RESEARCH REPORT

Marijuana withdrawal among adults seeking treatment for marijuana dependence

ALAN J. BUDNEY, PAMELA L. NOVY & JOHN R. HUGHES

University of Vermont, Burlington, Vermont, USA

Abstract

Aims. *The clinical relevance of marijuana withdrawal has not been established. This study is the first to document the incidence and severity of perceived marijuana withdrawal symptoms in a clinical sample of marijuana-dependent adults.* **Measurements**. *Fifty-four people seeking outpatient treatment for marijuana dependence completed a 22-item Marijuana Withdrawal Symptom checklist based on their most recent period of marijuana abstinence.* **Findings**. *The majority (57%) indicated that they had experienced ≥ six symptoms of at least moderate severity and 47% experienced ≥ four symptoms rated as severe. Withdrawal severity was greater in those with psychiatric symptomatology and more frequent marijuana use.* **Conclusions**. *This study provides further support for a cluster of withdrawal symptoms experienced following cessation of regular marijuana use. The affective and behavioral symptoms reported were consistent with those observed in previous laboratory and interview studies. Since withdrawal symptoms are frequently a target for clinical intervention with other substances of abuse, this may also be appropriate for marijuana.*

Introduction

Marijuana (cannabis) withdrawal is not recognized in the DSM-IV, as the manual states that there "have been some reports of withdrawal symptoms, but these have not yet been reliably shown to be clinically significant".[1] The ICD-10 allows for a diagnosis of marijuana withdrawal, but it does not provide descriptors of the symptoms that comprise such a syndrome.[2] Given that non-human and human inpatient studies have demonstrated clearly that withdrawal can occur following abrupt cessation of marijuana or tetrahydrocannabinol (THC) administration (see below), the reason for its omission from DSM-IV appears due to the lack of generalizable, controlled outpatient studies of the incidence and severity of marijuana withdrawal among regular users. Unfortunately, the exclusion of marijuana withdrawal from the DSM contributes to the perception that marijuana use has minimal risk for harm or development of dependence, and that the development of behavioral or pharmacological treatments specifically for marijuana dependence is not necessary. Indeed, these perceptions are inaccurate as marijuana use can produce dependence at rates comparable to other substances of abuse, increase psychiatric and medical problems and impair psychosocial functioning.[3–6] Many marijuana users have difficulty quitting and maintaining abstinence

from marijuana; moreover, response to treatment and relapse rates among people seeking treatment for marijuana dependence are similar to those observed with other substances of abuse.[7,8] Whether relapse in marijuana users is influenced by withdrawal symptoms has not been tested. If this were the case, then specific behavioral and pharmacological treatment for withdrawal could be useful in the treatment of marijuana dependence.

Early studies using rhesus monkeys showed clear evidence that withdrawal can occur following chronic administration of injected and oral THC.[9–11] Across these studies, abstinence effects observed included yawning, anorexia, piloerection, irritability, increase in gross motor movement, eye contact, tooth-baring, scratching, biting and licking fingers, hair-pulling, tremors, twitches, shaking, apparent hallucinations and disruption in operant responding. The discovery of the cannabinoid receptor (CB1) in the late 1980s and the subsequent development of a cannabinoid antagonist (SR 141716A) provided a more definitive means of testing for marijuana (THC) withdrawal. Antagonist challenge studies in which the cannabinoid antagonist is administered to animals following chronic dosing with THC have demonstrated a marked withdrawal syndrome in rats and dogs.[12–14]

Human inpatient laboratory studies confirmed the findings of the primate research. In these studies, subjects were typically confined to a research ward, provided free access to marijuana cigarettes for a specified number of weeks, and then access was discontinued.[15–18] A fairly uniform set of signs and symptoms were observed following cessation of marijuana use including irritability, restlessness, sleep difficulties, decreased appetite and unco-operativeness. A more rigorous test of withdrawal occurred in a series of studies in which subjects were administered relatively high doses of oral THC (10–30 mg) every 3–4 hours, 24 hours a day.[19,20] Cessation of THC dosing resulted in symptoms similar to those observed in the marijuana smoking studies. In addition, readministration of THC reduced subjective and objective withdrawal symptoms, and administration of a placebo resulted in no withdrawal symptoms when discontinued. These results were replicated in a recent, well-controlled laboratory study using smaller doses and a shorter duration of oral THC administration.[21] It is important to realize that inpatient studies where the subject's environment is restricted may substantially underestimate the severity of drug withdrawal because stimuli found in the user's usual environment can greatly increase withdrawal severity, e.g. conditioned withdrawal effects.[22–24] Thus, withdrawal from regular, heavy marijuana smoking in the natural environment may be substantially greater than that observed in these inpatient studies.

