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ORIGINAL INVESTIGATION

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Changes in aggressive behavior during withdrawal from long-term marijuana use

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Abstract *Rationale*: Even though marijuana is the most commonly abused illicit drug in the United States, it is still undetermined whether withdrawal after chronic use results in changes in aggressive behavior in humans. *Objective*: The present study investigated the pattern and duration of changes in aggressive behavior in long-term marijuana users during a 28-day abstinence period verified by daily urines. *Methods*: Chronic marijuana users who had smoked marijuana on at least 5000 occasions (the equivalent of smoking daily for approximately 14 years) and who were smoking regularly when recruited were studied on days 0 (when they were still smoking), 1 (during acute withdrawal), 3, 7 and 28 of a 28-day detoxification period. Aggressive behavior was measured using the Point Subtraction Aggression Paradigm. *Results*: Compared to controls and to the pre-withdrawal data, chronic marijuana users displayed more aggressive behavior on days 3 and 7 of marijuana abstinence. These increases in aggressive responding returned to pre-withdrawal levels after 28 days and were paralleled by small, non-significant changes in depression and anxiety scores. *Conclusions*: Our findings confirm previous reports of an abstinence syndrome associated with chronic marijuana use and suggest that aggressive behavior should be an additional component of this syndrome.

Key words Aggression · Marijuana · Withdrawal · THC · Human subjects

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Introduction

The effects of marijuana on aggressive behavior have been studied extensively over the years, with the majority of the studies focusing on the acute effects of marijuana. The results of these studies demonstrate that low doses of tetrahydrocannabinol (THC, the primary psychoactive constituent of marijuana) cause a slight increase in aggressive behavior, while administration of moderate or high doses suppresses and can even completely eliminate aggressive behavior (Taylor et al. 1976; Myerscough and Taylor 1985). For instance, Taylor et al. (1976) found that subjects receiving a low dose (0.1 mg/kg) of oral THC delivered significantly higher intensity shocks to their opponents during a competitive reaction time task than subjects receiving the medium (0.25 mg/kg) or high (0.4 mg/kg) THC doses. When provoked, only the subjects receiving the low THC dose retaliated with increased shock settings. Similarly, a study investigating verbal hostility and aggression in small group settings following smoked marijuana found that subjects receiving moderate doses display less irritability and hostile feelings than subjects receiving placebo (Salzman et al. 1976).

In contrast to the many studies investigating the acute effects of oral THC and smoked marijuana on aggression, there are no published laboratory studies, to our knowledge, investigating the effects of marijuana withdrawal on aggression. This lack of data represents a serious omission in the research literature because the existence of a marijuana withdrawal syndrome, although still controversial, has been demonstrated in a number of clinical case reports (Bensus 1971; Dilsaver et al. 1984; Rohr et al. 1989), human laboratory studies (Jones et al. 1976; Mendelson et al. 1976, 1984; Georgotas and Zeidenber 1979) and animal laboratory studies (Fredericks and Benowitz 1980; Beardsley et al. 1986; Yen-Koo et al. 1989). Specifically, these studies have shown that the abrupt discontinuation of marijuana after long-term use can result in a withdrawal

syndrome characterized by insomnia, restlessness, anorexia and irritability (Jones and Benowitz 1976; Jones et al. 1976; Mendelson et al. 1984; Tennant 1986; Rohr et al. 1989; Compton et al. 1990; Duffy and Milin 1996; Kouri et al. 1998). Furthermore, it has been demonstrated that many violent crimes are committed by individuals undergoing withdrawal from other drugs of abuse (Hanlon et al. 1990; National Institute of Justice 1989; Peters and Kearns 1992; Kouri et al. 1997). Because marijuana is the most widely used illicit drug in the United States (NIDA 1997) and many chronic users meet DSM-IV criteria for marijuana dependence (Budney et al. 1997), it is important to investigate whether withdrawal from chronic marijuana use is associated with increases in aggression.

The present study used an objective computerized paradigm of aggression to investigate, in a controlled laboratory setting, whether withdrawal from marijuana following chronic heavy use results in changes in aggressive behavior in humans. This computerized test, the Point Subtraction Aggression Paradigm (PSAP; Cherek 1981), has been used to detect changes in aggressive responding following acute administration of nicotine, caffeine, ethanol, secobarbital and testosterone (Cherek 1981; Cherek et al. 1983, 1985, 1989; Kouri et al. 1995a) and during abstinence from tobacco (Cherek et al. 1989). The external validity of this instrument has been demonstrated in a number of studies of male and female parolees with histories of violent behavior (Cherek et al. 1996, 1997, 1998).

