Review of the Validity and Significance of Cannabis Withdrawal Syndrome

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The authors review the literature examining the validity and significance of cannabis withdrawal syndrome. Findings from animal laboratory research are briefly reviewed, and human laboratory and clinical studies are surveyed in more detail. Converging evidence from basic laboratory and clinical studies indicates that a withdrawal syndrome reliably follows discontinuation of chronic heavy use of cannabis or tetrahydrocannabinol. Common symptoms are primarily emotional and behavioral, although appetite change, weight loss, and physical discomfort are also frequently reported. The onset and time course of these symptoms appear similar to those of other substance withdrawal syndromes. The magnitude and severity of these symptoms appear substantial, and these findings suggest that the syndrome has clinical importance. Diagnostic criteria for cannabis withdrawal syndrome are proposed.

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This critical review examines the validity and clinical significance of a cannabis withdrawal syndrome. The DSM-IV-TR criteria for a substance withdrawal disorder include the following elements: 1) the development of a substance-specific syndrome due to cessation or reduction in use; 2) the syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; 3) the symptoms are not due to a general medical condition and are not better accounted for by another mental disorder. A cannabis (marijuana) withdrawal syndrome is not included in DSM-IV-TR because, "[s]ymptoms of cannabis withdrawal…have been described…but their clinical significance is uncertain"(p. 235). The ICD-10 system acknowledges cannabis withdrawal but states that the syndrome is ill-defined and that diagnostic criteria cannot be established at this time. The demand for treatment for cannabis abuse has grown dramatically in the United States over the past decade (1), and a large proportion of adults and adolescents who participate in outpatient treatments have difficulty achieving and maintaining cannabis abstinence (2). Thus, determining whether or not a cannabis withdrawal syndrome exists and whether it is part of the reason cannabis users have difficulty quitting has become increasingly important.

Early reviews of cannabis withdrawal were brief and preceded important discoveries in cannabinoid pharmacology (3, 4). In a 2002 review, Smith (5) concluded that "studies conducted to date do not provide a strong evidence base for the drawing of any conclusion as to the existence of cannabis withdrawal syndrome in human users." This review cited 1) the lack of controlled studies, 2) absence of definitions of withdrawal, 3) poor ecological validity, 4) failure to document severity of symptoms, and 5) inconsistent onset and offset of symptoms. Several commentaries published adjacent to this review were not consistent with Smith's tentative conclusion and in contrast stated, for example, "…it is remarkable that there is as much consensus as there is…many studies report similar characteristics of the cannabis abstinence syndrome despite vagaries of the experimental protocols" (6). The current review was undertaken because more recent, well-controlled studies, which were not included in the Smith review, address his concerns and provide methodologically rigorous, convergent evidence that a valid and clinically significant cannabis withdrawal syndrome is prevalent in a substantial proportion of heavy cannabis users.

This review consists of 1) brief reviews of animal studies and early studies with humans; 2) an overview of recent, more rigorous outpatient and inpatient studies; 3) a review of epidemiological studies on the prevalence of cannabis withdrawal; 4) a discussion of how well the literature supports the validity and significance of a cannabis withdrawal syndrome; and 5) proposed criteria for a cannabis withdrawal syndrome.

Method

Literature search

Studies with human participants were located by means of MEDLINE and PsycFIRST computer searches, reference lists of articles located by these searches, and requests for recent or in-press articles identified in previously located articles. Keywords used in searches were "cannabis," "marijuana," and "withdrawal." Articles that were identified were included in the review if they provided data specific to withdrawal from tetrahydrocannabinol (THC) or cannabis. In addition, we searched abstracts of recent scientific conferences and contacted investigators who had conducted studies in this area to inquire if they had or knew of any recent manuscripts on cannabis withdrawal that had been published or were in press. Published abstracts were not included.

TABLE 1. Presence or Absence of Symptoms Reported in Studies of Cannabis Abstinence, 1946-2004

Study	Year	Sample Size	Study Subjects and Method	Presence or Absence of Symptoms[a]		
				Irritability	Nervousness/ Anxiety	Restlessness
Human experimental studies						
Williams et al. (21)	1946	6	Inpatients; abstinence from smoked marijuana and pyrahexyl		Y	Y
Dornbush et al. (22)	1972	5	Inpatients; abstinence from smoked marijuana; specific symptoms not reported			
Georgotas et al. (23)	1979	5	Inpatients; abstinence from smoked marijuana	Y		
Jones et al. (24–26)[b]	1976, 1981	12–53	Inpatients; abstinence from oral THC	Y	Y	Y
Nowlan and Cohen (27)	1977	30	Inpatients; abstinence from smoked marijuana	Y		Y
Stefanis et al. (29)	1976	16	Inpatients; abstinence from smoked hashish, marijuana	N	N	N
Haney et al. (30)	1999	12	Inpatients; abstinence from oral THC	Y	Y	Y
Haney et al. (31)	1999	12	Inpatients; abstinence from smoked marijuana	Y	Y	N
Haney et al. (35)	2001	10	Inpatients; abstinence from smoked marijuana	Y		Y
Hart et al. (32)[c]	2002		Inpatients; effects of smoked marijuana, oral THC	Y/N	N/N	N/N
Haney et al. (33)	2003	7	Inpatients; abstinence from smoked marijuana	Y	Y	Y
Haney et al. (34)	2004	7	Inpatients, outpatients; abstinence from smoked marijuana	Y	Y	
Kouri et al. (38)	1999	17	Outpatients; abstinence from smoked marijuana		Y	
Kouri et al. (39)	2000	30	Outpatients; abstinence from smoked marijuana	Y	Y	
Budney et al. (40)	2001	12	Outpatients; abstinence from smoked marijuana	Y	N	Y
Budney et al. (41)	2003	18	Outpatients; abstinence from smoked marijuana	Y	Y	Y
Interview/survey studies						
Crowley et al. (52)	1998	180	Inpatient adolescent, drug abusers; structured interview	Y	Y	Y
Weisbeck et al. (42)	1996	5,611	Alcoholics and probands; structured interview		Y	Y
Budney et al. (51)	1999	54	Adults enrolled in treatment; symptom checklist	Y	Y	Y
Total[d]				14/16	12/16	11/15

