

The Time Course and Significance of Cannabis Withdrawal

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Withdrawal symptoms following cessation of heavy cannabis (marijuana) use have been reported, yet their time course and clinical importance have not been established. A 50-day outpatient study assessed 18 marijuana users during a 5-day smoking-as-usual phase followed by a 45-day abstinence phase. Parallel assessment of 12 ex-users was obtained. A withdrawal pattern was observed for aggression, anger, anxiety, decreased appetite, decreased body weight, irritability, restlessness, shakiness, sleep problems, and stomach pain. Onset typically occurred between Days 1–3, peak effects between Days 2–6, and most effects lasted 4–14 days. The magnitude and time course of these effects appeared comparable to tobacco and other withdrawal syndromes. These effects likely contribute to the development of dependence and difficulty stopping use. Criteria for cannabis withdrawal are proposed.

Cannabis (marijuana) withdrawal is not included in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*; American Psychiatric Association, 2000) as it indicates that symptoms of possible withdrawal have been described with the use of high doses, but their clinical significance is uncertain. The *International Classification of Diseases (ICD-10)*; World Health Organization, 1992) allows for a diagnosis of marijuana withdrawal, but it does not provide descriptors of the symptoms that comprise such a syndrome. Since the publication of the fourth edition of the *DSM (DSM-IV)*; American Psychiatric Association, 1994), controlled studies indicate that a reliable set of abstinence symptoms are experienced by a substantial proportion of heavy marijuana users (Budney, Hughes, Moore, & Novy, 2001; Budney, Novy, & Hughes, 1999; Haney, Comer, Ward, Foltin, & Fischman, 1999; Haney, Ward, Comer, Foltin, & Fischman, 1999; Kouri & Pope, 2000).

Two inpatient studies demonstrated that abstinence following 4 days of administration of oral THC (tetrahydrocannabinol) or smoked marijuana significantly increased ratings of anxious, depressed, irritable, and stomach pain, and decreased quantity and quality of sleep and food intake compared to placebo control periods (Haney, Comer, et al., 1999; Haney, Ward, et al., 1999). These results extended findings from inpatient studies conducted in the 1970s (S. Cohen, Lessin, Hahn, & Tyrell, 1976; Georgotas

& Zeidenberg, 1979; Jones & Benowitz, 1976; Mendelson, Mello, Lex, & Bavli, 1984).

An outpatient study of daily smokers demonstrated greater levels of provoked aggression on Days 3 and 7, but not Day 28 of marijuana abstinence compared to baseline and a control group (Kouri, Pope, & Lukas, 1999). A similar study examined a wider range of symptoms and showed greater levels of anxiety, irritability, physical symptoms, physical tension, decreased mood, and decreased appetite compared to controls during a 28-day period of supervised abstinence (Kouri & Pope, 2000); those symptoms remained elevated for at least 7–14 days, as did Hamilton Depression (Hamilton, 1960) and Anxiety (Hamilton, 1959) scale scores. Most recently, an outpatient study validated specific effects of marijuana abstinence in heavy marijuana users, and showed they were reliable and of significant magnitude (Budney et al., 2001). Aggression, anger, craving for marijuana, decreased appetite, irritability, restlessness, sleep difficulty, strange dreams, and weight loss were documented during 3-day abstinence periods.

Studies of nonclinical and clinical samples of marijuana users support laboratory reports of cannabis withdrawal. Sixteen percent of those with a lifetime history of frequent marijuana use (> 21 days in a year) described marijuana withdrawal that included appetite change, nervousness, restlessness, and sleep difficulty (Weisbeck et al., 1996). The majority of adolescents in residential treatment and adults in outpatient treatment for cannabis dependence reported histories of marijuana withdrawal with symptom profiles similar to those observed in the laboratory studies (Budney et al., 1999; Budney, Radonovich, Higgins, & Wong, 1998; Copeland, Swift, & Rees, 2001; Crowley, Macdonald, Whitmore, & Mikulich, 1998; Stephens, Roffman, & Simpson, 1993).

The time course and severity of specific symptoms of marijuana withdrawal remains unclear. Only Kouri and Pope (2000) have examined an abstinence period longer than 5 days in an outpatient setting. Their data suggest that most symptoms begin during Day 1 of abstinence and subside by Day 10, whereas other symptoms may continue for over 1 month. However, the baseline assessment used to compare abstinence effects in that study included only one data point, a retrospective report of the past 6 months' functioning. Without a more reliable measure of baseline functioning immedi-

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Table 1
Demographic and Substance Use of Current and Ex-Marijuana Users

Variable	Current users (<i>n</i> = 18)	Ex-users (<i>n</i> = 12)	<i>p</i> ^a
Demographics			
Male (% , <i>n</i>)	61 (11)	75 (9)	.43
Age	30.9 (8.2)	36.5 (11.0)	.12
Race (% White, <i>n</i>)	94 (17)	100 (12)	.41
Years of education	13.6 (1.8)	14.0 (2.1)	.55
Monthly income ^b	1,672 (962)	2,549 (1,820)	.10
Substance use and dependence			
Years of regular marijuana use	12.8 (8.4)	11.7 (7.6)	.71
Marijuana episodes/day	3.6 (2.1)	3.1 (1.4) ^c	.55
Marijuana episodes/day, baseline	3.5 (1.7)		
Tobacco smoker (% , <i>n</i>)	39 (7)	17 (2)	.19
Days of alcohol use in past 30 days	10.9 (8.6)	2.8 (5.7)	.008

Note. Values are means (and standard deviations) unless otherwise marked.