Materials and methods

Study design

Male and female subjects between the ages of 30 and 55 years were recruited in the Boston area via newspaper advertisements seeking individuals for participation "in a study of marijuana abstinence". Two groups of subjects were recruited: *Current long-term heavy users of marijuana*. Subjects in this group had to report a history of at least 5000 separate "episodes" of marijuana use in their lifetime (the equivalent to smoking once per day for 13.7 years) and had to be smoking at least once daily at the time of recruitment. An "episode" was defined as an occasion of smoking separated by at least 1 h from another "episode." *Controls*: comprised of two types of subjects: a) individuals who had not smoked marijuana more than 50 times in their lives and had not smoked more than once per month in the last year; and b) individuals who had formerly smoked marijuana on a daily basis but who had not smoked more than once per week during the last 3 months. The rationale for using infrequent or former smokers, rather than marijuana-naive subjects as controls, was to minimize possible confounding variables that might differentiate individuals who had never tried marijuana from those who had. This decision was based on data from our laboratory demonstrating that heavy marijuana users do not differ from occasional users in a wide range of demographic and psychiatric measures (Kouri et al. 1995b).

Subjects were not accepted into the study if they reported a history of head injury with loss of consciousness, other significant medical or neurological illness, or current use of medications with psychotropic properties. In addition, subjects were excluded if they reported that they had used another class of drugs, including cocaine, stimulants, opioids, sedative-hypnotics, hallucinogens, or inhalants, more than 100 times in their lifetime, or had consumed more than five alcoholic drinks per day continuously for 1 month or more in their lifetime.

Subjects who completed the screening interview were then brought to the laboratory for a baseline evaluation that included a psychiatric and substance abuse history, a physical examination, standard laboratory chemistry and hematology screening tests, urine screening for drugs of abuse, and a full explanation of the experimental procedures. Starting at this point (study day 0) subjects were required to abstain from marijuana and any other drug of abuse for the next 28 days, monitored by daily supervised urine samples. Subjects were also instructed to limit their alcohol consumption to no more than two alcoholic drinks per day during the study; this restriction, however, did not imply a significant reduction in any of the subjects' regular pattern of alcohol consumption because no subject accepted into the study drank more than ten drinks per week. Subjects were also instructed to consume their usual amounts of caffeine and tobacco, provided that caffeine consumption did not exceed five cups of coffee per day. All subjects provided informed consent to participate in the study.

Analysis of urine samples and verification of abstinence

Urine samples were sent via air express to PharmChem Laboratories (Menlo Park, Calif., USA) where they were screened by immunoassay (EMIT) for 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH), cocaine metabolites, benzodiazepines, barbiturates, phencyclidine, opioids, and amphetamines, and by enzymatic assay (EA) for ethanol. Urinary creatinine concentrations were measured to assess urine concentration. The threshold for detection of THCCOOH was 20 ng/ml. Samples positive for THCCOOH were then tested by gas chromatography-mass spectroscopy (GC/MS) to obtain quantitative THCCOOH concentrations. Samples testing positive for alcohol or the other six classes of drugs of abuse were also confirmed by GC/MS.

For subjects in the control group, no detectable THCCOOH was tolerated at any time during the study. THCCOOH levels in the urine of subjects from the current users group were accepted provided that the levels did not show evidence of new marijuana use after study day 0. The operational definition for this criterion was that the cannabinoid/creatinine ratio on a given day could not rise by more than 50% from the ratio obtained on the previous day's urine sample (Huestis et al. 1995, 1996). None of the other six drugs of abuse, or ethanol levels greater than 0.02 mg/dl, were tolerated in any urine sample. Subjects with urine samples which violated any of the above criteria were withdrawn from the study.

Assessment of aggressive behavior

Aggressive responding was measured on study days 0, 1 (after 24 h of abstinence), 3, 7 and 28, using the Point Subtraction Aggression Paradigm (PSAP). For each test session, subjects arrived at the laboratory and were shown an experimental chamber equipped with a computer monitor, a response panel, a video camera and a reclining chair. Subjects were told that the study was "designed to measure motor performance and a series of physiological parameters" and that they would be paired with an anonymous same-sexed subject from the study who would sit in another experimental chamber and participate in the procedure with them. In fact, however, this second "subject" did not exist, but was actually a computer.