Two interview studies of non-clinical samples of marijuana users support the findings of the laboratory research on marijuana withdrawal. In one study, structured interviews of 5611 individuals indicated that 16% of those with a lifetime history of frequent marijuana use described a history of marijuana withdrawal.[25] Typical symptoms included nervousness, restlessness, sleep difficulty and appetite change. Similarly, in the DSM-IV field trials 25% of people who had smoked marijuana at least six times in their life reported experiencing marijuana withdrawal, while 85% of those who were marijuana dependent reported withdrawal or tolerance.[26] Crowley and colleagues documented similar descriptions of marijuana withdrawal among adolescent substance abusers in residential care.[27] Seventy-eight per cent of these patients met DSM-criteria for marijuana dependence and 67% of these described a history of marijuana withdrawal, with the most common symptoms being irritability, restlessness, depressed mood, sleep difficulty and fatigue/yawning. Although all these interview studies are limited by the retrospective data collection, the results suggest that some level of marijuana withdrawal occurs among a subset of regular marijuana users when they stop smoking marijuana.

An abbreviated summary of the extant literature on marijuana withdrawal in humans is presented in Table 1. This literature suggests that a fairly consistent cluster of symptoms occurs under varying situations when chronic marijuana (THC) administration is discontinued abruptly. The purpose of the present study was to determine whether reports of marijuana withdrawal among adults seeking treatment for marijuana dependence are similar to those reported in the laboratory and interview studies of nonclinical samples of marijuana users. This information is needed to assess the importance of developing clinical strategies for assisting marijuana-dependent patients to cope with withdrawal

Table 1. *Marijuana (THC) abstinence symptoms reported across human laboratory and interview studies*

	Human laboratory				Interview		
	Jones *et al.*, 1976	Nowlan & Cohen 1977	Georgatas *et al.*, 1979	Haney *et al.*, 1999	Weisbeck *et al.*, 1997	Crowley *et al.*, 1998	Total[a]
Irritable	Y	Y	Y	Y	NA	Y	5/5
Nerv/tens	Y	NA	NA	Y	Y	Y	4/4
Restless	Y	Y	NA	Y	Y	Y	4/4
Sleep diff.	Y	Y	Y	Y	Y	Y	5/5
⇓⇓⇓Appetite	Y	Y	Y	Y	Y	Y	5/5
Anger (aggress)	Y	NA	Y	NA	NA	NA	2/2
Depression	N	NA	NA	NA	Y	Y	2/3
Craving	NA	Y	N	NA	NA	NA	1/2

Y = Symptom reported in the study; N = symptom assessed, but did not occur; NA = Not able to determine if the symptom was assessed in the study. [a] Number of studies that found positive results/number of studies that had data available.

during quit attempts. In our outpatient marijuana abuse treatment clinic, 65% of marijuana-dependent patients reported a history of marijuana withdrawal,[7] which is consistent with that reported in a previous study of treatment-seeking marijuana abusers.[8] We developed a Marijuana Withdrawal Questionnaire to assess more carefully these reports of withdrawal. The present study reports findings from 54 patients who completed this questionnaire during an intake evaluation for entry into an outpatient marijuana treatment clinic. To our knowledge, this is the first report to document the incidence and severity of perceived marijuana withdrawal symptoms in a sample of adults who were seeking treatment for marijuana dependence.