^a Significance level for between-groups comparisons; chi-square tests for nominal variables and *t* tests for continuous variables. ^b In U.S. dollars. ^c Reflects level of prior cannabis use.

ately prior to the abstinence period, estimation of the magnitude of specific abstinence effects and the delineation of their time course (onset, duration, offset) is significantly limited.

This study involved daily assessment of heavy marijuana users during a 5-day baseline smoking-as-usual period followed by a 45-day abstinence period. The primary aim was to obtain controlled information on the occurrence of specific effects, their magnitude, time of onset, peak, and offset. Such data are needed to develop clinical guidelines for the assessment and treatment of cannabis withdrawal, and to determine whether the syndrome should be included in next version of the *DSM*.

Method

Participants

Current and ex-marijuana users were recruited through newspaper advertisements for a 50-day study on the effects of marijuana use. Criteria for current users included: heavy use of marijuana (> 25 days/month) during the previous 6 months; no plans to change their current pattern of marijuana use; report of two or more negative symptoms when stopping marijuana use in the past (15% were excluded for this reason); not currently dependent on other substances except nicotine; not using illicit substances other than marijuana during the previous 30 days; not taking psychotropic medication; not meeting a current *DSM-IV* criteria for an Axis I psychiatric disorder other than nicotine dependence; not pregnant; and not seeking treatment for marijuana-related problems. Inclusion criteria for ex-users were the same as for current users except they must not have used marijuana or other forms of cannabis for at least 1 year.

Thirty-one current users initiated the study; 18 completed at least 31 days of the 45-day abstinence phase and were included in analyses. Thirteen participants were eliminated for the following reasons: abstinence from marijuana during baseline (*n* = 2), failure to initiate abstinence (*n* = 1), marijuana use during the first 2 weeks (*n* = 6), opiate use (*n* = 3), and unacceptably low urine creatinine levels (*n* = 1). Fifteen ex-marijuana users were screened, and 12 completed the study. One was eliminated on Day 5 for opiate use, and 2 withdrew for unrelated health concerns.

Table 1 presents demographic and marijuana use characteristics of current and ex-users included in the primary analyses. Only one significant between-groups difference was observed; current users drank alcohol more frequently than ex-users.

Measures

The time-line follow-back method (Sobel & Sobel, 1992) assessed daily substance use during the 6 months preceding participation. A drug history interview obtained information on all types of substance use. The *DSM-IV* checklist (see Hudziak et al., 1993) was used to diagnose current, common Axis I psychiatric disorders.

The primary dependent measure, the Marijuana Withdrawal Checklist (MWC), is comprised of items for which participants indicate severity on a 4-point scale from 0 (*not at all*), 1 (*mild*), 2 (*moderate*), to 3 (*severe*), (Budney et al., 1999). A 15-item version of the MWC was administered daily via an interactive telephone recording system (described later). These 15 items reflect those reported with some frequency in prior marijuana withdrawal studies. Thirteen additional items were assessed at each laboratory visit (2–4 times/week). The interitem reliability of the MWC as assessed with scores on Abstinence Day 3 was good (Chronbach's α = .81). Prior studies showed that this measure was sensitive to effects of abstinence (Budney et al., 2001; Budney et al., 1999). A 14-item, positive symptom checklist administered at each lab visit was included to minimize expectancy effects and to assess positive changes associated with cessation of use.¹

A 10-item Marijuana Craving Questionnaire adapted from a valid tobacco-smoking urges questionnaire (Tiffany & Drobles, 1991) was administered at each lab visit and yielded a total craving and two subscale scores. Subscale 1 reflects intention and desire to smoke marijuana and anticipated pleasure; Subscale 2 reflects anticipation of relief from negative affect and withdrawal.

Additional measures administered at each laboratory visit included the Brief Symptom Inventory (BSI), a measure of psychiatric symptomatology that yields nine subscales (Somatization, Obsessive–Compulsive, Interpersonal–Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism; Derogatis, 1993). The Profile of Mood States (POMS) scale provided six mood subscale scores (Tension, Depression, Anger, Vigor, Fatigue, and Confusion; McNair, Lorr, & Droppleman, 1971). Three Sleep Inventory items administered daily via telephone assessed total amount of sleep, number of nocturnal awakenings, and subjective sleep quality (Carskadon et al., 1976).

¹ Copies of the MWC and the positive symptom checklist are available from Alan J. Budney.

Heart rate and blood pressure (sitting) were measured by an automated monitor (DINIMAP; Johnson & Johnson, Arlington, TX). Body weight was obtained on a standing mechanical scale (Detecto; Cardinal Scale Manufacturing Co, Webb City, MO) without shoes and heavy clothing.

Current users named a collateral observer with whom they spent at least 2 hr/day. Research staff telephoned the observer and administered the MWC in reference to the participant's behavior on Baseline Days 1, 3, and 5, and Abstinence Days 2, 4, 8, 15, 25, 39, and 45.

Procedures

The study always began on a Thursday to minimize the effect of specific days on symptom ratings. Women began on the Thursday following the onset of menses. The University of Vermont Institutional Review Board approved all procedures, and informed consent was obtained from participants and collateral observers.

Study measures were obtained using two methods. Daily assessments of the 15-item MWC, the Sleep Inventory items, and substance use were collected using an automated interactive voice response (IVR) system (Perrine, Mundt, Searles, & Lester, 1995; Searles, Perrine, Mundt, & Helzer, 1995) to minimize the disruptive effects of frequent laboratory visits. Participants telephoned the IVR system at the same time each day and responded to recorded questions via Touch-Tone telephone. Studies of alcohol and cigarette use have demonstrated that the IVR is a practical and reliable method of measurement (Perrine et al., 1995; Searles et al., 1995). Contingent payments were used to enhance compliance for making IVR calls. Compliance for both current and ex-users was high. Seven of 878 (0.8%) calls were missed by current users and 11 of 577 (1.9%) calls were missed by ex-users.