Subjects participated in one 20-min session during each experimental day. Prior to the first experimental session subjects were given both written and verbal instructions and were given a practice run controlled by the experimenter. During each session, subjects had the option of pressing one of the two buttons on the

response panel (labeled A or B). Button A responding was maintained by a fixed-ratio (FR) 100 schedule of point presentation (1 point = 50 cents). Button B responding ostensibly subtracted points from the fictitious opponent on an FR10 schedule and was defined as the aggressive response (Buss 1961). These two response options were concurrently available as non-reversible options (i.e. the first response on a button inactivated the other button until the FR was completed). Aggressive responding was provoked by random subtractions of the subject's points which were attributed to the fictitious opponent. These provocations were signaled by three 1-s beeps and followed immediately by the subtraction of one point from the subject's counter.

Completion of the FR 10 on button B initiated a 125-s provocation-free interval (PFI) during which point subtractions were not presented. At least one point subtraction had to occur before each 125-s PFI could be initiated; this ensured that subjects could not avoid point subtractions but could reduce the number of point subtractions occurring in each session by responding on button B (see Kouri et al. 1995a for a more detailed description of the procedure). In the absence of aggressive responding by the subject, up to 25 point subtractions (provocations) were presented per session. At the end of the study, the number of points accumulated by subjects during each study session was calculated and each subject received 0.50 per point accumulated.

At the beginning of each session, a non-operational device resembling a thermistor was wrapped around the subject's left wrist and a metal clamp was attached to his or her left ankle. Subjects were told that these devices monitored body temperature, pulse rate, and peripheral blood flow during the experimental session. These measures, as well as the information regarding the accumulation of points, were intended to divert attention from button B presses (the main dependent variable) and to emphasize that the accumulation of points and the physiologic data were the main measures of the study. The ultimate goal of measuring aggressive responding was never mentioned to the subjects. At the end of all five visits, subjects were asked to describe the person or persons they were paired with during the experiment in order to assess whether experimental deception had been successful. Only subjects stating that they believed they were playing against another person and not a computer were included in the final analyses.

Assessment of mood

To assess whether marijuana abstinence was associated with changes in mood and anxiety, subjects were administered the Hamilton Depression (Hamilton 1960) and Hamilton Anxiety Scale (Hamilton 1959) on days 0, 1, 7 and 28 of the study.

Statistical analysis

The main dependent variables were the number of aggressive responses (points taken away from the fictitious opponent) and non-aggressive responses (points accumulated). These data were analyzed using a repeated measures analysis of variance (ANOVA) comparing the two groups (current users versus controls) during the five visits. In addition, the number of aggressive responses per point subtraction during each study day was analyzed. This second analysis assessed whether aggressive responding by the subjects in the two groups was a function of the provocations (i.e. points subtracted from the subjects by the fictitious opponent). Post-hoc *t*-tests were performed on analyses with significant main effects.

The data from the Hamilton Depression and Hamilton Anxiety Scale were analyzed using a repeated measures ANOVA comparing the controls and the current users. Also, a correlational analysis of the anxiety and depression scores with the number of aggressive responses was performed in order to assess whether the magnitude of the changes in mood was associated with the magnitude of the changes in aggressive behavior at the different time points during the study.

Results

Nineteen current marijuana users and 20 controls participated in the study. All of the current marijuana users met DSM-IV criteria for marijuana dependence. Two subjects from the current marijuana user group were withdrawn from the study because their urine samples were positive for cocaine metabolites within the first 5 days of the study. Of the 20 controls, 14 had not smoked marijuana more than 50 times in their lives and had not smoked more than once per month in the last year and six were former daily marijuana smokers who had not smoked more than once per week during the last 3 months. An analysis of the data from the control group comparing the subjects who had formerly smoked marijuana on a daily basis with the data from the subjects who had not smoked marijuana more than 50 times in their lives revealed no significant differences between the two groups in any of the variables measured. Therefore, the data from the two groups of controls were pooled for comparison with the current user group data. All 17 current users and 20 controls reported that they believed they were playing against another person and were thus included in the analyses. Demographic characteristics of subjects in the control group and the current user group are described in Table 1.

Weekly alcohol consumption did not differ between the controls and current users, with subjects in the current user group consuming a mean of 2.3 ± 2.9 (mean ± SD, range 0–10) alcohol drinks per week and subjects in the control group consuming 1.75 ± 1.6 (range 0–6) alcohol drinks per week. Therefore, the study criterion of a maximum of two alcohol drinks per day did not represent a reduction in alcohol consumption for any of the study subjects..