Method
Participants
Participants were people seeking outpatient treatment for marijuana-related problems in a small metropolitan area (Burlington, VT, USA). All met DSM-III-R criteria for marijuana dependence as determined by the DSM Checklist.[28] Participants were recruited via newspaper advertisements, posters displayed in the community and public service announcements, all of which indicated that free treatment for marijuana-related problems was available. In addition, our recruitment sources included professional and other patient referrals. Individuals with severe psychiatric or medical problems (e.g. active psychosis, acute high risk for suicide, liver or renal failure) that would interfere with participation in

outpatient treatment were excluded. People who met DSM-III-R criteria for current alcohol or other drug dependence except nicotine were excluded. A total of eight people were excluded from this sample: two who did not meet marijuana dependence criteria, five who were alcohol-dependent and one who was cocaine-dependent. These selection criteria appear to reflect the typical person who seeks treatment specifically for marijuana-related problems.[7,8]

The mean age of the participants was 33.8 ± 8.0 years. All were Caucasian, as the community in which this study was conducted includes only 1–2% ethnic minorities. Fifteen per cent of the sample were women. Eighty-two per cent were daily users of marijuana. The average number of times marijuana was smoked per day across the sample was 4.1 ± 3.4. Fifty-four per cent of subjects were tobacco cigarette smokers who reported smoking a mean of 26.1 ± 16.5 cigarettes per day. Seventy-eight per cent were regular caffeine users. On average, subjects drank alcohol on 5.9 ± 9.1 days during the prior month. Forty-two per cent indicated they had problems with alcohol in the past. Thirty-two per cent reported past problems with cocaine. Forty-one per cent reported having a history of psychiatric problems, but structured interviews to determine specific psychiatric diagnoses were not conducted.

Intake assessment and measures
Written informed consent was obtained prior to the assessment. Intake workers under the super-

vision of a doctorate-level, clinical psychologist administered the following instruments: (a) DSM III-R checklist,[28] (b) Addiction Severity Index (ASI),[29] (c) drug-history question-naire, (d) Time-Line-Follow-Back interviews (TLFB),[30] (e) Brief Symptom Inventory (BSI),[31] (f) Beck Depression Inventory (BDI),[32] (g) University of Rhode Island Change Assessment revised for marijuana use (URICA)[33] and (h) Situational Confidence Questionnaire revised for marijuana use (SCQ).[34] Intake workers were trained to administer the DSM-III-R checklist and the ASI via manual review, observation and supervised practice interviews. The psychologist reviewed all diagnoses and reinterviewed subjects if the diagnosis was not clear.

The DSM-III-R checklist is a semi-structured interview used to diagnose common Axis I psy-chiatric disorders and anti-social personality dis-order.[28] Only the Psychoactive Substance Use Disorders section of the checklist was adminis-tered to make current substance-use diagnoses. The ASI is a clinical research interview used to assess problem severity in seven areas (medical, legal, alcohol, drug, employment, family and psychiatric).[29] ASI subscale composite scores were calculated for each problem area using the weighted combinations of individual items that provide reliable and valid measures of problem severity during the 30 days prior to the interview. A structured drug-history interview was used in combination with the TLFB[30] to collect infor-mation on frequency, quantity and patterns of substance use. TLFB is a reliable timeline method developed to assess problem drinker's reports of recent drinking, which we adapted to collect self-reported days and times per day of marijuana use. Information regarding the quan-tity of marijuana used (e.g. grams) was not obtained, as large within- and between-subject differences in the potency of marijuana used and the topography of marijuana smoking make quantity estimation of the active ingredient (delta-9-THC) highly variable and difficult to interpret.

The URICA provides an assessment of how ready an individual is to change a problem behavior;[33] we adapted this questionnaire for use with marijuana users. The URICA yields four subscale scores. A "readiness-to-change" score was computed by substracting the precontempla-tion subscale score from the sum of the contem-plation, action and maintenance subscales. The

Situational Confidence Questionnaire (SCQ) is a 39-item instrument that provides a measure of the individual's confidence in resisting use of alcohol across a variety of high-risk situations;[34] we adapted this questionnaire for use with mari-juana users. The Brief Symptom Inventory (BSI) is a 53-item self-report inventory measuring psychiatric distress levels across nine sub-scales and three global indices of distress.[35] The Beck Depression Inventory is a 21-item ques-tionnaire used to screen for severity of depressive symptomatology. Scoring of the self-report ques-tionnaires was conducted according to the respective manuals or instructions provided by the authors.

