

Marijuana Abstinence Effects in Marijuana Smokers Maintained in Their Home Environment

Alan J. Budney, PhD; John R. Hughes, MD; Brent A. Moore, PhD; Pam L. Novy, PhD

Background: Although withdrawal symptoms are commonly reported by persons seeking treatment for marijuana dependence, the validity and clinical significance of a marijuana withdrawal syndrome has not been established. This controlled outpatient study examined the reliability and specificity of the abstinence effects that occur when daily marijuana users abruptly stop smoking marijuana.

Methods: Twelve daily marijuana smokers were assessed on 16 consecutive days during which they smoked marijuana as usual (days 1-5), abstained from smoking marijuana (days 6-8), returned to smoking marijuana (days 9-13), and again abstained from smoking marijuana (days 14-16).

Results: An overall measure of withdrawal discomfort increased significantly during the abstinence phases and

returned to baseline when marijuana smoking resumed. Craving for marijuana, decreased appetite, sleep difficulty, and weight loss reliably changed across the smoking and abstinence phases. Aggression, anger, irritability, restlessness, and strange dreams increased significantly during one abstinence phase, but not the other. Collateral observers confirmed participant reports of these symptoms.

Conclusions: This study validated several specific effects of marijuana abstinence in heavy marijuana users, and showed they were reliable and clinically significant. These withdrawal effects appear similar in type and magnitude to those observed in studies of nicotine withdrawal.

Arch Gen Psychiatry. 2001;58:917-924

MARIJUANA smoking remains the most prevalent form of illicit drug use in the United States.¹ Treatment seeking for marijuana dependence increased during the 1990s.² Controlled trials³⁻⁵ evaluating treatments for marijuana dependence suggest that initiating and maintaining marijuana abstinence, like with other drug dependencies, is difficult. Whether an aversive withdrawal syndrome contributes to this difficulty is unclear.

Nonhuman studies of cessation of marijuana or cannabinoids have provided evidence of a withdrawal response. In rhesus monkeys, withdrawal occurred following cessation of injected and oral tetrahydrocannabinol (THC) administration.^{6,7} Recent antagonist challenge studies^{8,9} have demonstrated a marked precipitated cannabinoid withdrawal syndrome in rats and dogs.

Early inpatient laboratory studies¹⁰⁻¹² confirmed the animal research. Cessation following the administration of marijuana

cigarettes or oral THC produced decreased appetite, irritability, restlessness, sleep difficulties, and uncooperativeness. Two recent placebo-controlled inpatient studies^{13,14} extended these findings by examining abstinence effects following moderate dosing of oral THC or smoked marijuana. Both studies demonstrated withdrawal effects that included anxiety, decreased contentment and food intake, depressed mood, irritability, restlessness, sleep difficulty, and stomach pain.

The abstinence effects reported in the inpatient laboratory studies were less severe than were retrospective reports¹⁵ of withdrawal in marijuana-dependent outpatients. One explanation for this may be that inpatient studies do not include environmental stimuli that can produce conditioned withdrawal effects (eg, persons or things associated with smoking).^{16,17} A recent outpatient study¹⁸ of daily marijuana smokers reported increased anxiety, irritability, physical symptoms, negative mood, and decreased appetite during 28 days of abstinence, but the magnitude of these

From the Departments of Psychiatry (Drs Budney, Hughes, and Moore) and Psychology (Drs Budney and Hughes), The University of Vermont, Burlington; and the US Air Force, Biomedical Science Corps, Minot, ND (Dr Novy).

PARTICIPANTS AND METHODS

PARTICIPANTS

Seven male and 5 female (10 white and 2 Native American) volunteers, ranging in age from 18 to 50 years (mean \pm SD, 30.1 \pm 9.0 years), completed a 16-day outpatient study. Participants were recruited via newspaper advertisements seeking regular marijuana users for a non-treatment study on the effects of marijuana use. Participants had to report using marijuana at least 25 days per month during the previous 6 months, and experiencing at least 2 withdrawal symptoms during previous periods of cessation. Individuals were excluded if they met the *DSM-IV* criteria for an Axis I psychiatric disorder, including substance use disorders other than marijuana, nicotine, or caffeine dependence; used any illicit substances other than marijuana during the previous 30 days; were taking psychotropic medication; were pregnant; or were seeking treatment for marijuana-related problems. Approximately 25% of those who responded to the advertisements were eligible to participate. Most exclusions were for use of psychiatric medication or illicit drugs other than marijuana.

Participants were all regular heavy marijuana users. The mean \pm SD age at first use was 15.4 \pm 2.2 years, and the mean \pm SD years of regular use was 13.7 \pm 8.9 years. Subjects were primarily daily smokers (mean \pm SD, 28.5 \pm 2.8 days in the past month) who smoked multiple times per day (mean \pm SD, 3.3 \pm 1.3 episodes per day). Eleven participants (92%) met the *DSM-IV* criteria for marijuana dependence or abuse. Of the 12 participants, 3 were regular tobacco cigarette smokers.

MEASURES

The timeline follow-back method²⁰ assessed daily licit and illicit substance use during the prior 30 days. A drug history questionnaire assessed use of marijuana and other drugs. The *DSM-IV* Checklist²¹ was used to diagnose Axis I psychiatric disorders.