Comparison of the data from the current user group with the control group using a 2×5 repeated measures ANOVA revealed a significant group × time interaction on the number of aggressive responses: [$F(1,4) = 2.68$,

Table 1 Demographic characteristics of study subjects (mean ± SD). *C* Caucasian, *H* Hispanic, *S* single, *M* married, *D* divorced

	Age	Education	Gender	Ethnic background	Martial status	Tobacco smokers
Current users ($n = 17$)	35.4 ± 4.2	14.7 ± 1.6	13 M; 4 F	17 C	10 S, 4 M, 3 D	9
Controls ($n = 20$)	39.3 ± 7.4	15.7 ± 1.8	17 M; 3 F	17 C; 3 H	9 S, 9 M, 2 D	2

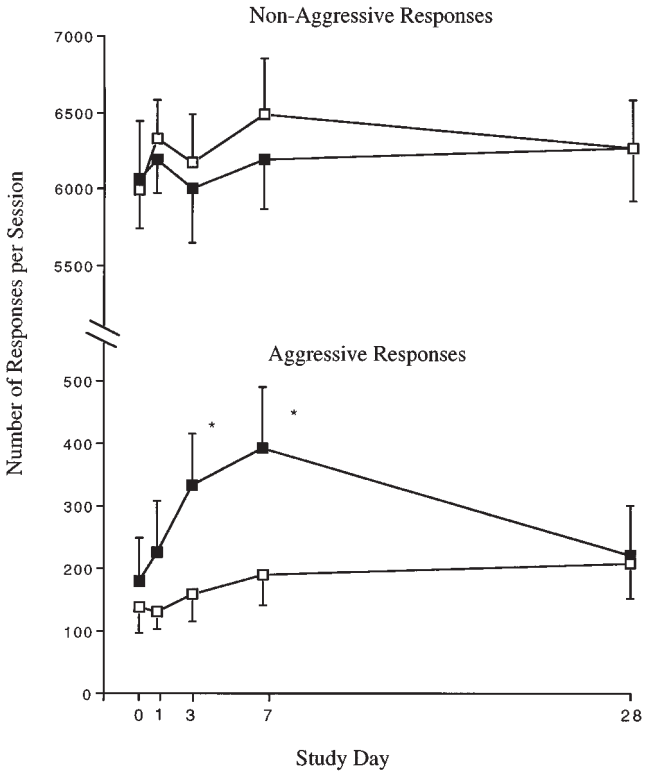

Fig. 1 Mean number (± SE) of aggressive and non-aggressive responses in 17 current marijuana smokers during abstinence (■) and 20 controls (□). *Significantly different from controls ($P < 0.05$)

$P = 0.03$] as well as the number of aggressive responses per point subtraction: [$F(1,4) = 2.42$, $P = 0.05$]. The number of non-aggressive responses did not differ between the two groups (Fig. 1). Post-hoc analyses revealed that the current marijuana users were significantly more aggressive than the controls on study days 3 and 7. These increases in aggressive responses on days 3 and 7 were paralleled by slight non-significant decreases in non-aggressive responses by this group, possibly because these subjects were spending more time making aggressive responses.

Analysis of the data from the current user group alone showed a significant effect of time on the number of aggressive responses (button B presses) [$F(16,4) = 3.75$, $P = 0.008$] and the number of aggressive responses per point subtraction: [$F(16,4) = 3.73$, $P = 0.009$]. The number of non-aggressive responses (button A presses) did not change over time. Post-hoc tests revealed that subjects in the current users group were significantly more aggressive on days 3 and 7 of marijuana abstinence compared to their pre-withdrawal levels of aggression. The number of aggressive responses on day 28 was not different from the pre-withdrawal baseline (day 0). Analysis of the data from the control group alone showed no significant changes over time on the number of aggressive responses, the number of aggressive responses per point subtraction, or the number of non-aggressive responses.