Marijuana Withdrawal Checklist
The Marijuana Withdrawal Checklist lists 22 symptoms. Twelve of these items were taken from previously published human laboratory studies of marijuana withdrawal (i.e. craving, irritability, nervousness, depression, anger, rest-lessness, sleep problems, decreased appetite, increased appetite, strange dreams, headaches, violent outbursts). The other 10 items were asso-ciated with other substance withdrawal syn-dromes and were used as filler items so that we could examine the specificity of marijuana with-drawal. In addition, we included an open-ended "other" section to capture any additional symp-toms subjects might report. Participants indi-cated which items were experienced during their most recent period of marijuana abstinence and rated each symptom's severity on a four-point scale (0 = not at all, 1 = mild, 2 = moderate, 3 = severe). Data were not available on how long ago the abstinence period occurred.

A total withdrawal discomfort score (WDS) was created by summing the severity ratings from the 10 symptoms reported by $\geq 40\%$ of the participants. The less frequently cited symptoms were excluded from this severity index as they were thought to have poorer specificity to mari-juana withdrawal, and might obscure or con-found relationships examined in exploratory analyses of factors related to withdrawal severity. The reliability of the 10-item WDS was $\alpha = 0.89$ supporting its use as a withdrawal severity scale. Of note, the Pearson correlation between the WDS and a total withdrawal score calcuated using all 22 checklist items was 0.92.

Table 2. *Percentage of patients who reported each withdrawal symptom and the severity rating* (N = 54)

	Mild rating ≥ 1	Moderate rating ≥ 2	Severe rating = 3
Mood			
Irritability	87	64	40
Nervousness	80	53	33
Depression	76	59	28
Anger	74	56	24
Behavioral			
Craving	93	78	44
Restlessness	76	48	22
Sleep problems	67	43	19
⇊⇊Appetite	50	30	11
Strange dreams	50	37	20
⇈⇈Appetite	38	19	6
Violent outbursts	36	17	6
Physical			
Headaches	46	28	9
Shakiness	39	15	7
Stuffy nose	32	11	6
Sweating	20	13	4
Hot flashes	20	9	6
Feverish	20	13	6
Diarrhea	17	11	7
Nausea	19	13	6
Muscle spasms	15	8	6
Chills	17	11	6
Hiccups	6	2	2

Data analyses

This initial report provides descriptive statistics regarding the number and severity of withdrawal symptoms reported across participants. In addition, univariate, correlational and regression analyses were conducted to explore potential predictor variables of withdrawal severity.

Results

Symptom frequency and severity

The majority of participants reported experiencing multiple symptoms of marijuana withdrawal (Table 2). Eighty-five per cent reported four or more symptoms; on average, participants acknowledged 9.6 ± 5.1 symptoms. Most also reported symptoms of substantial severity. For example, 57% reported 6 or more symptoms of at least moderate severity (rating of ≥ 2) and 47% reported four or more symptoms rated as severe (rating = 3).

Specific symptoms of abstinence

The 10 symptoms reported by ≥ 40% of the subjects were primarily affective and behavioral in nature, i.e. craving, irritability, nervousness, restlessness, depressed mood, increased anger, sleep difficulties, strange dreams, decreased appetite and headaches (Table 2). These 10 symptoms were a subset of the 12 checklist items gleaned from the extant literature on marijuana withdrawal. None of the 10 items that were included in the checklist because of their association with other substance withdrawal syndromes were reported as marijuana withdrawal symptoms by greater than 40% of our subjects.

Correlational analyses

Intercorrelations among the 10 most frequently reported symptoms are presented in Table 3. Most symptoms were moderately correlated with each other. Affective symptoms (irritability, depressed mood, nervousness and anger) were most highly correlated. An insufficient sample size precluded conducting a factor analysis to determine whether checklist items formed discrete subscales or latent constructs.