Each study day, participants completed the substance use diary, the Marijuana Withdrawal Checklist

(MWC), the Brief Symptom Inventory, the Marijuana Craving Questionnaire, the Sleep Inventory, and the Profile of Mood States scale. The MWC comprises 27 symptoms for which participants indicate severity during the prior 24 hours on a 4-point scale (0 indicates not at all; 1, mild; 2, moderate; and 3, severe). This checklist was modified from a previous version developed for use in a retrospective study¹⁵ of marijuana. To minimize expectancy effects, the MWC was labeled the "Behavior Checklist." A withdrawal discomfort score (WDS) was computed by summing the 10 MWC items most frequently reported in the prior study¹⁵ (anger, craving for marijuana, depressed mood, decreased appetite, headaches, irritability, nervousness, restlessness, sleep difficulty, and strange dreams). The internal reliability of the WDS was high ($\alpha = .89$).

The Marijuana Craving Questionnaire was adapted from a valid tobacco-smoking urges questionnaire.²² This questionnaire yields a total craving and 2 subscale scores. Subscale 1 reflects intention and desire to smoke marijuana and anticipated pleasure, and subscale 2 reflects anticipation of relief from negative affect and withdrawal.

The Brief Symptom Inventory is a valid measure of psychiatric symptoms that yields 9 scales (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism).²³ The Profile of Mood States scale provides 6 mood scale scores (tension, depression, anger, vigor, fatigue, and confusion).²⁴ A 5-item Sleep Inventory assessed total amount of sleep, sleep-onset latency, number of nocturnal awakenings, time of awakening, and subjective sleep quality (7-point scale).²⁵

At the start of each laboratory visit, heart rate and blood pressure (sitting) were measured via an automated monitor (DINIMAP; Johnson & Johnson, Arlington, Tex). Body weight was obtained on a standing mechanical scale (Detecto; Cardinal Scale Manufacturing Co, Webb City, Mo) without shoes and heavy clothing, and after a urine specimen was provided.

All participants named a collateral observer with whom they spent at least 2 hours per day. Each day, a research assistant telephoned the observer and administered the MWC in reference to the participant's behavior.

symptoms was difficult to discern because retrospective reports were used for the baseline assessment.

Marijuana withdrawal is not recognized in the *DSM-IV*,¹⁹ as it concludes that the clinical significance of the syndrome has yet to be established. A recent study¹⁵ indicated that most individuals seeking treatment for marijuana dependence report a withdrawal syndrome of substantial severity. Given the reliance on retrospective reports of withdrawal symptoms and the lack of baseline measures in that study, better-controlled outpatient studies to determine the validity and significance of a marijuana withdrawal syndrome are indicated.

The present study systematically examined the reliability and validity of abstinence effects following cessation of heavy marijuana use in an outpatient environment. Observation of marijuana users in their natural living environment during periods of regular marijuana use and abstinence should provide a more accurate evaluation of the magnitude and significance of the effects that occur when heavy marijuana use is discontinued.

RESULTS

MARIJUANA USE AND ABSTINENCE VERIFICATION

During baseline phases 1 and 2, participants smoked marijuana a mean of 3.9 \pm 2.1 and 4.5 \pm 2.0 times per day, respectively, and reported no use of other illicit psychoactive substances. During the abstinence phases, all subjects reported no use of marijuana or other psychoactive substances. All urinalysis results for substances other than marijuana were negative, and breath alcohol levels were all zero. Self-reported abstinence from marijuana was confirmed in all subjects using the previously mentioned quantitative procedure. Normalized 11-nor-9-carboxy- Δ 9-THC levels obtained during the abstinence phases differed significantly from levels obtained during the baseline phases ($F_{1,11} = 13.92$, $P = .003$) and decreased consistently across days in the abstinence phases ($F_{6,66} = 4.71$, $P < .001$) (**Figure 1**).

PROCEDURES

An ABAB within-subjects design was used. The 16-day outpatient study included a 5-day baseline (smoking-as-usual) phase 1, a 3-day marijuana abstinence phase 1, a second 5-day baseline phase 2 (smoking as usual), and a second 3-day marijuana abstinence phase 2. Symptom increases from baseline 1 to abstinence 1 indicated potential marijuana abstinence effects. Symptom decreases during baseline 2 following abstinence 1 confirmed that such abstinence effects were related to marijuana use. Symptom increases observed from baseline 2 to abstinence 2 indicated that these effects were reliable.

Study day 1 was scheduled for a Thursday to minimize the effect of specific days (weekend vs weekday) on symptom ratings. With this schedule, 3 weekdays were included in each phase of the study. Women with regular menstrual cycles began on the Thursday following the onset of menses to minimize potential premenstrual behavioral and mood changes. Participants made 30-minute visits to the laboratory at the same time each day (4-8 PM). The University of Vermont, Burlington, institutional review board approved all procedures, and informed consent was obtained before baseline phase 1.

During baseline 1, participants were requested not to change their usual pattern of marijuana smoking and to abstain from all psychoactive drugs, with the exception of alcohol, nicotine, and caffeine. They were instructed not to make significant changes in their diet or exercise habits. Participants were also instructed not to smoke marijuana for at least 2 hours before each visit. At each visit, physiological measures were taken, a urine specimen was collected, breath alcohol level was determined, and the affective and behavioral measures were completed.

On the day 5 baseline 1 visit, participants were instructed to abstain completely from marijuana and to continue with the daily laboratory visits. During abstinence phase 1, the same information as in baseline 1 was collected. On day 3 of abstinence 1, participants were asked whether they planned to resume their usual pattern of marijuana smoking. If they said yes, we asked if they would participate in the second half of the study. All participants planned to

return to smoking that day and provided consent to continue. Instructions for baseline 2 and abstinence 2 were identical to those for baseline 1 and abstinence 1.

