, Haney *et al.* [38**] demonstrated in seven daily cannabis users that administration of oral THC (50 mg; 10 mg administered five times daily) after an inpatient period of abstinence significantly reduced ratings of anxiety, misery, sleeping difficulties, chills, and marijuana craving, and suppressed decreased appetite and weight loss compared with administration of placebo. Preliminary findings from an outpatient study from our laboratory extended these findings showing a dose-dependent suppressant effect of oral THC on cannabis withdrawal in an outpatient setting (Budney *et al.*, unpublished data).

Clinical importance

The current scientific literature clearly indicates that cannabis withdrawal should be considered a true withdrawal syndrome [20,39] (Table 2). In summary, cannabis abstinence effects occur reliably, are not rare, have a well defined time course, abate with readministration of cannabis or THC, and are due to deprivation of a specific substance (THC). The one remaining important attribute is clinical importance (i.e., magnitude of distress or impairment from symptoms or ability of symptoms to undermine quit attempts), which until lately has been unclear. In fact, lack of evidence of clinical importance is cited as the reason for the omission of cannabis withdrawal from the DSM-IV ([39], p. 236). Below, we highlight arguments and recent data supporting the clinical importance of the syndrome.

First, we have compared cannabis withdrawal directly with nicotine withdrawal (a diagnosis accepted by the DSM and ICD as clinically important) and consistently find that the magnitude and time course of the cannabis withdrawal effects appear comparable to this well established syndrome [40,41*]. Second, persons living with cannabis users observe significant withdrawal effects, suggesting that such symptoms are disruptive to daily living [13,16]. Third, cannabis users report using cannabis to 'relieve withdrawal symptoms,' suggesting that withdrawal might contribute to ongoing abuse of cannabis [2,25,42,43]. Fourth, a substantial proportion of adults and adolescents in treatment for cannabis dependence acknowledge moderate-to-severe withdrawal symptoms, and many complain that these symptoms make cessation more difficult [31,32,44]. That said, experimental tests to determine whether cannabis withdrawal undermines quit attempts have not been conducted. For example, we are unaware of studies of whether users with more severe cannabis withdrawal early on after a quit attempt are more likely to relapse later. We would, however, note that alcohol, opiate, and other withdrawals are considered clinically important and are a treatment target, even though they too do not have convincing experimental tests of whether withdrawal undermines cessation [45].

Pharmacotherapy for withdrawal

An implicit indication that cannabis withdrawal is beginning to be accepted as clinically important is the

Table 2 Cannabis withdrawal meets criteria for true withdrawal syndrome

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| Abstinence effects occur reliably |
| Abstinence effects are not rare |
| Effects have a well defined, transient time course |
| Effects abate with readministration of cannabis or THC |
| Effects are due to deprivation of THC |
| Symptoms are clinically important |

THC, tetrahydrocannabinol.

publication of studies testing the effects of medications on cannabis withdrawal recently reviewed by Hart [6**]. Yet, only four human laboratory studies and one small clinical trial have been published. In two laboratory studies conducted by Haney *et al.* [38**,46], single doses of bupropion and divalproex worsened rather than improved some withdrawal symptoms and no positive effects were reported. A small within-subject clinical trial investigated divalproex as a treatment for cannabis dependence in adult outpatients and reported that it fared no better than placebo and was poorly tolerated by participants [47]. In a third single-dose study from Haney's laboratory [46], nefazodone effectively decreased some cannabis withdrawal symptoms but did not affect the majority of symptoms. The most potent demonstration of withdrawal suppression was observed in the single-dose study of oral THC conducted by Haney and colleagues [38**], in which 50 mg of THC decreased five withdrawal symptoms including craving in seven daily smokers. Most relevant to its potential use as a pharmacotherapy, this dose produced no adverse effects and was not subjectively distinguishable from placebo.

These studies were limited by their use of only one dose of each medication and evaluation of nontreatment seekers only. Hence their generality is not clear, and findings with alternative dosing regimens might reveal disparate findings. Nonetheless, such studies reflect the growing acceptance of cannabis dependence and withdrawal as legitimate clinical problems in need of potent treatment alternatives. The literature exploring pharmacotherapies for cannabis withdrawal and dependence is clearly in its infancy, but all indications suggest it will grow rapidly during the next few years.

Conclusion

These are exciting times for cannabis research. The discovery of the endogenous cannabinoid system, the identification and cloning of cannabinoid receptors, and development of cannabinoid agonists and antagonists have provided new insights into the neurobiological underpinnings of the psychoactive effects and dependence processes associated with the use of cannabis [7*,8**]. Careful behavioral, clinical, and epidemiological research on cannabis withdrawal conducted concurrently with these neurobiological endeavors has clearly demonstrated that reliable abstinence effects follow cessation of heavy cannabis use, and that these effects indeed represent a true withdrawal syndrome. The most recent outpatient laboratory studies and surveys of clinical populations have enhanced the external and ecological validity of the syndrome by documenting withdrawal in 'real world' settings. Such findings across a wide range of scientific exploration have legitimized cannabis as a drug of dependence to be taken

more seriously by the scientific, clinical, and lay communities.

This being said, one additional comment regarding the potential importance of cannabis withdrawal warrants mention. The common symptoms observed with cannabis withdrawal are primarily emotional and behavioral, although appetite change, weight loss, and some physical discomfort are also frequently reported (Table 1). Cannabis withdrawal does not typically cause significant medical or psychiatric problems as observed in some cases of opioid, alcohol, or benzodiazepine withdrawals. This does not mean that this abstinence phenomenon is not of clinical importance. Neurobiological and clinical studies suggest that these symptoms are the core symptoms of all withdrawal syndromes [39,48] and reflect the neurochemical changes observed in the limbic system [49–51]. Indeed some believe that these behavioral and affective symptoms are the central feature in withdrawal and are as important, if not more, as physical symptoms in undermining quit attempts.

Although there are strong arguments for the validity and clinical importance of the cannabis withdrawal syndrome, much remains to be learned about the syndrome. For example, prospective studies that directly assess whether cannabis withdrawal symptoms interfere with the establishment of abstinence or promote relapse are needed. Whether withdrawal occurs in many nondaily users is unclear. Given cannabis use is common among patients with severe psychiatric disorders, it will be important to determine if and how cannabis withdrawal affects those conditions. Finally, other basic questions remain unanswered: Do cannabis tolerance and withdrawal covary? Is it influenced by genotype, expectancies, or conditioning processes? What we do know is that cannabis withdrawal clearly warrants continued scientific study and clinical attention.

References and recommended reading

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 331).

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