Participants made 30-min visits to the laboratory on Days 1, 3, and 5 of the baseline phase, Days 1–4 of the abstinence phase, and twice per week thereafter. At each visit, physiological measures and body weight were obtained, urine and breath alcohol and CO samples were collected, and the MWC, BSI, POMS, and Marijuana Craving Questionnaire were administered. Compliance with lab visit attendance was 100%.

During the baseline phase, current users were instructed to smoke marijuana as they usually do (except not to smoke for at least 2 hr prior to laboratory visits), and to abstain from all other psychoactive drugs, with the exception of alcohol, nicotine, and caffeine. Participants were instructed not to make significant changes in their diet, exercise, caffeine, cigarette, or alcohol use throughout the study. Participation was terminated if marijuana abstinence was reported during baseline.

At the Day 5 baseline visit, current users were reminded that they were not to use marijuana for the next 45 days. Two methods of urinalysis were used to verify abstinence. A quantitative procedure was used for the first several weeks of the study. Gas chromatographic-mass spectroscopic levels of 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH), the primary marijuana metabolite, were normalized to urine creatinine concentration to obtain a metabolite-creatinine ratio. Abstinence was confirmed if the metabolite-creatinine ratio on any day did not increase by more than 50% from the ratio obtained the previous visit (Huestis & Cone, 1998). Second, specimens were tested for marijuana, cocaine, benzodiazepines, opioids, and methamphetamine using the qualitative Syva Rapid Test (Dade-Behring, San Jose, CA). Rapid tests were used in place of the quantitative analysis for cannabis after the Rapid Test indicated a cannabinoid-negative result (50 ng/ml cutoff).

Compensation of up to \$1,190 in vouchers was available to current users and \$580 to ex-users for successfully completing the study. For the current users, an escalating schedule of reinforcement was used to encourage participants to achieve and maintain a continuous period of abstinence from marijuana. Twice per week vouchers were earned if the urine specimen indicated no marijuana or other drug use. The value of the initial voucher was \$15 and each subsequent voucher increased in value by \$5. This type of voucher incentive program has demonstrated efficacy in

promoting abstinence in treatment-seeking marijuana and cocaine abusers (Budney et al., 2000; Higgins et al., 1994). Ex-users received \$10 vouchers for each lab visit. Both groups also earned vouchers for each IVR call and bonuses for making the calls on time. The vouchers were redeemed for retail goods designated by participants; no cash was provided.

Data Analysis

Analyses included the 18 current users who completed at least the first 31 days of the abstinence phase and the 12 ex-users who completed the study. The 31-day cutoff provided a sufficient time period for examining the time course. Comparisons of the 18 completers with the 6 users who failed to maintain abstinence (all used prior to Day 14) revealed no significant differences on the screening variables, and no differences on IVR item change scores from baseline to Abstinence Day 2 ($ps > .15$). Comparisons of demographic and substance use characteristics of the current and ex-users involved chi-square analysis for categorical variables, t tests for continuous variables, and analysis of ranked data for those variables with differences in variability across the two groups.

Repeated-measures analyses of variance (ANOVAs) were performed on dependent variables separately for current and ex-users. Daily IVR ratings were blocked into an initial 5-day baseline segment (mean score across the 5 days) and fifteen 3-day abstinence segments (mean score across the 3 days) resulting in a time factor of 16 repeated measures. This blocking procedure was used to reduce potential bias associated with spurious 1 day peaks or depressions, and to maintain robust statistical analysis because repeated-measures ANOVA is compromised when the number of variables exceeds the number of subjects. Measures collected at laboratory visits were blocked into one baseline score ($M = 3$ days) for the baseline phase, and twice weekly scores during abstinence phase, resulting in a time factor of 15 repeated measures. Because violations of homogeneity of covariance were common, Greenhouse-Geisser adjustments were used.

For IVR and laboratory measures, planned contrasts compared each abstinence segment score with the baseline score. This analytic approach is similar to that used with studies of nicotine withdrawal (Hughes, 1992). The dependent variables tested were each of the IVR items, the laboratory-based MWC items, the BSI and POMS subscales, the Marijuana Craving Questionnaire scores, the Sleep Inventory items, and the physiological variables. Also tested was a Withdrawal Discomfort Score (WDS) computed by summing 12 MWC items from the IVR assessment that increased postbaseline and showed patterns suggestive of withdrawal (aggression, anger, decreased appetite, depressed mood, irritability, nervousness/anxiety, restlessness, shakiness, sleep difficulty, stomach pains, strange dreams, sweating). Effect sizes (η^2) were calculated to provide an estimate of the relative size of the differences between the baseline phase and the 3-day

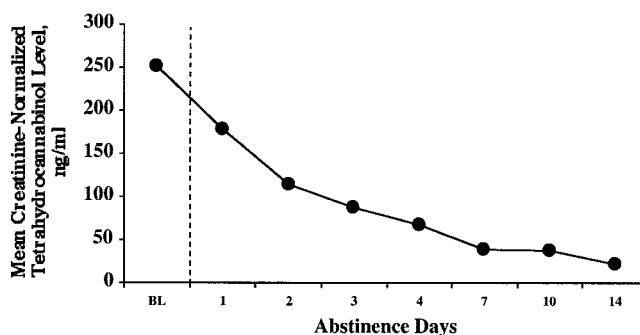


Figure 1. Mean creatinine-normalized tetrahydrocannabinol levels are presented across the first 2 weeks of the abstinence phase ($n = 18$). The value of the baseline (BL) data point reflects the mean of Days 1, 3, and 5.