Only participants whose urine screen results verified illicit drug abstinence throughout the study and marijuana abstinence during the abstinence phases were eligible to continue. A research assistant collected observed urine specimens. An enzyme-multiplied immunoassay technique tested for the use of drugs other than marijuana (benzodiazepines, cocaine, methamphetamine, and opioids) (Dade-Behring, San Jose, Calif). A quantitative analytic procedure was used to determine marijuana abstinence.²⁶ Gas chromatographic-mass spectroscopic levels of 11-nor-9-carboxy- Δ^9 -THC, the primary marijuana metabolite, were normalized to the urine creatinine concentration measured via a modified Jaffe alkaline picrate method 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 day.²⁶

Participants received a total of \$525 in 4 payments. Compensation for participation in the abstinence phases was provided only after urinalysis results confirmed marijuana abstinence.

DATA ANALYSIS

A series of repeated-measures analyses of variance were performed on dependent variables across days within each of the 4 phases. The primary analyses were a priori contrasts (2-tailed) comparing the mean scores of baseline 1 and abstinence 1, abstinence 1 and baseline 2, and baseline 2 and abstinence 2. If significant differences were observed on the planned contrasts, the day-by-phase interaction term was examined to determine if effects intensified or dissipated within each 3-day abstinence phase (time-course effects). Significance levels were not corrected for multiple comparisons, as the ABAB design allowed for replication of significant effects within the study. Data from weekend days during the 5-day baseline phases were excluded to provide comparable 3-day weekday segments for each phase. Data are given as mean \pm SD unless otherwise indicated.

AFFECTIVE AND BEHAVIORAL SYMPTOMS

The WDS significantly increased between baseline 1 and abstinence 1 ($F_{1,33}=13.57$, $P<.001$, effect size [d]=0.87), decreased between abstinence 1 and baseline 2 ($F_{1,33}=17.92$, $P<.001$, $d=1.00$), and increased again between abstinence 2 and baseline 2 ($F_{1,33}=9.67$, $P=.004$, $d=0.73$) (**Table** and **Figure 2**). These d values indicate a medium to large effect according to Cohen.²⁷

Significant differences between mean scores on 6 MWC items (aggression: $F_{1,33}=11.91$, $P=.002$; anger: $F_{1,33}=11.43$, $P=.002$; craving for marijuana: $F_{1,33}=13.47$, $P=.001$; decreased appetite: $F_{1,33}=7.85$, $P=.008$; irritability: $F_{1,33}=6.43$, $P=.02$; and sleep difficulty: $F_{1,33}=5.49$, $P=.03$) were observed in comparisons between baseline 1 and abstinence 1 (Figure 2). The d values for these items ranged from 0.52 to 0.87.

The 6 items showing significant change from baseline 1 to abstinence 1 all showed significant change back toward baseline values during baseline 2

(aggression: $F_{1,33}=11.91$, $P=.002$; anger: $F_{1,33}=9.74$, $P=.004$; craving for marijuana: $F_{1,33}=18.71$, $P<.001$; decreased appetite: $F_{1,33}=18.87$, $P<.001$; irritability: $F_{1,33}=7.05$, $P=.01$; and sleep difficulty: $F_{1,33}=4.90$, $P=.03$). Change toward baseline was also observed for restlessness ($F_{1,33}=3.87$, $P=.06$), which changed, but not significantly, from baseline 1 to abstinence 1 ($P=.06$).

Of the 6 items showing significant change from baseline 1 to abstinence 1, 3 replicated in the comparisons of baseline 2 with abstinence 2 (craving for marijuana: $F_{1,33}=10.74$, $P=.002$; decreased appetite: $F_{1,33}=10.39$, $P=.003$; and sleep difficulty: $F_{1,33}=9.76$, $P=.004$). A significant increase in one new item, strange dreams ($F_{1,33}=6.95$, $P=.01$), was observed. The d values for these items ranged from 0.61 to 0.80.

A significant difference between baseline 1 and abstinence 1 was observed on the hostility ($F_{1,33}=7.06$, $P=.01$, $d=0.63$) and interpersonal sensitivity ($F_{1,33}=$

4.35, $P=.05$, $d=0.50$) scales of the Brief Symptom Inventory. Hostility scale scores significantly decreased back toward baseline during baseline 2 ($F_{1,33}=8.61$, $P=.006$, $d=0.69$), but interpersonal sensitivity scale scores did not ($P=.67$). Neither scale showed significant ($P=.55$ and $.59$, respectively) change from baseline 2 to abstinence 2.

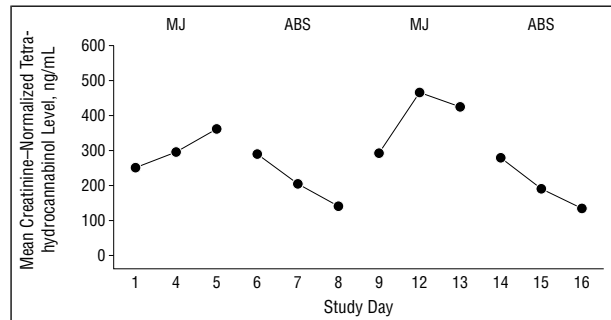


Figure 1. Mean creatinine-normalized tetrahydrocannabinol levels are presented across study days ($N=12$). MJ indicates marijuana smoking phase; ABS, marijuana abstinence phase.