[a] Y=symptom was reported; N=symptom was assessed but did not occur. Blank cells indicate either that the symptom was not assessed or that it could not be determined whether the symptom was assessed.
[b] The three references to research conducted by Jones et al. are presented jointly because the articles overlap and provide information from the same series of studies.
[c] The study reported on abstinence effects from both smoked marijuana and oral THC; the symptom reports indicate findings for smoked marijuana and oral THC, respectively.
[d] Number of studies that found positive results/number of studies with data available.

Studies were not excluded on the basis of specific methodological weaknesses. Instead, methodological limitations are discussed in the text. The review is comprehensive through January 2004.

Definition of Terms

The term "abstinence effect" will be used to indicate a change that occurs upon abstinence from cannabis. Previously, abstinence effects have been subtyped as transient, offset, or rebound (7). The typical clinical definition of a withdrawal effect requires a transient pattern reflecting a biphasic response (i.e., initial increase followed by a decline in symptoms) with a finite time course and return to baseline. Transient effects are distinguished from effects due to the simple offset of drug effects. Offset effects are uniphasic effects that appear to stabilize at a level that reflects either a return to a predrug state or the development of a new baseline produced by nonreversible effects of a drug. Offset effects are not considered true withdrawal, but they may still be clinically important. Rebound effects are a type of transient effect that exceeds the predrug baseline but does not return to the drug-use baseline. Typically, rebound effects refer to a reappearance or exacerbation of symptoms that were present before the use of the drug. Thus, predrug baseline data is necessary to definitively determine if a transient effect is a rebound effect. In human studies, such a predrug baseline is typically not available. Data from comparison groups of ex-users or never-users of the drug can be used in interpreting abstinence effects and to rule out effects due to time or experimental procedures. This review will comment on how well various studies discriminate between types of abstinence effects.

The term "cannabis" will refer to materials from the plant C*annabis sativa* or *C. indicus* that are directly ingested (through smoking or oral ingestion). "THC" will be used to refer to the primary psychoactive compound in cannabis, delta-9-tetrahydrocannabinol. The term "cannabinoid(s)" will be used to indicate the general class of active compounds similar to THC in molecular structure and effect.

Cannabinoid Withdrawal in Nonhumans

Early reviews of cannabis dependence in nonhumans concluded that THC is capable of producing dependence (tolerance and withdrawal) in animals but suggested that the abstinence effects were inconsistent and probably inconsequential (3, 4). Studies with primates showed transient abstinence effects after intravenous, intramuscular, or oral administration of THC (8–11). Abstinence effects included aggression, anorexia, biting, bruxism, irritability, hair-pulling, hyperreactivity, increased eye contact and gross motor movement, piloerection, reduction in operant responding for food, scratching, shaking, tooth-baring, visual hallucinations, yawning, and frequent periods of EEG

Presence or Absence of Symptoms[a]											
Sleep Difficulties	Strange Dreams	Decreased Appetite	Decreased Weight	Anger/ Aggression	Depressed Mood	Craving	Stomach Pain/ Physical Symptoms	Decreased Concentration	Sweating	Shakiness/ Hand Tremor	Chills
Y		Y	Y						Y	Y	Y
N											
Y		Y		Y		N					
Y		Y	Y	Y	N		Y		Y	Y	Y
Y		Y				Y					
		N		N	N		N				
Y		Y		N	Y		N	N	N	N	N
N		Y	N	N	N		Y	N	N	N	N
Y		Y			Y						
		N/N		N/N	Y/N		N/N	N/ N	N/N	N/N	N/ N
Y		Y	N		N		Y	N	N	N	N
Y	Y	Y	Y		Y	Y	Y	N	N	N	Y
				Y	Y						
N		Y			Y	N	Y	N			
Y	Y	Y	Y	Y	N	Y	N	N	N	N	N
Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y
Y		Y			Y		N	Y	Y	Y	
Y		Y			Y						
Y	Y	Y		Y	Y	Y			Y	Y	Y
13/16	4/4	15/18	5/7	6/11	9/16	4/7	6/12	1/10	5/12	5/12	5/11

desynchronization. In other studies with laboratory animals, however, researchers did *not* observe signs of a THC-related abstinence syndrome (12–15). Such inconsistent findings likely reflect the methodological difficulties of using an abstinence model to study cannabinoid withdrawal in laboratory animals (16).