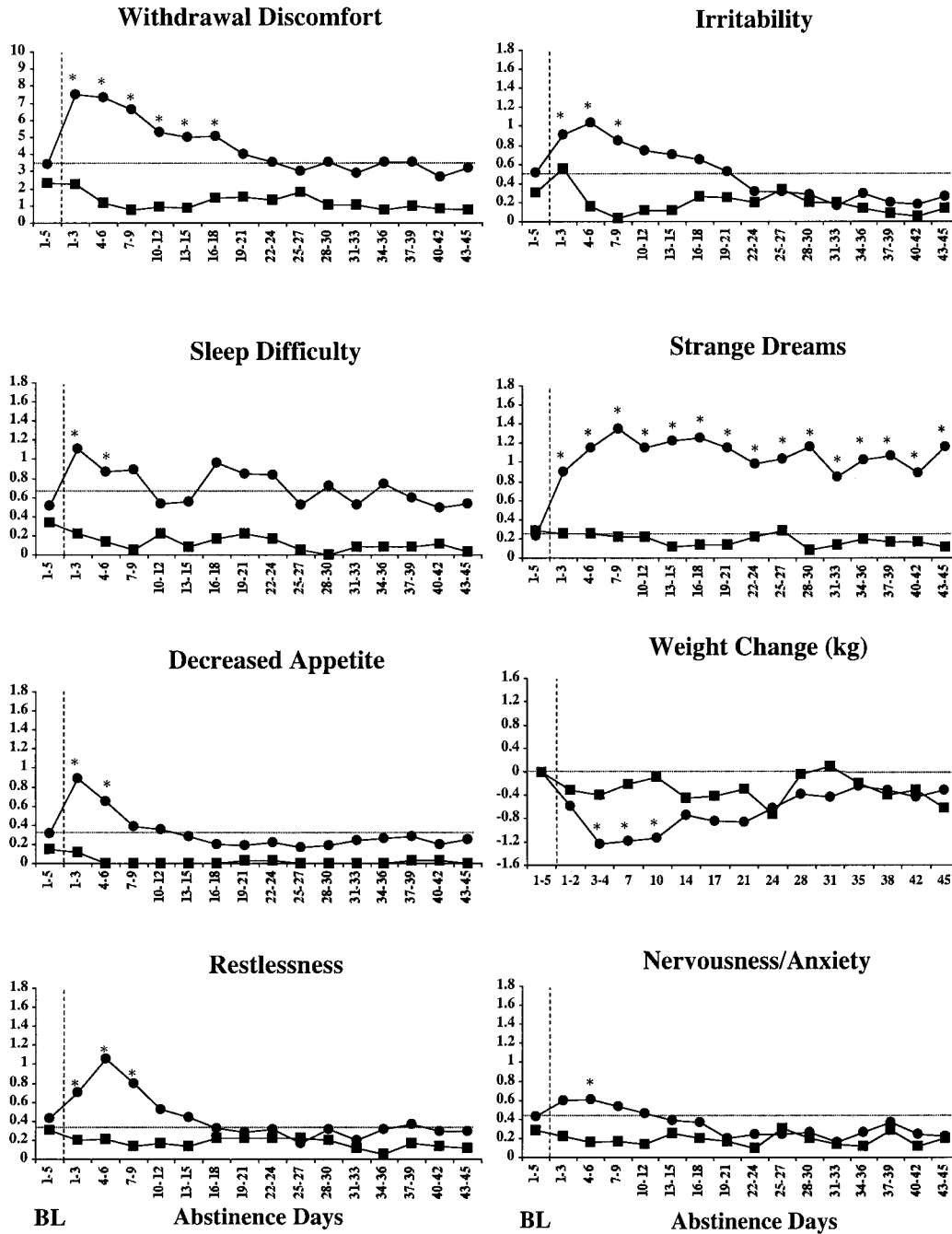
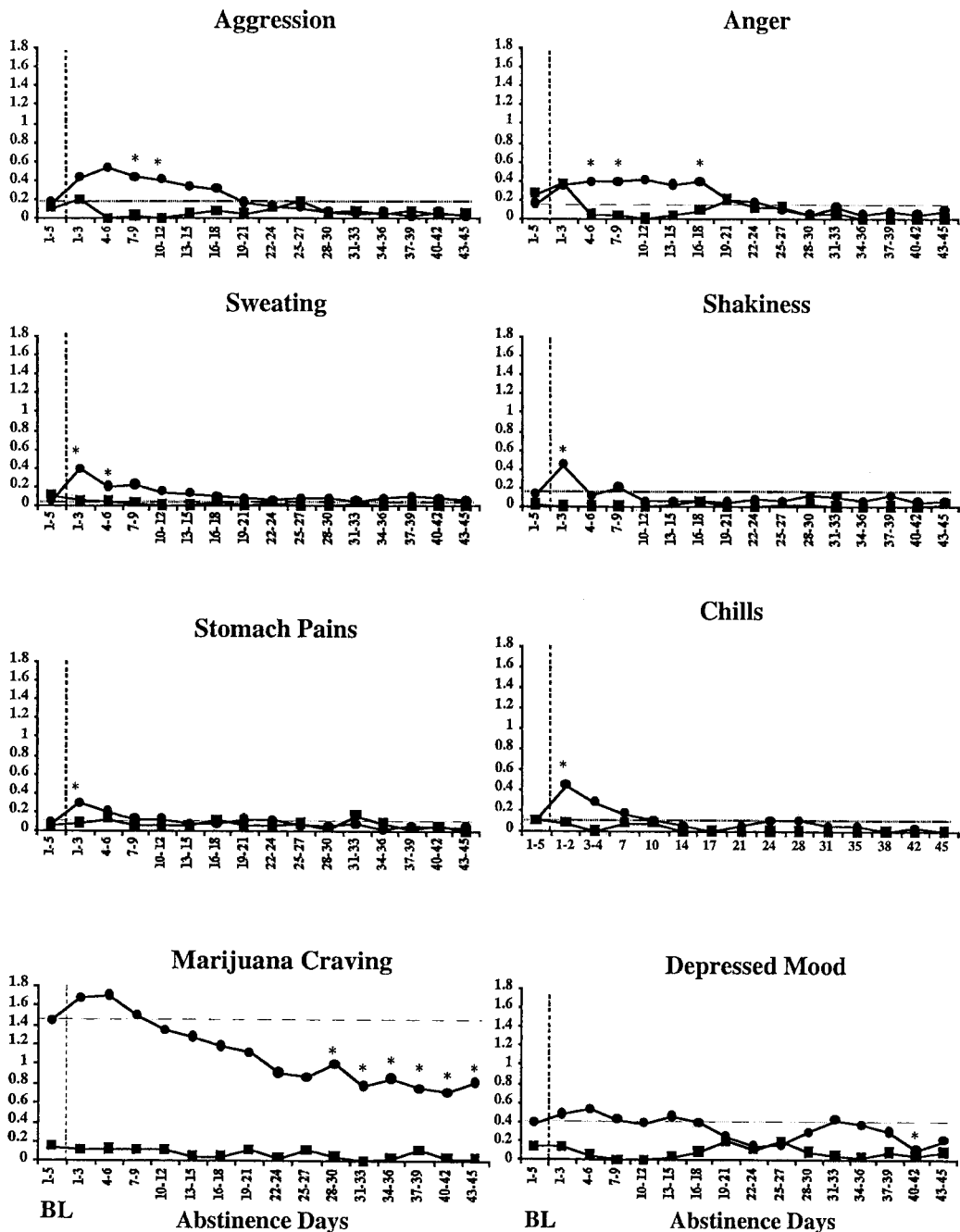