Total craving scores changed significantly from baseline 1 to abstinence 1 (3.4 ± 1.3 vs 4.2 ± 1.5 ; $F_{1,33}=9.09$, $P=.005$), from abstinence 1 to baseline 2 (4.2 ± 1.5 vs 2.9 ± 1.1 ; $F_{1,33}=22.06$, $P<.001$), and from baseline 2 to abstinence 2 (2.9 ± 1.1 vs 3.8 ± 1.2 ; $F_{1,33}=10.53$, $P=.003$). The d values ranged from 0.7 to 1.0. These patterns were replicated on both subscales (subscale 1, $P<.01$ for all 3 comparisons; and subscale 2, $P<.01$ for baseline 1 to abstinence 1 and for abstinence 1 to baseline 2 and $P=.07$ for baseline 2 to abstinence 2).

Of the 5 sleep items, only sleep quality ratings showed significant change between phases. The sleep quality score decreased significantly from baseline 1 to abstinence 1 (3.5 ± 1.8 vs 2.4 ± 1.3 ; $F_{1,33}=7.14$, $P=.01$, $d=0.63$) and from baseline 2 to abstinence 2 (3.8 ± 1.8 vs 2.9 ± 1.6 ; $F_{1,33}=4.02$, $P=.05$, $d=0.47$).

Differences between baseline 1 and abstinence 1 scores were observed on the anger (38.7 ± 2.1 vs 39.9 ± 3.2 ; $F_{1,24}=3.55$, $P=.07$), fatigue (40.0 ± 8.0 vs 37.0 ± 3.5 ; $F_{1,24}=8.30$, $P=.008$), and confusion (40.0 ± 7.2 vs 37.9 ± 5.6 ; $F_{1,24}=9.5$, $P=.005$) scales of the Profile of Mood States scales (d range, 0.51-0.84).

Ratings for the Marijuana Withdrawal Checklist*				
Symptom	Baseline 1	Abstinence 1	Baseline 2	Abstinence 2
Strong Evidence				
Withdrawal Discomfort score†‡§	4.8 (3.7)	8.8 (4.7)	4.2 (3.0)	7.6 (3.4)
Craving for marijuana‡§	1.1 (0.8)	1.9 (0.7)	1.0 (0.7)	1.7 (0.6)
Decreased appetite‡§	0.4 (0.6)	0.9 (0.9)	0.1 (0.3)	0.7 (0.7)
Sleep difficulty‡§	0.4 (0.6)	0.9 (0.9)	0.4 (0.6)	1.1 (0.9)
Moderate Evidence				
Increased aggression‡	0.1 (0.4)	0.6 (0.8)	0.1 (0.3)	0.3 (0.5)
Increased anger‡	0.0 (0.2)	0.4 (0.6)	0.1 (0.3)	0.1 (0.3)
Irritability‡	0.6 (0.7)	1.2 (0.8)	0.6 (0.6)	0.9 (0.8)
Strange dreams§	0.6 (0.9)	0.8 (1.0)	0.5 (0.7)	0.9 (1.0)
Restlessness ¶#	0.5 (0.6)	0.8 (0.7)	0.5 (0.6)	0.7 (0.8)
Weak or No Evidence				
Chills	0.2 (0.5)	0.2 (0.4)	0.0 (0.2)	0.1 (0.3)
Feverish feeling	0.1 (0.4)	0.1 (0.3)	0.0 (0.2)	0.1 (0.4)
Stuffy nose	0.4 (0.6)	0.2 (0.5)	0.2 (0.6)	0.3 (0.7)
Nausea	0.1 (0.3)	0.2 (0.6)	0.1 (0.3)	0.2 (0.5)
Diarrhea	0.1 (0.4)	0.2 (0.4)	0.1 (0.4)	0.1 (0.3)
Hot flashes#	0.0 (0.2)	0.2 (0.4)	0.0 (0.0)	0.1 (0.2)
Dizziness	0.1 (0.2)	0.1 (0.3)	0.0 (0.0)	0.1 (0.3)
Sweating	0.4 (0.6)	0.4 (0.6)	0.2 (0.4)	0.3 (0.6)
Hiccups	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.1 (0.3)
Yawning	0.3 (0.5)	0.2 (0.5)	0.0 (0.3)	0.3 (0.4)
Headaches	0.3 (0.6)	0.4 (0.9)	0.2 (0.5)	0.2 (0.5)
Shakiness	0.2 (0.4)	0.4 (0.6)	0.2 (0.4)	0.5 (0.8)
Muscle spasms	0.2 (0.5)	0.4 (0.6)	0.2 (0.4)	0.2 (0.6)
Stomach pains	0.2 (0.6)	0.2 (0.5)	0.2 (0.6)	0.2 (0.4)
Fatigue	0.6 (0.8)	0.5 (0.6)	0.4 (0.5)	0.6 (0.7)
Depressed mood	0.5 (0.6)	0.6 (0.8)	0.4 (0.6)	0.5 (0.7)
Difficulty concentrating	0.6 (0.6)	0.7 (0.8)	0.7 (0.8)	0.7 (0.8)
Nervousness	0.5 (0.6)	0.8 (0.8)	0.5 (0.6)	0.8 (0.8)
Violent outbursts	0.1 (0.4)	0.3 (0.6)	0.0 (0.2)	0.1 (0.4)

*Data are given as mean (SD). The range of scores for symptoms on the Marijuana Withdrawal Checklist is from 0 to 3 (0 indicates not at all; 1, mild; 2, moderate; and 3, severe).