The mean WDS was 14.4 ± 7.8 and ranged from 0 to 28. Correlations between WDS and

Table 3. *Inter-correlations of withdrawal symptoms reported by greater than 40% of subjects*

	Craving	Irrit	Nervous	Restless	Depress	Anger	Sleep	Dreams	Appetite	Headache
Craving	—	0.64	0.40	0.45	0.62	0.48	0.28	0.38	0.35	0.47
Irritable	—	—	0.61	0.38	0.67	0.51	0.21	0.19	0.33	0.41
Nerv/tens	—	—	—	0.59	0.78	0.72	0.48	0.39	0.42	0.39
Restless	—	—	—	—	0.59	0.44	0.69	0.47	0.44	0.45
Depression	—	—	—	—	—	0.69	0.47	0.36	0.45	0.49
Anger	—	—	—	—	—	—	0.34	0.34	0.28	0.30
Sleep difficulty	—	—	—	—	—	—	—	0.46	0.30	0.43
Strange dreams	—	—	—	—	—	—	—	—	0.35	0.39
⇂⇂⇂Appetite	—	—	—	—	—	—	—	—	—	0.34

Correlation coefficients > 0.26 are significant at $p < 0.05$. Correlation coefficients > 0.35 are significant at $p < 0.01$.

Table 4. *Correlations between withdrawal discomfort score and baseline variables*

	Correlation coefficient
Age	− 0.09
Gender (female)	0.24
Living with children (yes)	0.24
Years of marijuana use	0.04
Daily marijuana user (yes)	0.06
Times used per Day	0.35**
Cigarette smoker (yes)	0.20
Addiction Severity Index	
Medical	0.45**
Family/social	0.37**
Legal	− 0.12
Employment	− 0.16
Psychiatric	0.50**
Drug	0.44**
Alcohol	− 0.17
Brief Symptom Inventory	
Global symptom index	0.51**
Somatization	0.64**
Hostility	0.59**
Anxiety	0.49**
Obsess/comp	0.43**
Interpersonal sens	0.36**
Paranoid	0.34*
Psychoticism	0.33*
Depression	0.32*
Phobic	0.30*
Beck Depression Inventory	0.57**
Readiness to Change	0.40**
Situational confidence (total score)	− 0.33*

** $p < 0.01$; * $p < 0.05$.

socio-demographic, psychosocial, psychiatric and substance-use variables collected at intake were typically moderate ($r = 0.3$–0.6) and occurred with many of the variables (Table 4).

Univariate analyses

Because the psychiatric variables were all significantly correlated with withdrawal severity, we performed additional analyses to compare withdrawal reports of those with high vs. low psychiatric severity. To do this, we split the sample into two groups using the clinical cut-off (T score of 63) on the Global Symptom Index of the BSI. Both groups reported multiple, mild to severe withdrawal symptoms (Table 5). However, the high psychiatric group ($N = 33$) reported a greater number and more severe symptoms than the low psychiatric group ($N = 19$), and the mean WDS was greater in the high group (16.8 ± 7.0 vs. 9.4 ± 7.0, $p < 0.01$).

The relationship between past problems with substances other than marijuana abuse and marijuana withdrawal was explored to provide information on whether concurrent cessation of other abused substances may have influenced reports of marijuana withdrawal. An item from the drug history questionnaire (i.e. did you ever have a problem with any of the following substances) asked subjects to rate past problems with other substances on a four-point ($0 =$ no problem, $1 =$ sometimes a problem, $2 =$ often a problem, $3 =$ always a problem). Subjects were dichotomized into two groups based on their response to this item. Those who reported any past problems of other substance abuse (a greater than 0 response for any substance) were included in the history-positive group (H + :$N = 27$) and those who reported no history of problems were considered history-negative (H-: $N = 24$). Both groups reported substantial marijuana withdrawal. The mean WDS of the H + group

Table 5. *The number and severity of marijuana withdrawal symptoms reported by participants with high versus low psychiatric symptom severity*

Withdrawal symptom severity[a]	Number of withdrawal symptoms					
	≥ 4		≥ 6		≥ 8	
	High psych	Low psych	High psych	Low psych	High psych	Low psych
Mild (≥ 1)	91%	74%	88%	53%	82%	42%
Moderate (≥ 2)	79%	42%	67%	37%	51%	16%
Severe ($= 3$)	42%	16%	30%	10%	09%	05%

High psych ($N = 33$): this group included those with a T-score ≥ 63 on the Global Symptom Index of the BSI. Low psych ($N = 19$): this group included those with a T-score ≤ 62 on the Global Symptom Index of the BSI. [a] Item severity ratings from the Withdrawal Checklist range from 0 to 3 (none = 0, mild = 1, moderate = 2, severe = 3).