Figure 2. Mean interactive voice response symptom values across baseline and 3-day abstinence phase segments for 18 users and 12 ex-users. Range for individual items is 0–3; range for withdrawal discomfort score is 0–36. The value of the baseline (BL) data point reflects the mean of Days 1, 3, and 5. Dashed horizontal line represents baseline mean score. Circles represent current users. Squares represent ex-users. * $p < .05$, between specific 3-day abstinence periods and baseline mean or between body weight at specific abstinence days and baseline.

peak period for each significant symptom from the daily IVR-obtained MWC (J. Cohen, 1992; Tabachnick & Fidell, 1996).

Analyses included data from all 45 abstinence days for all participants. In cases in which IVR calls were missed (8 for users, 11 for ex-users), the

mean score from the two available scores for that 3-day segment was used. For the 3 participants who ended the study early (Abstinence Days 32, 39, and 42), the 3-day mean scores most proximate to the termination day were imputed to replace missing values. Most symptoms returned to baseline by



Day 20, hence, this procedure was not expected to produce a significant confound.

thereafter was confirmed with qualitative testing. All ex-users provided cannabinoid-negative specimens throughout the study.

Results

Former Marijuana Users

Abstinence Verification

Abstinence from marijuana was confirmed in users and ex-users. In the user group, creatinine-normalized THCCOOH levels decreased significantly during the first 2 weeks of the abstinence phase, $F(7, 119) = 17.58, p = .001$ (see Figure 1), and abstinence

For ex-users, none of the 15 MWC items collected via IVR changed significantly over time ($p > .05$; see Figure 2). The WDS scores of the baseline and the first 3-day period were slightly higher than the last fourteen 3-day periods. Measures collected during laboratory visits confirmed the patterns seen with the IVR,

and showed that body weight, blood pressure, and heart rate did not change (data not shown).

Current Marijuana Users

IVR measures. Ten of the 15 MWC symptoms (aggression, anger, decreased appetite, irritability, nervousness/anxiety, restlessness, shakiness, sleep difficulty, stomach pains, sweating) and the WDS showed a transient pattern of change consistent with withdrawal (see Table 2 and Figure 2). Strange dreams remained elevated throughout abstinence, and craving for marijuana was significantly lower than baseline starting with the ninth Abstinence period (Days 28–30). Nausea changed significantly over time, but none of the abstinence period segments differed significantly from baseline. Depressed mood and headaches did not change significantly over time.

Time of onset was examined for the 10 items that showed a pattern indicative of withdrawal plus strange dreams. Unlike the prior analyses based on means over 3-day periods, in this analysis mean scores from each of the first 7 days of the abstinence phase were compared with the mean of the baseline period for each item. Onset was defined as the 1st day the mean score differed significantly from the baseline mean ($p < .05$). The onset of most symptoms occurred between Days 1 and 3; however, some symptoms did not occur until Days 4–6 (see Table 2).