The discovery of the endogenous cannabinoid system, identification of cannabinoid receptors, and synthesis of a cannabinoid antagonist (SR141716A) made it possible to test for cannabinoid withdrawal in animals by using a precipitated withdrawal paradigm. A recent review of this literature (16) indicated that, across multiple nonhuman species, the administration of SR141716A induced clear behavioral signs of precipitated withdrawal. In addition, the specific cannabinoid receptor site (CB1) for the action of this withdrawal effect has been determined by using CB1-knockout mice (16, 17). Last, increases in corticotropin-releasing factor and reduction in dopamine cell activity during THC withdrawal closely resemble those seen during withdrawal from opiates and other major drugs of dependence (16, 18, 19). Such effects are consistent with the symptoms of negative emotion common to withdrawal syndromes in humans and have led to speculation that negative affect may be the common hallmark of withdrawal across most drugs of dependence (20). In summary, whereas abrupt termination of THC administration after chronic dosing (abstinence withdrawal model) produced inconsistent findings in nonhuman studies before 1990, the precipitated withdrawal model produced immediate, consistent, and pronounced cannabinoid withdrawal symptoms across a variety of species.

Early Human Experimental Studies

Few controlled experimental studies on cannabis withdrawal in humans were available before Wikler's review (3) of marijuana dependence in 1976 (Table 1). An early inpatient study showed mild abstinence symptoms (transient jitteriness) after cessation of marijuana smoking and more robust symptoms (restlessness, sleep problems, poor appetite, and disorientation) after cessation of a synthetic cannabinoid, pyrahexyl (21). In another early inpatient study, researchers failed to observe symptoms after cessation of daily marijuana smoking (22).

Compton et al. (4) reviewed human inpatient studies from the mid 1970s and early 1980s (23–27). Across these studies, participants received access to marijuana ciga-

rettes or oral THC for a specified time period and remained in an inpatient setting when access to marijuana or THC was discontinued (Table 1). The following abstinence symptoms were reported in at least one study: decreased appetite/weight loss, hostility, irritability, mild nausea, uncooperativeness, restlessness, sleep EEG changes (increased REM sleep), and sleep difficulties/insomnia. These reports typically did not provide systematic quantitative data but rather obtained simple yes/no reports or experimenter observation of symptoms. Other similarly designed inpatient studies did *not* observe significant mood or behavioral signs of withdrawal after cessation of marijuana or hashish smoking (22, 28, 29).

In perhaps the most rigorous of the early inpatient studies (24–26), clinical observations postcessation of 16–20 days of oral THC (210 mg/day) indicated that the majority of subjects experienced irritability, restlessness, insomnia, and anorexia. These symptoms began within 5–6 hours of the last dose and diminished within 96 hours. Reduction in weight and sleep EEG changes (i.e., increased REM) were also observed. Participants who received placebo during the drug administration phase did not exhibit such changes. (The three references to research conducted by Jones and colleagues [24–26] are presented jointly because the articles overlap and describe information from the same series of studies.)

In summary, the early cannabis withdrawal literature describing studies with humans, like the literature on studies with nonhumans, showed that abrupt cessation from marijuana or oral THC produced abstinence effects under certain circumstances, but these effects were inconsistent and not measured systematically, and their clinical importance was unclear.

Recent Human Experimental Studies

Inpatient Studies

More recent inpatient studies clearly enhance the internal validity of the evidence for a cannabis withdrawal syndrome. In a 1999 study by Haney et al. (30), 12 heavy marijuana smokers (mean of 4 joints/day) received placebo pills on study days 1–3, 8–11, and 16–19; 20 mg of oral THC four times a day on days 4–7; and 30 mg of oral THC four times a day on days 12–15. Compared to the placebo baseline phase, abstinence from THC (i.e., placebo periods after THC use) was associated with significantly increased ratings of anxiety, depression, and irritability; decreased ratings of quantity and quality of sleep; and decreased food intake. Systematic relations between the THC dose and the magnitude of abstinence effects were not generally observed, although increased anxiety and restlessness were reported only after the higher dose.

A similar study, again with daily marijuana smokers, tested for abstinence effects after cessation of two doses (THC concentrations of 1.8% and 3.1%, respectively) of smoked marijuana cigarettes (31). Both doses were administered four times per study day. Results paralleled those reported in the oral THC study. Abstinence increased ratings of irritability, anxiety, and stomach pain; decreased ratings of contentment, friendliness, talkativeness, sociability, and energy; and also decreased food intake. No robust abstinence effects on social behavior or performance were observed. In contrast to the oral THC study, this study of marijuana smokers did not report sleep disturbance during the abstinence phases. Clear dose-related differences in abstinence effects were not observed. Most mood symptoms peaked on day 3 or 4 of the abstinence phases.

A third similarly designed study compared the effects of smoked marijuana and oral THC (32). Abstinence effects were observed for smoked marijuana but not for oral THC. Failure to observe abstinence effects from oral THC may have been due to use of a lower dose of oral THC and the shorter durations of drug administration and abstinence periods, compared with previous oral THC studies. Last, as documented in Table 1, abstinence effects after cessation of smoked marijuana were replicated under placebo conditions in three other inpatient studies designed to test the effect of medications on marijuana abstinence symptoms (33–35). In summary, several well-controlled inpatient studies repeatedly confirmed that abstinence effects such as irritability, weight loss, and sleep difficulty occur reliably. It is noteworthy that these studies controlled for potential confounders by using placebo conditions and excluding persons who abused other substances, had an active psychiatric disorder, or were taking psychoactive medication.