(16.1 ± 6.9) was greater than the H- group (12.7 ± 8.3), but this difference was not statistically significant ($p = 0.12$). A similar analysis comparing tobacco smokers versus non-smokers also revealed no significant between-groups difference on the WDS ($p = 0.16$).

Regression analyses

A stepwise regression using PROC STEPWISE (36) and a 0.15 significance level cut-off for entry into the model was performed to examine which variables were the best potential predictors of withdrawal severity. Only five independent variables were examined in this *post-hoc* analysis because of the sample size ($N = 54$). Each of the chosen variables was significantly correlated with withdrawal severity; each was not highly correlated with the other selected variables ($r < 0.40$); and each hypothetically represented a discrete association to withdrawal severity. The somatization score from the BSI was used because it was the psychiatric variable most highly correlated with withdrawal severity. The number of times marijuana was smoked per day was included as a measure of dose (i.e. frequency and quantity of use). The ASI Drug severity score reflected the overall severity of the patient's current drug abuse problems. The URICA readiness to change score was included as a measure of willingness to change marijuana use. The total score from the Situational Confidence Questionnaire was used to reflect confidence in abstaining from marijuana use. The regression yielded a final equation that included the somatization score ($p < 0.01$, partial $R^2 = 0.43$, the ASI drug score ($p < 0.05$, partial $R^2 = 0.08$), and times per day

marijuana was smoked ($p < 0.05$, partial $R^2 = 0.05$). The total R^2 achieved with this model was 0.56.

Discussion

The large majority of adults seeking outpatient treatment for marijuana dependence in this study reported a history of many withdrawal symptoms during previous periods of abstinence from marijuana (e.g. 85% reported $\geq$ four symptoms). Often these symptoms were rated severe (e.g. 47% reported $\geq$ four severe symptoms). These patients described behavioral and affective symptoms following cessation of marijuana use that were remarkably similar to those observed across prior laboratory and interview studies (see Table 1). The consistency of the specific symptoms reported within this study and across other studies suggests that a valid marijuana withdrawal syndrome occurs in a substantial number of marijuana abusers who abruptly stop using marijuana. Moreover, the number and magnitude of the perceived withdrawal symptoms described by our patients suggests that these abstinence effects may contribute to the development of marijuana dependence problems and may negatively influence attempts to stop marijuana use.

Before commenting on these findings, it merits note that they should be interpreted with caution due to the following methodological limitations. First, the symptom reports were collected retrospectively and were subject to memory bias (data were not available on how long ago withdrawal occurred). Prospective studies that assess symptom reports in marijuana-dependent

patients prior to, during, and following quit attempts are needed to obviate the potential for recall bias. Secondly, although we excluded marijuana-dependent subjects who were currently abusing other substances, many reported past problems with other substances (e.g. alcohol and cocaine). The historic reports of marijuana withdrawal collected in this study could have been confounded by simultaneous withdrawal from other substances (data were not available to address whether other drug use changed during the abstinence period). However, the fact that our *post-hoc* analyses failed to show a significant difference in marijuana withdrawal severity between subjects with versus without a history of other substance problems supports a conclusion that the reports of marijuana withdrawal provided in this study were not merely misattributions of withdrawal from other substances. Thirdly, our symptom questionnaire was labeled the "marijuana withdrawal checklist". Such labeling may have contributed to a positive response set resulting in an increased rate of false-positive symptom reports. Moreover, subjects were not provided with definitions to anchor their responses on the four-point severity scale. Related to this, we did not have baseline data with which to compare the abstinence symptom reports; that is, we do not know whether the withdrawal symptom reports different significantly from symptoms experienced during periods of marijuana use.

With these limitations in mind, we comment on a few aspects of the findings. First, this study adds to the clinical data supporting the validity and potential clinical significance of a marijuana (cannabis) withdrawal syndrome. On average, our patients reported 6.4 symptoms of at least moderate severity. This number of symptoms exceeds the number (2–4) needed to meet criteria for any of the extant DSM-IV substance-withdrawal disorders.[1] In contrast to the conclusion of the DSM-IV substance-disorders committee (i.e. "the literature … appears to make a compelling case for this rare but real disorder"[37]), the present study suggests that marijuana withdrawal may commonly occur among patients seeking treatment for marijuana dependence.