Peak effects were defined as the maximum increase from baseline observed during the first 2 weeks of the abstinence phase. Mean peak increases across significant symptoms ranged from +0.4 to +1.8 points on the 0- to 3-point MWC items (see Table 2). Most peak effects were observed between Days 2 and 6. Effect sizes (partial η^2) for each item showing significant change indicated medium to large effects across symptoms.

The offset of symptoms was defined as the 1st day following the peak day that the mean magnitude of the effect was no longer significantly different from the baseline mean. Most symptoms offset by Day 15, although anger and aggression remained elevated to 20 days and strange dreams did not return to baseline (see Table 2). The duration of symptom effects, defined as day of return to baseline minus day of onset, ranged from 4 to 14 days.

Figure 2 suggests that some symptoms did not return to the level of the ex-users; 2 (group) \times 5 (time) ANOVAs (time factor represents the five 3-day segments following the return to baseline for most symptoms, Days 19–45) were performed to determine which symptoms did not reach the ex-user level. Strange dreams, $F(1, 28) = 22.8, p < .001$, sleep difficulty, $F(1, 28) = 27.8, p < .001$, and craving for marijuana, $F(1, 28) = 21.2, p < .001$, remained significantly elevated compared to ex-users. No significant group differences were observed for the other IVR symptom items, and no interaction effects were observed.

Table 2
Daily Interactive Voice Response (IVR) Variables for Current Marijuana Users ($n = 18$)

Symptom	Change over time ^a		Onset day ^b	Peak day ^c	Offset day ^d	Maximum increase ^e		Effect Size (partial η^2) ^f	Valid symptoms ^g	
	F	p				M	SD		n	%
Withdrawal discomfort score	7.9	<.01	1	2	16	6.2	3.5	.69		
Strange dreams	3.3	<.01	2	9		1.8	0.8	.70	14	78
Sleep difficulty	2.1	.05	1	2	12	1.3	0.7	.52	11	61
Decreased appetite	6.4	<.01	1	2	12	0.8	0.5	.60	10	56
Irritability	8.9	<.01	1	6	15	1.0	0.7	.39	9	50
Anger	3.5	<.01	6	13	20	0.8	0.6	.25	9	50
Aggression	4.0	<.01	4	6	20	0.9	0.8	.27	8	44
Restlessness	6.1	<.01	2	4	12	0.9	0.6	.62	8	44
Nervousness	3.1	.01	4	9	12	0.9	0.6	.22	6	33
Sweating	2.9	.04	2	2	16	0.6	0.4	.29	6	33
Shakiness	4.7	<.01	1	1	4	0.4	0.4	.40	4	22
Stomach pains	2.8	.03	1	1	12	0.4	0.4	.22	3	17
Craving for marijuana ^h	7.2	<.01								
Nausea ^h	2.9	.02								
Depressed mood ^h	2.1	.07								
Headaches ^h	1.3	.30								
Amount of sleep	1.1	.35								
No. of wakings	1.3	.29								
Sleep quality	1.4	.20								
No. of cigarettes	1.6	.23								
Caffeine drinks	0.5	.73								
Alcohol drinks	1.7	.12								
Over the counter	1.1	.38								

^a One-way analyses of variance (16 time segments). ^b First abstinence day that the mean score significantly differed from baseline mean. ^c Abstinence day with the greatest mean increase from the baseline mean. ^d First abstinence day following peak day for which the mean was no longer significantly different from baseline mean. ^e Greatest increase from baseline observed during the first 2 weeks of abstinence. ^f Effect size calculated for change from baseline to peak period. ^g One or more point mean increase (3-day floating average) from baseline mean occurring during first 10 days of abstinence. ^h Symptom changed over time but did not show a withdrawal pattern, that is, did not show significant increase compared to baseline during the first 2 weeks of abstinence (see Figure 2); therefore, no data on time course are provided.

Laboratory measures. The MWC data collected during laboratory visits provided convergent validity for the observations gleaned from the daily IVR assessments. These data (not shown here) were generally not as sensitive as the IVR data, but most findings either replicated the IVR patterns, or a trend emerged in the same direction as that observed with the IVR. Of the 13 additional MWC items included in the laboratory assessment, only chills and difficulty concentrating showed significant changes over time ($p < .05$). Ratings of chills during the first 2 days of the abstinence phase increased (see Figure 2). Twenty-one days into the abstinence phase, concentration improved compared with baseline; thus, it was not considered a withdrawal symptom. Diarrhea, dizziness, fever/hot flashes, headache, hiccups, increased confusion, muscle spasms, stuffy nose, and yawning did not increase during the abstinence phase. Of the positive symptoms assessed, only control of aggression changed over time, which indicated less control during the first 2 weeks of abstinence ($p < .05$). The total score and two subscale scores for the Marijuana Craving Questionnaire decreased after the first 3 weeks of the abstinence phase, consistent with the MWC craving rating ($p < .05$).

The BSI Anxiety and Hostility subscales increased significantly over time, but the only significant planned comparison was between the Anxiety score during the first week of abstinence and baseline ($p < .05$). The Somatization, Obsessive-Compulsive, Interpersonal-Sensitivity, and Psychoticism subscales improved following the 1st week of abstinence ($p < .05$). The Depression, Paranoid Ideation, and Phobic Anxiety subscales did not change significantly over time. The POMS Tension subscale increased and the Confusion subscale decreased during the 1st week of abstinence ($p < .05$). The Depression, Vigor, Anger, and Fatigue subscales did not change significantly over time.

Body weight was significantly decreased compared to baseline during the first 3 weeks of the abstinence phase ($p < .05$; see Figure 2). Mean peak weight loss was 1.4 kg (range = 0.2–5.0 kg). Heart rate and blood pressure did not change.