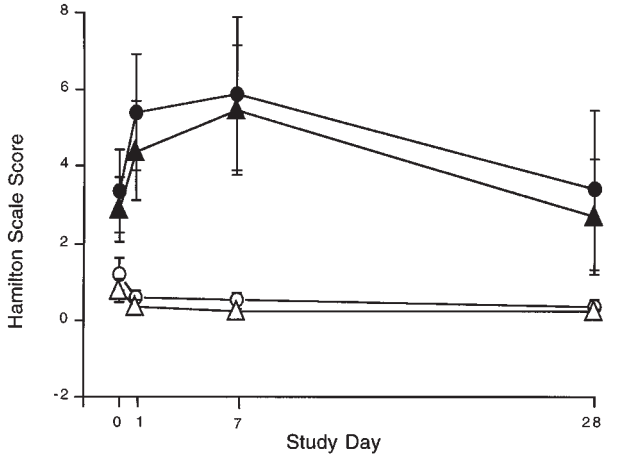

Fig. 2 Mean (± SE) scores of the Hamilton Depression and Hamilton Anxiety scales in 17 current marijuana smokers during abstinence and 20 controls. ● Current uses Depression score, ○ controls Depression score, ▲ current users Anxiety score, △ control Anxiety score

Analysis of the data from the Hamilton Depression Scale showed a significant main effect of group: [$F(1) = 12.1$, $P = 0.001$], with the current users being more depressed overall than the controls. However, there was no significant time effect or group × time. Similarly, analysis of the Hamilton Anxiety Scale data showed a significant main effect of group: [$F(1) = 9.8$, $P = 0.003$] with the current users being overall more anxious than the controls, but no time effect or group × time interaction. Figure 2 depicts the depression and anxiety scores from the current users and controls, with all scores being well below clinically significant levels. In addition, a correlational analysis revealed that the anxiety and depression scores of the current users were not significantly correlated with the number of aggressive responses at any of the time points studied.

The mean urinary THCCOOH levels of the subjects in the current user group over the 28-day abstinence period are depicted in Fig. 3. The data are normalized to a urinary creatinine concentration of 100 mg/dl in order to control for differences in subjects' urinary concentration. Of the 17 subjects in this group, five reached non-detectable levels (less than 20 ng/ml) within the first week of abstinence, four during the second week, two during the third week and the remaining six subjects still had detectable THCCOOH urinary levels at the end of the 28-day abstinence period. There were no significant correlations between the number of days it took subjects to provide a clean urine and the number of aggressive or non-aggressive responses made. Furthermore, when comparing the data from the six subjects with detectable levels after 28 days with the data from the subjects with clean urines, there were no significant differences in the number of aggressive responses, the number of non-aggressive responses or the number of aggressive responses per point subtractions.

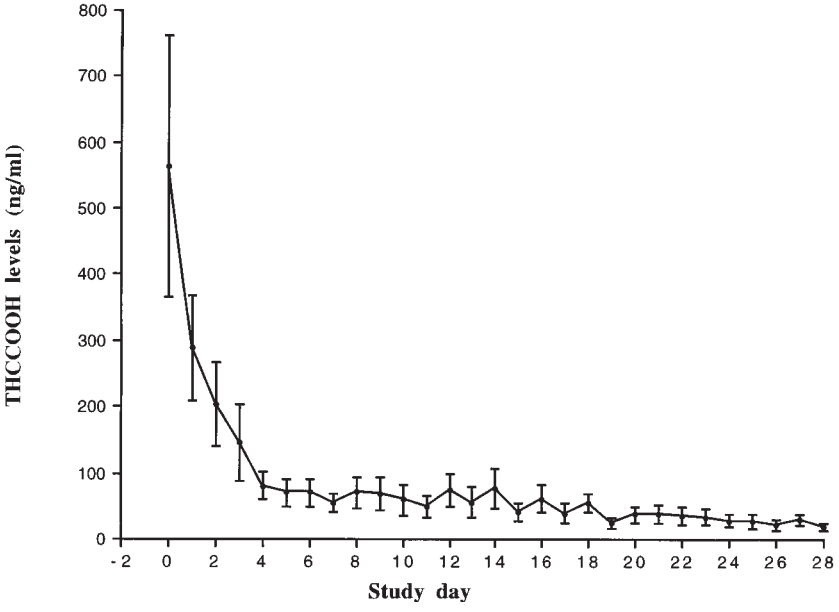

Fig. 3 Mean (± SE) urinary 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) levels in 17 current marijuana users. (note: all THCCOOH concentrations have been normalized to a urinary creatinine concentration of 100 mg/dl)

Discussion

The data from the present study demonstrated that, under laboratory conditions, abstinence from marijuana after chronic use is associated with increases in aggressive responding. Specifically, during the first week of abstinence, chronic heavy marijuana users displayed levels of aggression that were significantly higher than before becoming abstinent and higher than the levels displayed by matched controls. These increases in aggression occurred in the absence of any changes in the number of non-aggressive responses, suggesting that they could not be explained by a non-specific withdrawal-induced increase in responding.

