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RESEARCH REPORT

An evaluation of the history of a marijuana withdrawal syndrome in a large population

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Abstract

Case reports and laboratory research indicate the existence of a cannabis withdrawal syndrome. However, the data tell us little about the prevalence and clinical characteristics of a marijuana withdrawal syndrome in people who have used the drug but who did not enter treatment for cannabis dependence. Face-to-face semi-structured interviews applying standard diagnostic criteria were used in the present study to gather data from 5611 men and women, recruited between 1991 and 1995 through the Collaborative Study of the Genetics of Alcoholism (COGA). Almost 41% of the sample had no history of marijuana use (Group 1), 28% had consumed this drug less than 21 times in any single year (Group 2), and 31% used it at least that frequently (Groups 3 and 4). Almost 16% of the more frequent marijuana users related a history of a marijuana withdrawal syndrome, and these Group 4 subjects had used the drug almost daily for an average of almost 70 months. The typical withdrawal symptoms included "nervous, tense, restlessness", "sleep disturbance" and "appetite change". While Group 4 subjects were more likely to have developed dependence on most types of drugs, even when alcohol and drug use patterns were statistically taken into account, marijuana use was still significantly related to a self-report of a history of marijuana withdrawal.

Introduction

Most, but not all (McMillan *et al*., 1971; Harris, Walters & McLendon, 1974; Leite & Carlini, 1974; Wikler, 1976; Compton *et al*., 1990) animal studies report evidence of a rebound or withdrawal syndrome following high doses of delta-9-tetrahydrocannabinol (THC). For example, Deneau & Kaymakcalan (1971) treated six rhesus monkeys over a 5-week span with up to 0.4 mg/kg of THC every 6 hours intravenously (i.v.). Twelve hours after drug cessation, all monkeys experienced symptoms lasting approximately 5 days and characterized by aggressiveness, irritability, tremor, twitching, piloerection, anorexia, sexual excitement and bizarre behaviors that might be interpreted as hallucinations. Similarly, Fredericks & Benowitz (1980) injected four rhesus monkeys with 0.5 mg/kg of THC every 6 hours for 3 weeks, and observed tooth baring, eye contact and gross motor activity when the drug was stopped. Possible withdrawal effects related to decreased food intake were also noted in two of three rhesus monkeys treated for 10 days with a continuous i.v. infusion of THC (0.05 mg/kg per hour), a disrupted behavior which was reversed by

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readministration of THC (Beardsley, Balster & Harris, 1986). Finally, in the only primate study using oral drug, two rhesus monkeys received 37.5 mg/kg of THC for 50 days, with both demonstrating increased aggressiveness after drug cessation, and one animal showing prolonged EEG desynchronization and behaviors that might indicate hallucinations (Stadnicki *et al.*, 1974).

There is also information from at least two types of human studies regarding the characteristics of a marijuana withdrawal syndrome. The first, and potentially less conclusive, were anecdotal reports that included individual case histories, casual observations of regular users who were denied access to their drugs (Dilsaver, Leckrone & Greden, 1984; Rohr, Skowlund & Martin, 1989), and clinical case reports (Fraser, 1949; Soueif, 1967; Bensus, 1971). These highlighted the possible existence of a syndrome, but did little to reassure the reader that the condition might not just have reflected general levels of stress, predisposing personality characteristics, additional psychopathology in the subjects, or the consequences of intoxication or withdrawal from other substances (Compton *et al.*, 1990).

The second type of human study incorporated more formal research protocols. Here, individuals with histories of marijuana use lived in a controlled environment where they were either encouraged to self-administer marijuana products, or were given pre-programmed amounts of THC. Over a period of weeks subjects received the THC, access to other substances was controlled, and the potential development of symptoms upon cessation of drug use was elvaluated (Williams *et al.*, 1946; Cohen *et al.*, 1976; Greenberg *et al.*, 1976; Jones, Benowitz & Bachman, 1976; Mendelson *et al.*, 1976; Nowlan & Cohen, 1977; Georgotas & Zeidenberg, 1979; Mendelson *et al.*, 1984). Most studies agreed that a withdrawal syndrome was likely to begin within 24 hours of abstinence, peak in intensity on days 2–4, and then diminish with few or no symptoms remaining by day 7 (Kielholz & Ladewig, 1970; Jones *et al.*, 1976; Mendelson *et al.*, 1976; Georgotas & Zeidenberg, 1979). Most also agreed that subjects reported a decreased appetite, nausea, demonstrated weight loss (Jones *et al.*, 1976; Nowlan & Cohen, 1977; Georgotas & Zeidenberg, 1979), showed sleeplessness which was reported to be associated with an increase in rapid eye movement sleep (Feinberg *et al.*, 1975, 1976; Karacan *et al.*, 1976), and many subjects evidenced either irritability or hyperactivity (Fraser, 1949; Jones *et al.*, 1976; Nowlan & Cohen, 1977; Georgotas & Zeidenberg, 1979). Some researchers reported evidence of a tremor or muscle twitching and sweating during withdrawal (Kielholz & Ladewig, 1970; Jones *et al.*, 1976). Additional symptoms that have been noted include increases in body temperature and salivary output (Jones *et al.*, 1976). In only one of these studies (Jones *et al.*, 1976) did the authors attempt to document that the symptoms associated with a potential withdrawal were decreased by the administration of THC.