Outpatient Studies

Outpatient studies are important because inpatient studies do not include many of the environmental stimuli (e.g., persons or things associated with smoking) that can produce conditioned withdrawal effects, and thus inpatient studies may underestimate the severity of drug withdrawal (36, 37). An initial outpatient study (38) examined aggression during a 28-day period of verified cannabis abstinence using a novel laboratory analog test of provoked aggression with chronic (daily) marijuana smokers who did not abuse other substances, did not have a current psychiatric condition, and did not take psychoactive medication. Greater levels of aggression were observed on days 3 and 7 of abstinence, compared with day 0 (baseline). This increased aggression abated by day 28, showing that this effect was transient. These daily marijuana smokers made significantly more aggressive responses than a comparison group of 20 former or infrequent marijuana smokers.

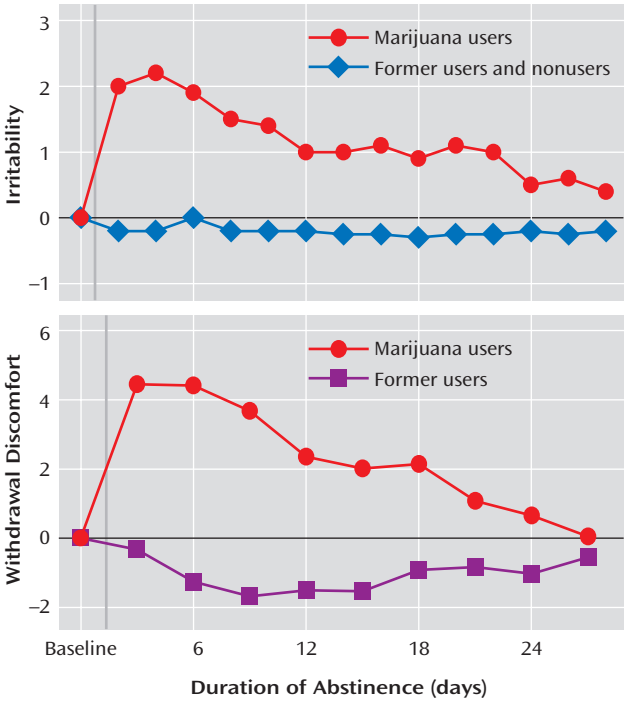
This outpatient study and the aforementioned inpatient and animal studies were available at the time of Smith's review (5), discussed earlier. Thus, although robust findings from animal and inpatient studies and suggestive data from outpatient studies were available, what was lacking at the time of the prior review were comprehensive prospective studies with adequate baseline data, demonstra-

tions of clinically significant symptoms, and a clear delineation of the time course of withdrawal. Since that review, three additional rigorous outpatient studies have been reported that we believe provide these elements.

A more comprehensive outpatient study (39) of cannabis withdrawal compared current daily cannabis smokers (same inclusion/exclusion criteria as the aforementioned study [38]), former cannabis smokers, and nonusers during a 28-day period of verified abstinence. A prewithdrawal baseline was estimated with a single retrospective rating of 14 symptoms over the past 6 months. Among the daily users, appetite was decreased (compared with baseline) on days 1–9 of abstinence, anxiety was higher on days 1–11, irritability was greater on days 1–14, mood was lower on days 3 and 9, physical tension was greater on days 1–10, and physical symptoms were greater on days 1–8, 10–13, 15–18, and 27. The daily users showed greater levels of anxiety, irritability, negative mood, physical symptoms, and decreased appetite during the abstinence period but not at baseline, compared with the two comparison groups. Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale scores of the daily users were also greater than the comparison-group scores on days 1 and 7 of abstinence but not on day 28. The daily users' levels of irritability (Figure 1) and physical tension remained significantly elevated above the comparison groups' levels throughout the entire 28-day study. As such, whether these two symptoms are true withdrawal symptoms rather than offset effects is unclear. Interpretation of these results is somewhat limited by the single retrospective baseline measure. Thus, the true magnitude of the observed abstinence symptoms and the time of offset are difficult to discern. Nonetheless, the systematic changes in symptom scores during the abstinence period and the systematic differences over time between the users and the comparison groups suggest that these findings reflect reliable cannabis withdrawal effects.

A third outpatient study (40) collected daily prospective baseline measures and thus remediated the problem of the prior outpatient study. Twelve daily marijuana smokers (who used marijuana an average of 3.6 times/day and did not use other illicit drugs, abuse alcohol, have an axis I psychiatric disorder, or take psychoactive medication) provided self-ratings of withdrawal discomfort on 16 consecutive days during which they smoked marijuana as usual (days 1–5, or the baseline period), abstained from smoking (days 6–8), returned to smoking (days 9–13), and again abstained (days 14–16). Overall withdrawal discomfort increased significantly during the two abstinence phases, compared to the original baseline period, and returned to baseline when marijuana smoking resumed during the third phase (Figure 2). Craving for marijuana, decreased appetite, sleep difficulty, and weight loss reliably changed across each smoking and abstinence phase. Aggression, anger, irritability, restlessness, and strange dreams increased during both abstinence phases, but the effect was statistically significant only in the first abstinence phase. Onset for most abstinence symptoms occurred within 48 hours of cessation. Telephone interviews with collateral observers living with the participants confirmed participants' reports of increased irritability, aggression, and restlessness during abstinence. In summary, these test-retest results demonstrated the within-subject reliability and internal validity of marijuana abstinence effects in an outpatient setting. In addition, the validation of symptoms by home-based observers suggested that the effects were of a clinically significant magnitude. This study clearly established time of onset of most symptoms, but the short cessation period (3 days) limited examination of duration and peak effects.