†The range for the Withdrawal Discomfort score is from 0 to 30.

‡ $P<.05$ for baseline 1 vs abstinence 1.

§ $P<.05$ for baseline 2 vs abstinence 2.

|| $P<.05$ for abstinence 1 vs baseline 2.

¶ $P<.10$ for baseline 1 vs abstinence 1.

$P<.10$ for abstinence 1 vs baseline 2.

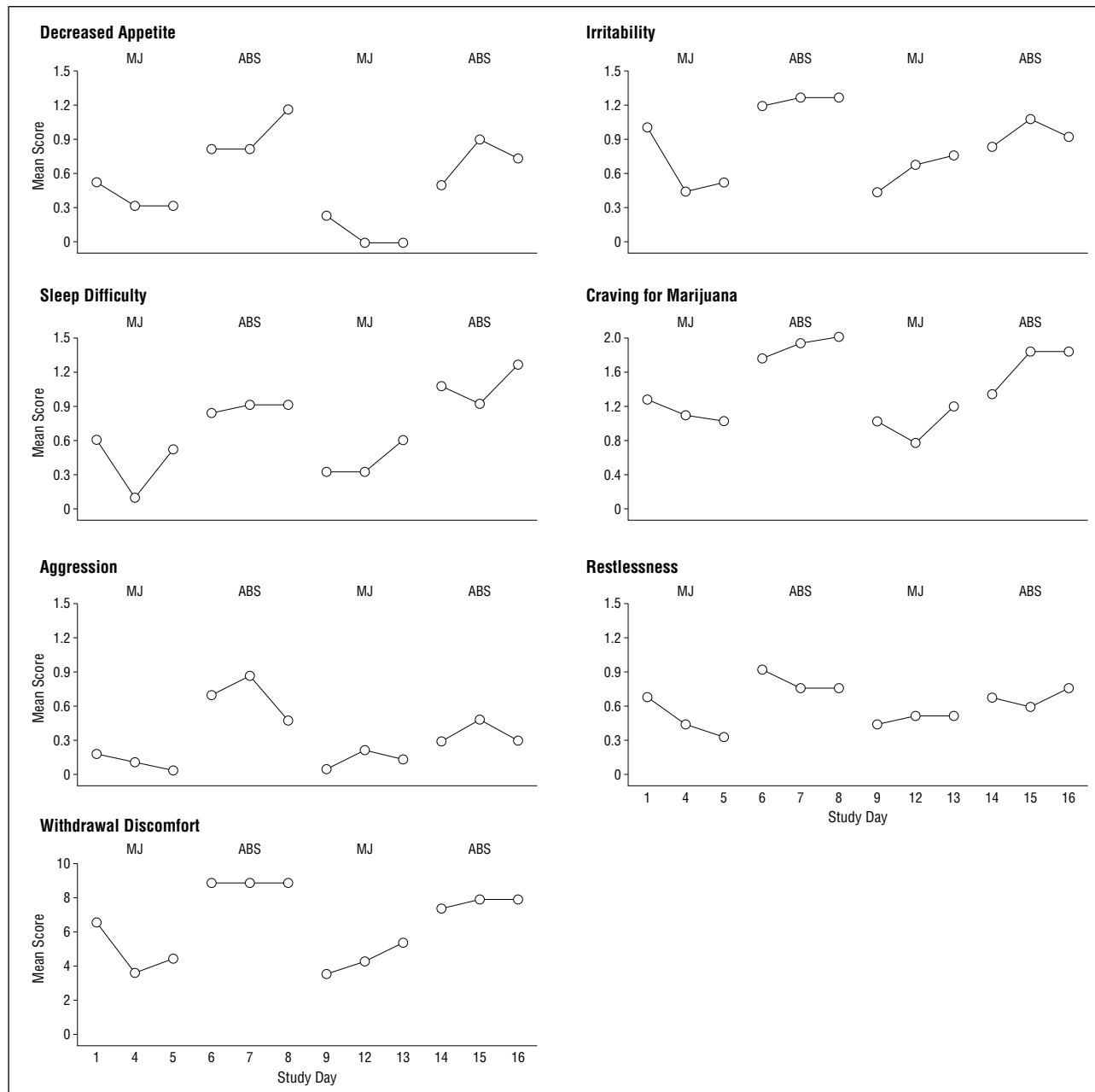


Figure 2. Mean scores for 6 Marijuana Withdrawal Checklist items and the mean Withdrawal Discomfort score are presented across study days (N=12). MJ indicates marijuana smoking phase; ABS, marijuana abstinence phase.

A significant return toward baseline was observed on the anger scale score from abstinence 1 to baseline 2 (39.9 ± 3.2 vs 38.0 ± 1.8 ; $F_{1,24} = 8.49$, $P = .008$, $d = 0.80$), but not on the fatigue and confusion scales scores. No Profile of Mood States depression scales showed significant change from baseline 2 to abstinence 2.

PHYSIOLOGICAL MEASURES

The mean body weight decreased significantly from baseline 1 to abstinence 1 ($F_{1,33} = 5.77$, $P = .02$, $d = 0.57$), increased from abstinence 1 to baseline 2 ($F_{1,33} = 5.09$, $P = .003$, $d = 0.53$), and decreased from baseline 2 to abstinence 2 ($F_{1,33} = 11.23$, $P = .002$, $d = 0.79$) (**Figure 3**). Heart rate and

blood pressure did not differ significantly between the baseline and abstinence phases ($P > .05$).