Table 3
Collateral Reports of Marijuana Withdrawal Symptoms ($n = 14$)

Symptom	Time ^a		Abstinence segments different than baseline ^b (week)
	<i>F</i>	<i>p</i>	
Withdrawal discomfort score	6.8	<.01	1–5
Shakiness	0.8	.44	
Depressed mood	1.6	.21	
Decreased appetite	0.8	.56	
Nausea	1.2	.31	
Irritability	7.5	<.01	1–6
Sleep difficulty	1	.40	
Sweating	2.6	.11	
Craving for marijuana	0.8	.47	
Restlessness	3.9	.02	1–2
Nervousness	4.2	.01	1–4
Increased aggression	3.3	.03	2–4
Headaches	0.3	.83	
Stomach pains	0.9	.41	
Strange dreams	5.8	<.01	1–6
Increased anger	2.7	.05	2

^a One-way analyses of variance. ^b Significant differences ($p < .05$) between baseline mean score and weekly mean score.

Clinical importance. Three methods were used to determine if the observed symptom changes were of potential clinical importance: magnitude of change on the MWC items (including effect sizes), incidence of substantial symptom change scores, and reports from collateral observers. The group means of peak effects across individual symptoms reflected 10% to 45% (0.4–1.8 points) increases on the 0- to 3-point severity scale, and effect sizes were in the medium to large range (see Table 2). To estimate the incidence of change of significant magnitude at the individual level, we defined significant symptoms as occurring if a participant's mean score on an individual MWC item showed an increase of at least 1 point during any 3-day period compared with his or her mean baseline score. The most common significant symptoms occurring in at least 40% of participants were aggression, anger, decreased appetite, irritability, restlessness, strange dreams, and sleep difficulty (see Table 2). Seventy-eight percent ($n = 14$) experienced four or more significant symptoms, and 83% reported two or more. *DSM-IV* withdrawal syndromes require two to four symptoms.

Four of the 18 collateral observers who participated provided incomplete MWC data and were not included in analyses. The observers reported significant increases on six MWC items (aggression, anger, irritability, restlessness, nervousness, and strange dreams) and the WDS (see Table 3). Symptom onset was reported during the 1st or 2nd week of abstinence, and offset varied substantially by symptom. Additional observer comments during phone assessments included: "huge mood fluctuations each day," "concerned about leaving the children with him," "couldn't believe the change in personality; he didn't say a word all weekend and was anxious around the kids."

Other Substance Use

The cigarette use of the 7 regular tobacco smokers in the current user group did not change significantly over time (see Table 2). The number of caffeinated drinks and use of over-the-counter medications also did not change significantly over time. Change in alcohol use approached significance, but the observed pattern varied above and below baseline throughout the abstinence period, and thus did not suggest change related to abstinence across participants. Participants in both groups reported no use of other illicit psychoactive substances, and all urinalysis tests for substances other than marijuana were negative.

Comment

Daily marijuana users experienced significant discomfort lasting 2–3 weeks following cessation from marijuana use. This study extended prior findings by examining a longer period of marijuana abstinence, using a smoking-as-usual baseline period, and including a control group of ex-users. This design facilitated a valid method for determining the onset, magnitude, duration, and validity of the abstinence syndrome. The time course of the marijuana withdrawal syndrome appeared similar to that observed with other drugs of abuse (Hughes, Higgins, & Bickel, 1994).

Ten symptoms showed a pattern of change over time indicative of what is traditionally thought of as true withdrawal (Hughes, Higgins, & Hatsukami, 1990); that is, onset closely followed

cessation, and duration was time-limited. The time course of four other symptoms was more difficult to interpret. Sleep difficulty increased during the 1st week of abstinence, and returned to baseline during the 2nd week. However, ratings continued to fluctuate above baseline throughout the abstinence phase. Another sleep-related item, strange dreams, remained significantly elevated throughout the abstinence phase. Thus, it is difficult to interpret these changes. One possibility is that sleep disturbance is a withdrawal symptom that lasts longer than the period studied here. A second possibility is that those who chose to use marijuana had a sleep problem prior to marijuana smoking that was improved by marijuana use and then returned upon cessation of marijuana.

Craving for marijuana showed a nonsignificant increase during the 1st week of abstinence and then significantly decreased during the last 2 weeks of abstinence. Prior studies have reported mixed results or have not assessed craving during marijuana abstinence (Budney et al., 2001; Budney et al., 1999; Haney, Comer et al., 1999; Haney, Ward et al., 1999; Kouri & Pope, 2000). Many studies of nicotine withdrawal show a similar pattern of craving as observed here (West & Schneider, 1987). Although craving is a ubiquitous experience reported during abstinence from most substances, its acceptance as a withdrawal symptom has been controversial. Measurement issues and high baseline rates have led to its omission as a substance withdrawal criterion in the *DSM-IV-TR* (see also Hughes, 1994; Sayette et al., 2000).

Depressed mood also increased slightly during the 1st week of abstinence and then decreased, but the pattern was variable and the increase was not statistically significant (see Figure 2). Controlled studies have provided mixed reports regarding depression (Budney et al., 2001; Kouri & Pope, 2000), and studies of treatment seekers have consistently identified depressed mood as a withdrawal symptom (Budney et al., 1999; Crowley et al., 1998; Weisbeck et al., 1996; see Table 4). Sample selection might contribute to such differences. Laboratory studies have excluded persons with mood disorders, yet depressed mood following nicotine abstinence is most likely to occur in those with a history of depression (Breslau, Kilbey, & Andreski, 1992; Pomerleau, Marks, & Pomerleau, 2000). The same might be true of cannabis abstinence (Budney et al., 1999).