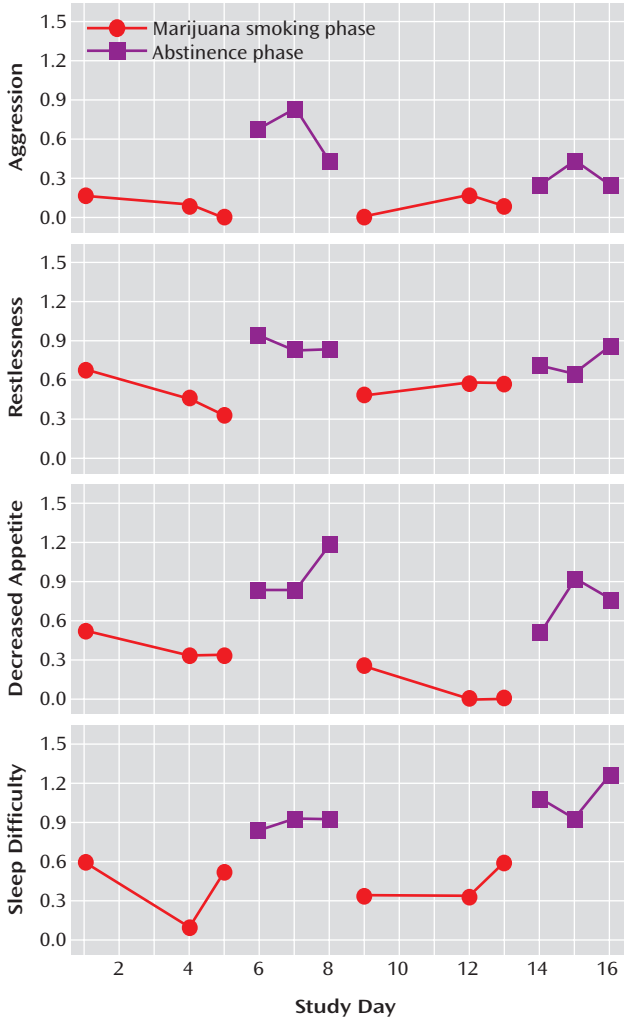
FIGURE 1. Change From Baseline in Irritability and Withdrawal Discomfort in Two Studies of Effects of 28 Days of Abstinence From Cannabis in Outpatient Marijuana Users[a]



[a] Top panel shows data on the time course and magnitude of a typical abstinence effect. Symptom scale values ranged from 1 to 10; y-axis values are the mean change from baseline across participants (N=30). Each subsequent data point represents a symptom change score for each abstinence day. Bottom panel illustrates the magnitude and time course of a summary withdrawal discomfort score. Y-axis values are the mean change from baseline across participants (N=18). Each subsequent data point represents the mean of a 3-day block of abstinence scores. Top panel adapted with permission from Kouri and Pope (39). Copyrighted © 2000. American Psychological Association. Bottom panel adapted with permission from Budney et al. (41). Copyrighted © 2003. American Psychological Association.

A fourth study replicated and extended these findings (41). This 50-day study assessed 18 daily cannabis users (same inclusion/exclusion criteria as the prior study) during a 5-day baseline (smoking as usual) period and a 45-day cannabis abstinence period. A comparison group of 11 former cannabis smokers was used to assist with interpre-

FIGURE 2. Mean Scores for Four Withdrawal Checklist Items Across Time in a 16-Day Study of Effects of Abstinence From Cannabis in Outpatient Marijuana Users (N=12)[a]



[a] Participants smoked marijuana as usual on days 1–5 (baseline period), abstained from smoking on days 6–8, returned to smoking on days 9–13, and again abstained on days 14–16. Checklist item values ranged from 0 to 3. Adapted with permission from Budney et al. (40), *Archives of General Psychiatry*, 2001, vol. 58, pp. 917–924. Copyrighted © 2001. American Medical Association. All rights reserved.

tation of findings. The effects and symptoms that changed significantly from baseline during the abstinence period were almost identical to those in the prior study and included anger and aggression, decreased appetite, irritability, nervousness, restlessness, shakiness, sleep difficulty, stomach pain, strange dreams, sweating, and weight loss. The onset of most effects occurred between days 1 and 3. The time of peak severity occurred between days 2 and 6, with most symptoms peaking around day 4 (Figure 1). Effect sizes for each symptom were in the medium to large range. Most effects were transient, i.e., returned to baseline levels by the end of second week of abstinence, although strange dreams and sleep difficulties showed significant elevations throughout the study. All effects, with the exception of sleep difficulties and craving for marijuana, returned to the level observed in the comparison group of former users. Again, collateral observers confirmed reports of aggression, irritability, restlessness, and sleep difficulty. In summary, this study documented 1) the time course of withdrawal, 2) the substantial magnitude of symptoms, and 3) the transience of most symptoms. In addition, the observation that most symptoms returned to baseline levels and to the level observed in the former users (with absolute symptom values approximating zero) suggests that these findings were not rebound effects indicative of symptoms that existed before the use of cannabis.

