The question of whether a clinically significant marijuana (cannabis) withdrawal syndrome exists remains controversial. In spite of the mounting clinical and preclinical evidence suggesting that such a syndrome exists, the DSM-IV does not include marijuana withdrawal as a diagnostic category.

The clinical syndrome has been characterized by restlessness, anorexia, irritability and insomnia that begin less than 24 hours after discontinuation of marijuana, peak in intensity on days 2 to 4, and last for seven to 10 days (Budney et al., 1999; Haney et al., 1999; Mendelson et al., 1984).

The question of whether this syndrome is clinically significant is important, not only because marijuana is the most commonly used illicit drug in the United States (Johnston et al., 2001), but also because marijuana has been shown to produce dependence at rates comparable to other drugs of abuse (Kandel et al., 1997; Kessler et al., 1994) and because relapse rates among individuals seeking treatment for marijuana dependence are similar to those with other drugs of abuse (Budney et al., 1998; Stephens et al., 1993). Furthermore, many violent crimes are committed by individuals undergoing withdrawal from drugs of abuse, including marijuana (Kouri et al., 1997; Peters and Kearns, 1992). If a clinically significant marijuana withdrawal syndrome does exist, the omission of this syndrome from the DSM-IV might contribute to the perception that behavioral or pharmacological treatment regimens for marijuana dependence are not necessary.

We conducted two studies in our laboratory to determine whether abstinence from marijuana after long-term use results in withdrawal symptoms, to identify those symptoms and to quantify their severity (Kouri and Pope, 2000; Kouri et al., 1999). The first study focused specifically on whether abrupt discontinuation of marijuana following chronic use results in changes in aggressive behavior (Kouri et al., 1999). To measure aggressive behavior, we used the Point Subtraction Aggression Paradigm (PSAP). This computer test has been used to detect changes in aggressive responses following acute administration of a number of drugs, and its external validity has been demonstrated in a number of studies of male and female parolees with histories of violent behavior (Cherek and Lane, 1999; Cherek et al., 1996).

Subjects in our study were long-term heavy users of marijuana who reported a history of at least 5,000 separate episodes of marijuana use in their lifetime (the equivalent to smoking once per day for 13.7 years), were smoking at least once daily at the time of recruitment and met DSM-IV criteria for marijuana dependence without meeting criteria for a current Axis I disorder. Subjects were excluded if they reported that they had used another class of drugs more than 100 times in their lifetimes or had consumed more than five alcoholic drinks per day continuously for one month or more in their lifetimes.

The controls were composed of two groups: 1) 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 2) individuals who had formerly smoked marijuana on a daily basis but who had not smoked more than once per week during the last three 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. We based this decision 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., 1995).

During the study, subjects were required to abstain from smoking marijuana and using any other drugs for 28 consecutive days. To verify abstinence, subjects had to come to the laboratory every day to provide supervised urine samples that we analyzed quantitatively for tetrahydrocannabinol (THC) metabolites. We measured aggressive responses with the PSAP on study days 0 (before abstinence), 1 (after 24 hours of abstinence), 3, 7 and 28.
Subjects were told they would be playing a computer game against an anonymous same-sex subject from the study. In fact, however, this second subject was actually a computer. During the course of each 20-minute computer session, subjects had the option of pressing one of two buttons on the PSAP response panel (labeled "A" or "B"). Pressing button A resulted in the accumulation of points that were exchanged for money at the end of the study. Pressing this button was defined as a non-aggressive response. By pressing button B, subjects could subtract points from the fictitious opponent. Points taken from the opponent, however, were not added to the subject's counter, and pressing button B was defined as an aggressive response. Aggressive responding was provoked by random subtractions of the subject's points, which were attributed to the fictitious opponent.