The majority of reports published to date on marijuana withdrawal in humans have relied entirely or almost entirely on self-report measures to assess abstinence symptoms. Most of these studies have found irritability to be one of the most common symptoms reported by subjects (Jones et al. 1976, 1981; Mendelson et al. 1976, 1984; Georgotas and Zeidenberg 1979; Budney et al. 1998, Haney et al. 1998; Kouri et al. 1998). The present study compliments the findings from previous investigations by providing data obtained with an objective paradigm of aggression which measures the subject's actual behavior following provocation instead of the subject's report of how he or she would behave when faced with provocation.

The increases in aggressive responding in our current users on study days 3 and 7 may be related to withdrawal-related changes in mood. Although not statistically or clinically significant, our subjects experienced slight increases in anxiety and depression scores of the Hamilton scales during the first week of marijuana abstinence. It is possible that a more comprehensive assessment of symptoms would have revealed more pronounced mood changes during marijuana withdrawal which may have paralleled the changes in aggressive responding. We are currently exploring this in our laboratory.

An important issue in interpreting our findings is the external validity of the PSAP: does increased aggression on the PSAP correspond to actual increased aggression in the real world? The data support such an association. For example, subjects with histories of violent behavior respond significantly more aggressively on the PSAP than subjects without such a history (Cherek et al. 1996, 1997, 1998) and the number of aggressive responses made by subjects on the PSAP significantly correlates with psychometric measures of aggression (Cherek et al. 1997, 1998). These findings suggest that the increases in aggressive behavior observed here in the laboratory probably reflect actual changes in aggressiveness experienced by the subjects undergoing marijuana withdrawal.

The aggressive behavior observed in our subjects followed a specific time course, rising to reach statistical significance on days 3 and 7 of marijuana abstinence, then declining to near baseline levels by day 28. The transient nature of these changes is consistent with previous investigations of marijuana withdrawal reporting the appearance of symptoms within 24 h of abstinence, with a peak in intensity on days 2–4 (Jones et al. 1976; Mendelson et al. 1976, 1984; Georgotas and Zeidemberg 1979). However, in contrast to our findings of peak aggressive responding on day 7 of abstinence, a number of previous reports of marijuana withdrawal have found that most symptoms are no longer present by day 7 (Jones et al. 1976; Mendelson et al. 1976, 1984; Georgotas and Zeidemberg 1979). This apparent discrepancy in peak symptom severity

may be explained by the fact that it is very likely that different symptoms peak at different times during withdrawal and that individuals may be unaware of certain symptoms that may become pronounced under specific situations. Since the present study measured changes in aggressive behavior exclusively, it is possible that other symptoms such as irritability or anxiety may have peaked on days 2–4 in our subjects, consistent with previous reports, but that aggressive responding peaks at a later date, as found in the present study. In addition, since the data in this study were obtained with an aggression paradigm that measures the subject's actual behavior following provocation instead of the subject's report of how he or she would behave when faced with provocation, perhaps subjects during marijuana withdrawal are unaware of their elevated levels of aggression until they are provoked. Furthermore, given the temporal distribution of the testing in the present study, it is not possible to assess at what time point, between day 8 and day 28, the observed increases in aggressive behavior typically subside. Future studies designed specifically to investigate the time course and pattern of changes in symptoms after marijuana abstinence need to be conducted.

It is also important to note that although our monitoring of marijuana abstinence via daily observed urine samples provide strong evidence that the subjects had ceased smoking, we cannot exclude the possibility that some subjects might have surreptitiously smoked very small amounts of marijuana not detected during the abstinence period. However, if this were the case, the data from the present study would simply represent a somewhat more conservative estimate of the magnitude of changes in aggressive responding experienced by individuals during marijuana abstinence, as compared to that which would be obtained if all subjects were experiencing withdrawal with no marijuana at all.

Identifying the nature, severity and temporal characteristics of withdrawal symptoms during marijuana abstinence is crucial in developing treatment strategies for individuals attempting to stop their marijuana use. Symptoms of marijuana withdrawal, although subtle compared to those associated with alcohol, opiate or cocaine withdrawal, may play an important role in relapse among individuals who may continue to use in order to prevent the appearance of abstinence symptoms. This is particularly important because reviews of the literature estimate that 20–30% of those who have used marijuana more than a few times may develop dependence on it (Hall et al. 1994). In conclusion, the data from the present study provides additional empirical evidence of a marijuana withdrawal syndrome and suggest that increases in aggressive behavior should be an additional component of this syndrome.

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