The results of these four controlled outpatient studies are remarkably consistent and provide validity for a cannabis abstinence syndrome. The generalizability of these studies is limited because the inclusion of only daily users likely produced more severe symptoms than if light or nondaily users were studied. On the other hand, all four studies excluded treatment seekers, persons with significant psychiatric disorder, and persons who used other substances or abused alcohol. Exclusion of such participants likely resulted in less severe withdrawal symptoms than might have been observed if such participants were included (7).

Survey Studies

Although survey studies cannot provide empirical demonstration of the validity of an abstinence syndrome, they can provide real-world replications of experimental trials and estimates of how common marijuana withdrawal is. Structured interviews from the Collaborative Study of the Genetics of Alcoholism sample indicated that 16% of those with a lifetime history of regular cannabis use (>21 times/year) described a lifetime history of cannabis withdrawal, i.e., reported at least two symptoms from a seven-item withdrawal checklist (42, 43). Among those who also met the criteria for a lifetime cannabis dependence diagnosis, 40% reported symptoms of withdrawal. In the DSM-IV field trials, 25% of persons who had smoked cannabis at least six times in their life reported experiencing cannabis withdrawal in the past; however, specific symptoms were not defined (44). An Australian study indicated that 20%–25% of long-term cannabis users (use three to four times per week for at least 10 years) in the general population responded affirmatively to an ICD-10 or DSM-III-R dependence criteria question on withdrawal (45). In a second Australian study of long-term cannabis users (weekly use for at least 3 years), 32% responded affirmatively to a 12-month ICD-10 dependence criteria question on cannabis withdrawal (46).

Across studies of adults seeking treatment for cannabis abuse/dependence, 51%–95% reported cannabis withdrawal during the past year in structured diagnostic interviews (47–50). In the only study that inquired about specific withdrawal symptoms in adults seeking treatment for cannabis dependence (51), 85% reported experiencing at least four symptoms of at least mild severity the last time

they abstained from cannabis for at least 24 hours. The most frequently reported symptoms (reported by more than 70% of the sample) were cravings, irritability, nervousness, depressed mood, restlessness, sleep difficulty, and anger. It is noteworthy that 67% rated four or more symptoms as moderately severe and 47% rated four or more symptoms as severe, the highest category on the 4-point scale. In the only study of adolescents, 67% of a group in residential care for drug abuse described a history of cannabis withdrawal, with the most common symptoms being irritability, restlessness, depressed mood, sleep difficulty, and fatigue/yawning (52).

These survey studies all relied on retrospective reports, did not control for symptoms experienced during regular cannabis-use periods (baseline), and did not discern whether the participants had stopped any other substance use simultaneous with the referent period of cannabis cessation. Thus, the validity and causality of the symptom reports cannot be clearly established. Nonetheless, the symptom profiles reported in these studies are remarkably similar to those reported in the experimental studies reviewed earlier, providing convergent validity for the syndrome. The consistency of these survey findings strongly suggests that cannabis withdrawal occurs among a substantial subset of regular marijuana users who stop smoking cannabis, and, most likely, the prevalence of such withdrawal is greater among heavier users and particularly among those seeking treatment for cannabis dependence.

Cannabis Withdrawal Syndrome

We have proposed that designation of a true withdrawal syndrome requires evidence that the negative abstinence effects 1) occur reliably, 2) are not exceptionally rare, 3) have a specific time course that includes a return to baseline state (i.e., are transient effects), 4) abate with readministration of the drug, 5) are due to deprivation of a specific substance, and 6) are clinically significant (7). In this section, we briefly comment on how well the extant data on cannabis abstinence effects address these criteria.

Reliability

In terms of test-retest reliability, three studies have examined cannabis abstinence effects across repeated abstinence periods within the same participants (30, 31, 40). Two inpatient studies examining two different dosing conditions for both smoked cannabis and oral THC found similar effects across two 4-day abstinence phases, with slightly more pronounced effects observed after cessation of higher doses (30, 31). An outpatient study found that specific symptoms increased reliably during two abstinence phases, but most effects appeared more robust in the first abstinence phase compared to the second (40). In terms of interrater reliability, across two outpatient studies, independent observers living with the participants observed significant increases in irritability, anger/aggression, and restlessness/nervousness during abstinence periods, confirming the users' reports of these symptoms (40, 41).

Regarding cross-study reliability, the most consistently reported symptoms are anxiety, decreased appetite/weight loss, irritability, restlessness, sleep problems, and strange dreams (Table 1). These symptoms were associated with abstinence in at least 70% of the studies in which they were measured. Other clinically important symptoms such as anger/aggression, physical discomfort (usually stomach related), depressed mood, increased craving for marijuana, and increased sweating and shakiness occurred less consistently. These latter symptoms might be less reliable across studies because of methodological and measurement variability; they might occur only in more severe cases or with higher dosing schedules, or they might reflect individual variation in symptom expression or unique characteristics of the study samples. In summary, several cannabis withdrawal symptoms possess within-subject, interrater, and across-study reliability.