Although the magnitude of the symptoms reported here may not appear large, there are reasons to believe that they are of clinical importance and might reflect an underestimation of withdrawal severity in general and clinical populations of heavy marijuana users. First, mean data are presented; hence, participants who did not experience a specific symptom are included in calculations of peak changes. As in other substance withdrawal syndromes, there exists large intra-individual variation in expression of cannabis withdrawal (Hughes et al., 1994). Individual participants experienced symptoms that were clearly observable by persons living with them, suggesting that the symptoms were potentially disruptive to daily living. Second, studies of tobacco withdrawal that used similar methods and measures report a magnitude of change and discomfort comparable to that observed here with marijuana abstinence (Hatsukami, Dahlgren, Zimmerman, & Hughes, 1988; Hughes, 1992). Third, persons on psychotropic medication or with current Axis I disorders were excluded. Psychiatric symptomatology appears associated with increased severity of withdrawal syndromes in general, including marijuana (Breslau et al., 1992;

Table 4
Proposed Withdrawal Symptom List for DSM Consideration

Symptoms	CS reporting symptom	AS reporting symptom ^a
Common		
Decreased appetite/weight loss	6/6	11/11
Irritability	6/6	10/10
Nervousness/anxiety	5/6	6/6
Anger/aggression	3/4	8/8
Restlessness	3/4	9/10
Sleep difficulty/strange dreams	3/5	9/11
Less common/equivocal		
Depressed mood	3/5	5/8
Stomach/physical pain	3/5	4/7
Chills	1/4	4/7
Shakiness	1/4	3/6
Sweating	1/4	2/5

Note. The table shows number of studies that reported positive findings divided by the number of studies with information available. CS = controlled studies; AS = all studies. Controlled studies (include baseline symptom comparison); Jones & Benowitz (1976); includes baseline comparison data and uncontrolled data; Haney, Comer, et al. (1999); Haney, Ward, et al. (1999); Kouri et al. (1999); Kouri & Pope (2000); Budney et al. (2001); and the current article. Other studies: Nowlan & Cohen (1977); Georgotas & Zeidenberg (1979); Weisbeck et al. (1976); Crowley et al. (1998); and Budney et al. (1999).

^a Includes both controlled and other studies.

Budney et al., 1999; Pomerleau et al., 2000). Fourth, treatment seekers were excluded, yet clinical populations show increased withdrawal compared to self-quitters and laboratory study participants in studies of nicotine cessation (Hughes, 1994). Last, study dropouts who did not achieve abstinence or relapsed to marijuana might represent individuals with more significant withdrawal (Gilbert et al., 1999).

The importance of cannabis withdrawal has been questioned, and the lack of data addressing the clinical consequence and prevalence of the syndrome is the reason for its omission from the *DSM-IV-TR*. Over 75% of participants in this study experienced at least four symptoms of substantial magnitude, and a previous outpatient study reported significant symptomatology in 60% of participants (Kouri & Pope, 2000). The *DSM-IV-TR* criteria for other withdrawal syndromes require the presence of two to four symptoms depending on the substance. We believe the cumulative data across inpatient, outpatient, clinical, and general population studies on abstinence effects following cannabis or THC administration suggest that this withdrawal syndrome is reliable, valid, and merits consideration for inclusion in the next revision of the *DSM* (see Table 4). Table 4 lists proposed symptoms for a cannabis withdrawal disorder. Common symptoms reflect those observed consistently across studies of cannabis withdrawal and reported by a substantial proportion of participants studied. Less common or equivocal symptoms have been observed across some studies, are experienced by a minority of study participants, or are of lesser magnitude.

That said, a number of methodological limitations in this study merit comment. First, the sample size was small. Moreover, only daily marijuana smokers who reported two or more withdrawal symptoms during a previous abstinence episode and who were not

seeking treatment were assessed. The findings therefore may have limited generality. However, the marijuana use profile of this sample was quite similar to that reported by users who seek treatment for marijuana dependence (Budney, Higgins, Radonovich, & Novy, 2000; Copeland et al., 2001; Stephens, Roffman, & Curtin, 2000), suggesting that the results likely generalize to treatment seekers. The 58% abstinence rate achieved in this study may appear high and indicative of the insignificance of the cannabis withdrawal syndrome. However, we believe this abstinence rate was relatively low given the large earnings available for remaining abstinent and completing the study. Outcome studies of marijuana-dependent treatment seekers suggest that rates of abstinence achieved during treatment are comparable to that achieved with other types of drug dependence (Budney & Moore, 2002). Larger, more generalizable studies of the incidence of cannabis withdrawal are needed to determine more precise estimates of how many cannabis users are likely to experience a withdrawal syndrome, and whether there exist reliable predictors of the syndrome.

Cannabis withdrawal does not appear to include the significant physical, medical, or psychiatric problems sometimes observed with opioid, sedative, or alcohol withdrawal. Nonetheless, the mood and behavioral symptoms that appear to be the hallmark of cannabis withdrawal along with impaired sleep and decreased appetite may be as, if not more important than, physical symptoms in contributing to the development of dependence and the undermining of abstinence attempts (Koob & LeMoal, 2001). Careful delineation of the cannabis withdrawal syndrome such as that provided here is necessary to evaluate its importance and to guide clinical interventions. These findings should be used to educate users, clinicians, and others about the expected severity and duration of withdrawal from cannabis, and advance it as a valid target of treatment.

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