A classic opioid- or alcohol-like withdrawal that includes discrete physiological and medical consequences is clearly not reported in most cases of marijuana withdrawal. However, the behavioral and affective withdrawal symptoms reported in this study do overlap with those observed in other substance withdrawal syndromes.[38] Thus, if the clinical import of marijuana withdrawal is to be determined by comparing it to the physical/medical aspects of opioid or alcohol withdrawal, resistance to the acceptance of a significant marijuana withdrawal syndrome should be expected to continue. Historically, the use of such standards led to the opposition of and delay in the acceptance of alcohol, cocaine, nicotine and sedative withdrawal.[39] On the other hand, if the affective and behavioral symptoms reported by our marijuana patients are recognized as being important and similar to those observed during withdrawal from most other substances of abuse[1,38], then the clinical relevance of marijuana withdrawal should more readily become apparent.

Indeed, recent non-human research examining the effects of cannabinoid withdrawal on specific areas of the brain (i.e. limbic system) has provided additional evidence indicating that its effects are similar to other drug withdrawal syndromes.[40] For example, investigators have identified that a decrease in brain reward function occurs during withdrawal from most major drugs of abuse.[41] The authors of these studies suggest that the behavioral consequences of the neurobiological changes observed during withdrawal are consistent with the type of symptoms (i.e. irritability, discomfort and negative affect) reported by our patients and patients withdrawing from other substances. Furthermore, they believe these common withdrawal symptoms may be as, if not more, important than drug-specific physiological consequences (e.g. piloerection, severe sweating or seizures) in determining whether the effects caused by the cessation of a substance contribute to the development of dependence and produce a clinically significant withdrawal syndrome.

The variable most highly correlated with withdrawal severity in the present study was psychiatric functioning. This finding emphasizes the need for baseline data to determine whether the described withdrawal symptoms merely reflect the usual symptom reports of people with significant psychiatric co-morbidity. A time—course analysis is also needed to examine the possibility that the abstinence effects we have described are not true withdrawal symptoms but are actually the simple off-set of drug effects seen in people who use marijuana to "self-medicate"

psychiatric symptoms. For example, if absti-
nence symptoms are increased compared to
baseline and remain increased (i.e. do not return
to baseline over time), this would indicate a
return to a pre-marijuana use state, and thus
simple drug off-set effects. An alternative
interpretation supported by our *post-hoc* analysis
which showed that participants without clinically
significant psychiatric symptomatology also
reported substantial withdrawal is that marijuana
withdrawal occurs independent of psychiatric
symptoms, yet its severity may be exacerbated by
such pre-existing problems. This interpretation
is bolstered by the fact that this pattern has been
shown in several studies of nicotine with-
drawal.[42,43]

Our finding that the dose of the drug (times
smoked per day) was related linearly to with-
drawal severity further supports the contention
that a valid withdrawal syndrome exists. Dose of
drug predicts withdrawal severity across most
substances.[38] Empirical support for this relation-
ship has also been demonstrated with oral mari-
juana (THC) in human inpatient studies (20).
Moreover, clinical case studies of very heavy
marijuana users and reports from other cultures
where very potent marijuana or hashish is com-
mon suggest that a relatively severe withdrawal
syndrome can occur.[44–48] Thus, the relationship
of dose or potency to the severity of marijuana
withdrawal may have important clinical rel-
evance.

Much is yet to be learned regarding the clini-
cal significance of marijuana withdrawal. Gener-
alizable, controlled outpatient studies of
post-cessation effects are needed to determine:
(a) which effects are reliable and clinically rel-
evant; (b) their severity and time—course; and
(c) their role in cessation attempts and marijuana
relapse. Moreover, studies with larger sample
sizes will allow for the examination of the factor
structure of Withdrawal Checklist items and
facilitate a more comprehensive exploration of
potential predictors of withdrawal severity.
Indeed, if the mood and behavioral symptoms
reported by our marijuana patients are found to
be reliable and valid, then the inclusion of mari-
juana withdrawal in documents such as the
DSM would assist in educating the greater sci-
entific and lay communities regarding the abuse
and harm potential associated with regular mari-
juana use. The delineation of a specific syn-
drome might also provide an important clinical

target for the development of behavioral and
pharmacological treatments of marijuana depen-
dence.

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