Incidence/Prevalence

The incidence of specific abstinence effects gleaned from experimental laboratory studies suggests that the majority of daily marijuana users experience withdrawal symptoms upon abrupt cessation of use. An early inpatient study reported that 55%–89% of participants experienced irritability, restlessness, insomnia, or anorexia after discontinuation of oral THC (24–26). One outpatient laboratory study reported that more than 50% of heavy cannabis users experienced an increase in symptom severity of at least 30% (3 points on a 10-point scale) on five discrete symptoms (39). Another outpatient study (41) reported that 40% of participants experienced increases of at least 25% (1 point on a 4-point scale) on eight discrete symptoms and that 78% reported such increases for four or more symptoms.

The retrospective survey studies also suggest that withdrawal symptoms are experienced by the majority of chronic, heavy cannabis users. Large population studies indicate cannabis withdrawal occurs among a subpopulation of users, with higher prevalence and more symptoms reported by more chronic, frequent, and dependent users (42–44). The majority of adults seeking treatment for cannabis abuse or dependence report a history of experiencing cannabis withdrawal (47–50), and most report a co-occurrence of four or more symptoms of substantial severity (51). A substantial proportion of adolescents seeking treatment for substance abuse also indicate that they have experienced multiple cannabis withdrawal symptoms (52). In summary, cannabis withdrawal symptoms are reported by a significant proportion of heavy (daily or dependent) marijuana users. The incidence of experiencing multiple symptoms upon cessation of use appears to be more than 50%, and, among treatment seekers, the proportion is likely higher.

Time Course

The onset of cannabis abstinence symptoms has consistently been observed during the first 1–2 days postcessation of cannabis or oral THC administration across several inpatient and outpatient studies (25, 30, 31, 39–41). In the only two outpatient studies that examined extended periods of abstinence, peak effects typically occurred between days 2 and 6 (39, 41). Most symptoms appeared to return to baseline or to comparison-group level within 1–2 weeks, with moderate variability noted across symptoms and individuals. Most abstinence symptoms followed a transient pattern, peaking shortly after cessation and returning to baseline over time. Sleep problems, particularly unusual dreams, did not return to baseline by the end of a 45-day abstinence period and thus cannot be classified as transient (41). Irritability and physical tension also did not return to baseline during the 28-day abstinence study (39), although irritability did return to baseline in the 45-day study (41). The observation that most transient symptoms returned to baseline and comparison-group levels, combined with the exclusion of persons with psychiatric disorder from these studies, suggests that these abstinence effects are not rebound effects indicative of the participants' condition before initiation of cannabis smoking. In summary, a well-defined time of onset, peak, and duration has been defined for several symptoms.

Pharmacological Specificity and Reversal of the Syndrome With Drug Readministration

Demonstration of precipitated withdrawal using the CB1 receptor antagonist in animal research has provided some indication of the pharmacological specificity of cannabinoid abstinence effects (16). In humans, smoking cannabis after a period of cannabis or oral THC abstinence attenuates abstinence symptoms (24, 31, 40); multiple abstinence symptoms show an abrupt reduction and return to baseline with the administration of cannabis during the first 24–96 hours of abstinence. Although these findings cannot establish that deprivation of THC itself causes withdrawal, several other lines of evidence suggest that the cannabis withdrawal syndrome is specific to THC in humans. One study showed that smoking placebo cannabis cigarettes (THC removed) after a period of cannabis smoking produced abstinence effects (31). Other studies have shown that deprivation of oral THC after administration of oral THC produces abstinence effects (24, 26, 30). Most recently, a well-designed inpatient/outpatient study (34) showed that low doses of oral THC (10 mg five times per day) administered during abstinence from daily marijuana smoking significantly decreased abstinence effect ratings, compared with placebo THC. It is noteworthy that the active THC dose was subjectively indistinguishable from placebo. Another method to demonstrate pharmacological specificity would be to administer a cannabinoid antagonist to determine whether it precipitates withdrawal, but this strategy has not yet been attempted in humans. In summary, although not all the possible tests of pharmacological specificity have been investigated, several lines of existing evidence support the conclusion that cannabis withdrawal is specific to THC deprivation.

Generalizability

The experimental laboratory studies reviewed here have examined what might best be labeled "heavy, regular" cannabis users. Participants have typically been daily users of cannabis, most used cannabis multiple times per day, and most met the DSM criteria for dependence. Although such cannabis users might be thought of as a small subset, conservative estimates indicate that there are more than 2.6 million daily cannabis users in the United States (53). Nonetheless, the selection criteria used in these experimental studies (studying only heavy cannabis users, and in some studies only those who reported cannabis withdrawal symptoms during past cessation episodes) would suggest that the resulting estimates of withdrawal may be inflated. Other factors, however, might have had the converse effect. Participants were not seeking treatment and were likely less dependent than treatment seekers. Also, participants were asked to refrain from smoking only temporarily for the purposes of the study, which should produce less withdrawal than that seen in a true quit attempt (7). In summary, cannabis withdrawal effects clearly occur in the majority of heavy, daily users. How common and severe cannabis withdrawal is among adolescents and less-than-daily users will require further study.