COLLATERAL OBSERVER

Collateral observer ratings of irritability ($F_{1,33} = 6.74$, $P = .01$) and restlessness ($F_{1,33} = 5.16$, $P = .03$) increased significantly from baseline 1 to abstinence 1 and decreased significantly from abstinence 1 to baseline 2 (irritability: $F_{1,33} = 5.34$, $P = .03$; and restlessness: $F_{1,33} = 10.01$, $P = .003$), but did not show significant increases during abstinence 2 ($P = .10$ and $.12$, respectively). Aggression ratings increased, but not significantly, from baseline 1 to abstinence 2 ($F_{1,33} = 3.54$, $P = .07$), decreased signifi-

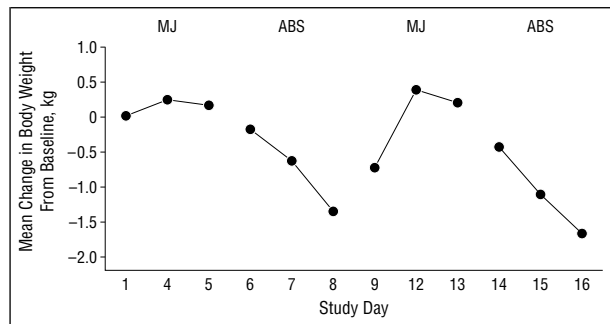


Figure 3. The mean change in body weight from baseline is presented across study days (N=12). Significant differences ($P<.05$) were observed between phases and between days within the abstinence phases. MJ indicates marijuana smoking phase; ABS, marijuana abstinence phase.

cantly from abstinence 1 to baseline 2 ($F_{1,33}=4.36, P=.04$), and increased significantly from baseline 2 to abstinence 2 ($F_{1,33}=5.41, P=.03$). The d values ranged from 0.80 to 1.28.

TIME-COURSE EFFECTS

Body weight showed significant change across days within phases (ie, time-course effects) ($F_{6,66}=7.58, P=.001$) such that weight appeared to decrease linearly across both abstinence phases (Figure 3). No significant differences were observed across days within the abstinence phases for any of the other dependent variables that changed significantly between phases ($P>.05$).

OTHER SUBSTANCE USE

The 3 regular tobacco cigarette smokers used a similar number of cigarettes during the baseline and abstinence phases. Two occasional cigarette smokers (<2 days per week) reported smoking during the abstinence phases but not during the baseline phases. The number of alcoholic and caffeinated drinks did not differ between the abstinence and baseline phases.

COMMENT

This outpatient study validated specific symptoms of marijuana withdrawal, and showed they were reliable and clinically significant. These symptoms increased during marijuana abstinence, returned to baseline when marijuana smoking resumed, and increased again when abstinence was reinitiated, suggesting that they were caused by cessation of marijuana use. Collateral observers confirmed participant reports, providing further support for their validity and significance.

These findings support and extend those from recent studies^{13,14} of marijuana abstinence effects conducted in residential settings. Such consistent reports of emotional and behavioral symptoms across settings suggest that these types of symptoms are the hallmark of the acute marijuana abstinence syndrome. The severity of the symptoms appeared to be greater in the present outpatient study, perhaps because the inpatient environment diminished the experience of marijuana abstinence effects. For example, increased aggression was observed in

this outpatient study, but not in the inpatient studies. Aggression may be a more severe form of the irritability that was observed during the inpatient studies. Hence, the aggression reported in the outpatient study might be an example of how environmental factors such as provocation can be crucial to the expression of an abstinence symptom. Indeed, increased aggression has also been observed during marijuana abstinence in a laboratory model of provoked aggression.²⁸

The withdrawal symptoms observed in the present study were also consistent with those reported in clinical and general population studies.^{15,29-31} For example, 67% of marijuana-dependent adolescents in residential care described a history of marijuana withdrawal symptoms that included irritability, restlessness, depressed mood, sleep difficulty, and fatigue or yawning.²⁹ A previous study¹⁵ of adults seeking treatment for marijuana dependence showed a similar but more severe pattern of withdrawal symptoms than that observed in the present study (mean WDS, 14.8 vs 8.2). This difference may be a consequence of contrasting methods of symptom reporting. Alternatively, treatment seekers may represent the marijuana users who experience the most severe withdrawal symptoms. The participants in the present study reported marijuana use patterns similar to the treatment seekers assessed in a previous study.¹⁵ Of the 4 study participants who experienced the greatest withdrawal severity, 3 had previously sought treatment for marijuana dependence. This explanation for the increased withdrawal severity is consistent with studies³² showing that tobacco cigarette smokers attending cessation programs report greater withdrawal severity than self-quitters or those that stop smoking for a study but are not planning to quit.

The affective symptoms observed during short-term marijuana abstinence overlap substantially with those observed in other drug withdrawal syndromes.³³ Studies^{34,35} in laboratory animals indicate that reductions in mesolimbic dopamine transmission and elevations in extracellular-releasing factor concentrations observed in the limbic system following withdrawal from cannabinoids closely resemble the responses seen with other major drugs of abuse. The behavioral consequences of these neurobiological changes observed during withdrawal are consistent with the type of negative affective symptoms reported by our participants and by patients withdrawing from other substances. Such findings have led to speculation that negative affect may be the common hallmark of withdrawal across most drugs of abuse.³⁶

The symptoms and severity of marijuana withdrawal appear to most closely resemble those observed during nicotine withdrawal. We compared the WDSs of our participants with those reported during nicotine withdrawal in 2 nicotine withdrawal studies^{37,38} similar to the present study. Both of these studies used an identical 0 to 3 scale that included all of the items in our WDS plus one additional item (somatic complaints). For comparison, we used the average change in WDS from baseline 1 to abstinence 1. The WDS increased 181% in the present study, compared with 142% and 226% in the 2 nicotine withdrawal studies.