On study day 0 (before marijuana abstinence) and study day 1 (24 hours of marijuana abstinence), the current marijuana users did not differ from past heavy users or light users in the number of aggressive or non-aggressive responses they made. However, current marijuana users were significantly more aggressive on days 3 and 7 of marijuana abstinence compared to their pre-withdrawal levels of aggression and compared to the controls. By day 28, the number of aggressive responses from the current marijuana users was not different from their pre-withdrawal baseline levels or the controls (Figure).

These data demonstrate that abstinence from marijuana after chronic use is associated with increases in aggressive responding following provocation. Specifically, during the first week of abstinence, current marijuana users displayed levels of aggression that were significantly higher than before abstinence and higher than the levels displayed by matched controls. Interestingly, the increases in aggressive responding followed a specific time course and then returned to pre-withdrawal levels after 28 days of abstinence. The transient nature of these changes is consistent with other reports of marijuana withdrawal.

The second study was designed to further characterize symptoms of marijuana withdrawal and to quantify their magnitude (Kouri and Pope, 2000). We used the same study entry criteria as in the first study and subjects were required to come to the laboratory every day to provide urine samples and to fill out a daily diary.

The items assessed in the daily diaries were: mood, appetite, sleep, anxiety, irritability, physical tension or agitation, physical symptoms, ability to concentrate, desire to use marijuana, and desire to resume using marijuana at the end of the study. The questions were presented on a 10-point Likert scale with the qualifiers "extremely low" at the zero end of the scale and "extremely high" at the 10-point end of the scale. We obtained pre-withdrawal baseline levels for all of the diary items via a personal interview with each subject before the beginning of the withdrawal period. Thirty current marijuana users and 30 controls (16 former heavy users and 14 light users) participated in the study. Before the beginning of the abstinence period, the current marijuana users were not different from the former users or the light users on any of the items assessed in the diaries except for the ability to concentrate item. The current users reported a lower ability to concentrate than the controls. Interestingly, the former heavy users were not different from the light users on any of the diary scores during the course of the study. In contrast, the current users reported increases in irritability, anxiety, physical tension and physical symptoms, and decreases in mood and appetite starting on day 1 and peaking between days 7 and 10 of marijuana abstinence.

It is important to note that although, as a group, the current marijuana users experienced an increase in withdrawal symptoms compared to the controls, only 60% of the subjects in the current users group reported a change in symptoms of at least three points in magnitude. The fact that 40% of subjects who had used marijuana regularly for an average of 22 years did not report experiencing severe withdrawal symptoms during abstinence might suggest that physical dependence on marijuana is not as strong as that observed with other drugs of abuse. This may be due, at least in part, to the long half-life of THC. However, many subjects reported that when trying to remain abstinent in the past, the presence of withdrawal symptoms had played an important role in their relapse. Thus, alleviation of abstinence symptoms may contribute to the maintenance of daily marijuana use in chronic users.

Another significant finding is that after 28 days of marijuana abstinence, all of the symptoms returned to pre-withdrawal levels except for irritability and physical tension. It is possible that these two symptoms remained slightly elevated because they represented a premorbid characteristic of the current users and were not a result of marijuana withdrawal. If this is the case, the fact that the former users did not have elevated scores on these two items may reflect a characteristic that potentially differentiates individuals with a history of heavy marijuana use who have successfully stopped from individuals who continue to smoke regularly.

Taken together, the data from these two studies provide further evidence of the existence of a
marijuana withdrawal syndrome. An important aspect of both of our studies is that we used two control groups: 1) former heavy marijuana users and 2) individuals who had rarely smoked marijuana during their lives. It is noteworthy that these control groups were indistinguishable from one another in diary scores or number of aggressive responses on the PSAP, whereas both were significantly distinguishable from the current marijuana users. This observation argues that the elevated diary scores and aggressive responses of the current marijuana users were attributable to marijuana withdrawal, rather than a mere history of marijuana use or some other aspect of subject selection or study design. Future studies should focus not on whether a marijuana withdrawal syndrome exists but rather on determining the clinical significance of this syndrome and the role withdrawal symptoms play in perpetuating marijuana use.

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