Clinical Significance

Recent studies provide converging evidence for the clinical significance of the withdrawal syndrome. DSM-IV-TR requires two to four symptoms for diagnoses of different substance withdrawal syndromes. First, among cannabis-dependent outpatients, 67% retrospectively reported experiencing four or more symptoms of at least moderate severity (51), and in controlled experimental studies, more than one-half of non-treatment-seeking daily cannabis users experienced multiple withdrawal symptoms (39, 41). Second, a comparison of experimental studies of tobacco and cannabis abstinence that used similar measures to assess abstinence symptoms showed that the magnitude of change from baseline appears similar for five symptoms common to both syndromes, suggesting that the severity of cannabis withdrawal is comparable to that of the well-established tobacco withdrawal syndrome (54). Third, abstinence symptoms are clearly observable to persons living with the participant, and the comments of these observers suggested that symptoms are disruptive to daily living (40, 41). Last, the majority of persons enrolled in treatment for cannabis dependence acknowledged cannabis withdrawal symptoms, labeled at least some of these symptoms as moderate to severe, and complained that they made cessation more difficult (48, 50, 51). The common symptoms of cannabis withdrawal are primarily

emotional and behavioral and do not typically cause significant physical, medical, or psychiatric disorders. However, this pattern does not mean that cannabis withdrawal is clinically unimportant. Other substance withdrawal syndromes (cocaine, nicotine) were included in the DSM in large part because of acknowledgment that behavioral and emotional withdrawal symptoms are as important, if not more important, than physical symptoms in undermining abstinence. In fact, although older studies suggested that physical symptoms indicated true biological effects, more recent animal studies suggest that emotional and behavioral symptoms of abstinence are the core symptoms of abstinence-related CNS effects and may be more important in precipitating dependence or relapse than physical symptoms (20). However, an important gap in the literature on the clinical significance of cannabis withdrawal is the absence of any studies showing that cannabis users with greater withdrawal symptoms are more likely to relapse or less likely to initiate an abstinence attempt. In summary, several lines of evidence indicate that the cannabis withdrawal syndrome causes significant distress in many heavy cannabis users; however, an adequate test of whether such distress influences quit attempts or relapse is not yet available.

Conclusions

The review of studies of cannabis withdrawal by Smith (5) cited discrepancies in symptoms across studies, lack of controls, ignorance about the time course, lack of studies in real-world settings, limited data on pharmacological specificity, lack of demonstration of clinical significance, lack of documentation of transient effects, and the possibility that the effects are due to psychiatric/personality comorbidity. Our review documents that several recent well-controlled experimental studies of cannabis withdrawal have adequately addressed these methodological issues. These studies have more clearly defined the syndrome and confirmed the symptom profile observed in earlier reports. They have also enhanced the external and ecological validity of the syndrome by documenting withdrawal in real-world settings. The magnitude of symptoms in these studies is substantial, as evidenced by ratings of collateral observers and comparisons with other well-established withdrawal syndromes such as tobacco withdrawal. Most symptoms have been shown to be true transient withdrawal symptoms, with a time course similar to the symptoms of other withdrawal syndromes, and have been shown not to be due to concurrent psychopathology.

We propose that the cannabis withdrawal syndrome is reliable, valid, and clinically important and should be included in the next revision of DSM. Appendix 1 lists symptoms we propose as criteria for a cannabis withdrawal disorder (41). The common symptoms reflect those observed consistently across studies of cannabis withdrawal and reported by a substantial proportion of participants studied (Table 1). The less common or equivocal symptoms have been observed across some studies, are experienced by a minority of study participants, or are of lesser magnitude. Other symptoms appear in more than one study but not in the majority of studies. We believe endorsement of at least four of these symptoms and evidence that these symptoms produced clinically significant distress or dysfunction should lead to a diagnosis of cannabis withdrawal. Furthermore, adoption of a diagnosis of cannabis withdrawal would eliminate one of the discrepancies in substance use disorders between DSM and ICD nosologies.

Although we argue that there exists sufficient empirical information to validate the clinical importance of a cannabis withdrawal syndrome, several areas of exploration are especially worthy of further research. The first and foremost research direction is to determine whether cannabis withdrawal symptoms interfere with the establishment of abstinence or promote relapse among persons who are attempting to quit. Prospective studies of cannabis users who are seeking treatment or who plan to quit on their own are needed to determine whether those who have greater withdrawal symptoms are less likely to be able to maintain longer-term abstinence. Second, some withdrawal syndromes are thought to be able to induce a reoccurrence of prior psychiatric disorder (7); thus, we must learn whether the cannabis withdrawal syndrome can precipitate relapse of a prior psychiatric disorder. The controlled studies described herein did not include persons with histories of significant psychiatric disorder, yet we know that many persons who are cannabis dependent have coexisting psychiatric problems (41, 49, 50, 55). Third, severity of withdrawal syndromes is typically related to the amount of drug use, yet we know little about the relationship between amount or duration of cannabis use and the associated severity of the withdrawal response. Fourth, whether cannabis withdrawal occurs in chronic, less-than-daily users must be determined. Last, and certainly not least, we need to test whether various pharmacological and behavioral treatments can abate cannabis withdrawal; initial human laboratory studies of potential pharmacotherapies suggest that this may be a fruitful area of investigation (33–35).

APPENDIX 1. Proposed Cannabis Withdrawal Syndrome Criteria

Common symptoms
Anger or aggression
Decreased appetite or weight loss
Irritability
Nervousness/anxiety
Restlessness
Sleep difficulties, including strange dreams
Less common symptoms/equivocal symptoms
Chills
Depressed mood
Stomach pain
Shakiness
Sweating

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