Marijuana withdrawal, like nicotine withdrawal, appears less severe than alcohol or opioid withdrawal because it does not produce dramatic physical symptoms. Nevertheless, the behavioral and emotional withdrawal symptoms associated with marijuana withdrawal and other drug withdrawal syndromes may be as, if not more, important than physical symptoms in contributing to the development of dependence and the undermining of abstinence attempts.

Limitations of the present study include the following. First, the sample included only daily heavy marijuana smokers who reported withdrawal symptoms during prior periods of marijuana abstinence. As such, this study does not address the prevalence of withdrawal, and the findings cannot be generalized to less severe marijuana users or to those who use medically supervised marijuana. Whether most marijuana smokers who do not use as frequently as those studied herein experience clinically significant withdrawal must be determined in future studies.

Second, the short cessation period prevented an examination of the course of the marijuana abstinence syndrome. With the exception of body weight, none of the observed abstinence effects showed evidence of change during the abstinence periods, which is consistent with prior short-term inpatient studies. A recent outpatient study¹⁸ suggested that some symptoms of marijuana withdrawal might remain elevated for at least 3 to 4 weeks. Controlled studies³² of the time course are necessary to determine whether the abstinence effects observed in the existing studies reflect true time-limited withdrawal effects or merely represent offset effects that occur during abstinence and then stabilize.

Third, the ABAB experimental design most likely affected the experience of marijuana abstinence. Participants knew that abstinence would last only 3 days, and before abstinence phase 2, they had a recent experience with abstinence (phase 1). Hence, withdrawal severity during phase 2 may have been affected by the recent experience coping with a short period of abstinence, a change in expectancies, or a decrease in THC levels.

Fourth, we did not assess neurocognitive effects of abstinence. Prior studies³⁹ reported that heavy marijuana users exhibit cognitive impairment following at least one day of abstinence, but suggested that these effects were more likely due to a residue of drug in the brain or neurotoxic effects of long-term use rather than withdrawal. Minimal effects of withdrawal on cognitive and psychomotor performance tasks were observed in recent inpatient studies.^{13,14} Because heavy marijuana use has clearly been associated with cognitive deficits, more study of neurocognitive functioning during cessation attempts is warranted.

Fifth, we did not statistically control for multiple comparison tests and, thus, increased the risk of false-positive findings. All significant findings were consistent with previous research on marijuana withdrawal, and unexpected significant findings did not emerge, suggesting that the primary findings were not spurious.

The present study provides new and confirmatory evidence about marijuana withdrawal. The study de-

finied several valid and reliable symptoms that produce a significant amount of observable distress in long-term heavy marijuana users. Like other drug withdrawal syndromes, individual variability exists. Many questions about marijuana withdrawal remain unanswered. Which and how many marijuana users experience significant withdrawal is not known. How marijuana withdrawal affects quit attempts has not been studied. We know that quit rates during treatment for marijuana dependence are similar to those for other drug dependencies, indicating that these patients find it difficult to stop.³⁻⁵ If marijuana withdrawal undermines these cessation attempts, then behavioral or pharmacological treatments targeting withdrawal may be helpful in the treatment of marijuana dependence.

Accepted for publication March 23, 2001.

This study was supported by research grants R01-DA12471, T32-DA07242, and K02-00109 from the National Institute on Drug Abuse, Bethesda, Md.

Presented in part at the College of Problems on Drug Dependence Conference, San Juan, Puerto Rico, June 19, 2000.

We thank Marilyn Huestis for consultation on the urinalysis testing procedures.

Corresponding author and reprints: Alan J. Budney, PhD, Department of Psychiatry, The University of Vermont, 54 W Twin Oaks Terr, Suite 9, S Burlington, VT 05403 (e-mail: abudney@zoo.uvm.edu).

REFERENCES

1. Substance Abuse and Mental Health Services Administration. *Summary of Findings From the 1998 National Household Survey on Drug Abuse*. Rockville, Md: US Dept of Health and Human Services; 1999.
2. Substance Abuse and Mental Health Services Administration. *National Admissions to Substance Abuse Treatment Services: The Treatment Episode Data Set (TEDS), 1992-1996*. Rockville, Md: US Dept of Health and Human Services; 1998.
3. Budney AJ, Higgins ST, Radonovich KJ, Novy PL. Adding voucher-based incentives to coping skills and motivational enhancement improves outcomes during treatment for marijuana dependence. *J Consult Clin Psychol*. 2000;68:1051-1061.
4. Stephens RS, Roffman RA, Simpson EE. Treating adult marijuana dependence: a test of the relapse prevention model. *J Consult Clin Psychol*. 1994; 62:92-99.
5. Stephens RS, Roffman RA, Curtin L. Comparison of extended versus brief treatments for marijuana use. *J Consult Clin Psychol*. 2000;68:898-908.
6. Kaymakcalan S. Tolerance to and dependence on cannabis. *Bull Narc*. 1973;25: 39-47.
7. Beardsley PM, Balster RL, Harris LS. Dependence on tetrahydrocannabinol in rhesus monkeys. *J Pharmacol Exp Ther*. 1986;239:311-319.
8. Aceto M, Scates S, Lowe J, Martin B. Dependence on Δ -9 tetrahydrocannabinol: studies on precipitated and abrupt withdrawal. *J Pharmacol Exp Ther*. 1996;278: 1290-1295.
9. Lichtman AH, Wiley JL, LaVecchia KL, Nevaser ST, Arthur DB, Wilson DM, Martin BR. Effects of SR 141716A after acute or chronic cannabinoid administration in dogs. *Eur J Pharmacol*. 1998;357:139-148.
10. Mendelson JH, Mello NK, Lex BW, Bavli S. Marijuana withdrawal syndrome in a woman. *Am J Psychiatry*. 1984;141:1289-1290.
11. Jones RT, Benowitz N. The 30-day trip: clinical studies of cannabis tolerance and dependence. In: Braude MC, Szara S, eds. *Pharmacology of Marijuana*. New York, NY: Raven Press; 1976:627-642.
12. Cohen S, Lessin PJ, Hahn PM, Tyrell ED. A 94-day cannabis study. In: Braude MC, Szara S, eds. *Pharmacology of Marijuana*. New York, NY: Raven Press; 1976: 621-626.
13. Haney M, Comer SD, Ward AS, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology (Berl)*. 1999;14:385-394.

14. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology (Berl)*. 1999; 14:395-404.
15. Budney AJ, Novy PL, Hughes JR. Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction*. 1999;94:1311-1322.
16. Siegel S. Classical conditioning, drug tolerance, and drug dependence. In: Israel Y, Glaser FB, Kalant H, Popham RE, Schmidt W, Smart RG, eds. *Research Advances in Alcohol and Drug Problems*. New York, NY: Plenum Press; 1983:207-246.
17. Wikler A. *Opioid Dependence: Mechanisms and Treatment*. New York, NY: Plenum Press; 1980.
18. Kouri EM, Pope HG. Abstinence symptoms during withdrawal from chronic marijuana use. *Exp Clin Psychopharmacol*. 2000;8:483-492.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
20. Sobel LC, Sobel MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Allen JP, Litten RZ, eds. *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods*. Totowa, NJ: Humana Press; 1992:41-72.
21. Hudziak J, Helzer JE, Wetzel MW, Kessel KB, McGee B, Janca A, Przybeck T. The use of the *DSM-III-R* Checklist for initial diagnostic assessments. *Compr Psychiatry*. 1993;34:375-383.
22. Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. *Br J Addict*. 1991;86:1467-1476.
23. Derogatis LR. *Brief Symptom Inventory: Administration, Scoring and Procedures Manual*. Minneapolis, Minn: National Computer Systems Inc; 1993.
24. McNair DM, Lorr M, Droppleman LF. *Manual for the Profile of Mood States*. San Diego, Calif: Educational and Industrial Testing Service; 1971.
25. Carskadon MA, Dement WC, Mitler MM, Guilleminault MD, Zarcone VD, Spiegel R. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. *Am J Psychiatry*. 1976;133:1382-1388.
26. Huestis MA, Cone EJ. Differentiating new marijuana use from residual drug excretion in occasional marijuana users. *J Anal Toxicol*. 1998;22:445-454.
27. Cohen J. A power primer. *Quant Methods Psychol*. 1992;112:155-159.
28. Kouri EM, Pope HG, Lukas SE. Changes in aggressive behavior during withdrawal from long-term marijuana use. *Psychopharmacology (Berl)*. 1999;143: 302-308.
29. Crowley TJ, Macdonald MJ, Whitmore EA, Mikulich SK. Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. *Drug Alcohol Depend*. 1998;50:27-37.
30. Cottler LB, Schuckit MA, Helzer JE, Crowley T, Woody G, Nathan P, Hughes J. The *DSM-IV* field trial for substance use disorders: major results. *Drug Alcohol Depend*. 1995;38:59-69.
31. Weisbeck GA, Schuckit MA, Kalmijn JA, Tipp JE, Bucholz KK, Smith TL. An evaluation of the history of a marijuana withdrawal syndrome in a large population. *Addiction*. 1996;91:1469-1478.
32. Hughes J, Higgins S, Hatsukami D. Effects of abstinence from tobacco: a critical review. In: Kozlowski LT, Annis H, Cappell HD, Glaser F, Goodstadt M, Israel Y, Kalant H, Sellers EM, Vinglis J, eds. *Research Advances in Alcohol and Drug Problems*. New York, NY: Plenum Press; 1990:317-398.
33. Hughes JR, Higgins ST, Bickel WK. Nicotine withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. *Addiction*. 1994;89:1461-1470.
34. deFonseca FR, Carrera MRA, Navarro M, Koob GF, Weiss F. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. *Science*. 1997;276:2050-2054.
35. Diana M, Melis M, Muntoni AL, Gessa GL. Mesolimbic dopaminergic decline after cannabinoid withdrawal. *Proc Natl Acad Sci U S A*. 1998;95:10269-10273.
36. Koob GF, Caine SB, Parsons L, Markou A, Weiss F. Opponent process model and psychostimulant addiction. *Pharmacol Biochem Behav*. 1997;57:513-521.
37. Hughes JR. Tobacco withdrawal in self-quitters. *J Consult Clin Psychol*. 1992; 60:689-697.
38. Hatsukami DK, Dahlgren L, Zimmerman R, Hughes JR. Symptoms of tobacco withdrawal from total cigarette cessation versus partial cigarette reduction. *Psychopharmacology (Berl)*. 1988;94:242-247.
39. Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA*. 1996;275:521-527.