In summary, both animal and human research indicate that symptoms consistent with a marijuana withdrawal syndrome are observed following acute abstinence after receiving relatively high doses of marijuana. Most complaints included restlessness, irritability, insomnia and decreases in appetite. As described by Jones (1983) these symptoms resembled what could be expected following withdrawal associated with modest doses of alcohol or other brain depressants or opiates (Schuckit, 1995). While it appears that a marijuana withdrawal syndrome can be produced in a laboratory setting, it is unclear from these data how frequently these symptoms are observed in a general population with a self-regulated pattern of drug use. The present paper utilizes data generated from face-to-face interviews with a large sample of alcohol-dependent individuals, their families and controls in order to evaluate the prevalence and possible clinical relevance of a marijuana withdrawal syndrome.

Methods

The data reported here were generated through the Collaborative Study on the Genetics of Alcoholism (COGA), an ongoing pedigree study of alcohol-dependent men and women. The 5611 interviews used here were generated from face-to-face sessions carried out between January, 1991 and March, 1995, and included 758 alcohol-dependent probands (177 women), 4064 first-degree and extended relatives of these probands (2430 women), as well as 789 subjects from control families (405 women). The interviews were administered by staff at the six COGA centers in San Diego, St Louis, Iowa City, Farmington, New York and Indianapolis.

The original alcohol-dependent probands represent a consecutive series of inpatients, out-

patients and aftercare program participants in substance use disorder programs in the six cities. All probands (but not necessarily their relatives or controls) met criteria for alcohol dependence as defined by DSM-III-R (American Psychiatric Association, 1987), as well as definite alcoholism as defined by Feighner *et al.* (1972). Potential probands were excluded if they did not speak English or had a history of repeated i.v. drug use, and only subjects whose nuclear family had five or more individuals available for evaluation were included. No subject was excluded from the study because of any additional DSM-III-R Axis I or Axis II disorder. Control families were selected through a variety of mechanisms across the six sites including a random survey of young men at a university, individuals entering care for non-substance-related disorders, through the use of drivers' license records and via advertising.

Informed consent was obtained to carry out evaluations with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview, which was given by trained personnel with established high levels of reliability (Bucholz *et al.*, 1994). Developed from portions of already existing structured interviews (Coryell, Cloninger & Reich, 1978; Endicott & Spitzer, 1978; Robins *et al.*, 1985; Robins *et al.*, 1988; Spitzer *et al.*, 1992), the SSAGA systematically reviews multiple diagnostic systems for 17 Axis I disorders, the antisocial personality disorder (ASPD) and psychotic symptoms relevant to DSM-III-R.

Separate SSAGA sections were used to elicit information on demography, psychiatric histories, alcohol and drug use patterns, as well as problems associated with substance intake. The drug use and problem sections for all subjects included a query regarding the life-time history of ever having used marijuana, hashish or other cannabinoids, gathering more detailed information from individuals who had used these substances at least 21 times in any year. A positive response to that frequency of use resulted in a series of questions relating to ages of use, periods of abstinence, as well as information regarding areas of potential cannabis-related problems for abuse or dependence. For individuals who had taken other drugs of abuse, similar relevant information was gathered (Schuckit, 1995).

In the present analyses the sample was broken down into groups based on the history of exposure to marijuana and evidence of a potential marijuana withdrawal syndrome. Thus, Group 1 included 2300 subjects (41.0%) who denied ever having used marijuana, Group 2 comprised the 1576 (28.1%) who admitted to using marijuana but only 20 or fewer times in any single year, and Groups 3 and 4 related to the 1735 (30.9%) men and women who had used marijuana on 21 or more occasions in a single year. This included the 270 individuals in Group 4 (4.8% of the 5611 interviewed subjects and 15.6% of the 1735 more frequent users) who reported having had two or more marijuana withdrawal symptoms clustering together, and 1465 people (26.1% of the total) who used marijuana at this frequency but denied any clustering of possible withdrawal symptoms (Group 3).

The diagnosis of possible marijuana withdrawal was based on the self-report of any of the seven symptoms suggested to be relevant to a marijuana withdrawal syndrome in the literature (Williams *et al.*, 1946; Cohen *et al.*, 1976; Greenberg *et al.*, 1976; Jones *et al.*, 1976; Mendelson *et al.*, 1976; Nowlan & Cohen, 1977; Georgotas & Zeidenberg, 1979). These included feeling nervous, tense, restless or irritable; having problems sleeping; developing a twitch or tremor; having sweats or a fever; experiencing nausea or vomiting; having had diarrhea or stomach aches; or reporting an appetite change associated with cutting down or stopping marijuana or other cannabinoid use following a period of regular intake. Because the literature is not clear on the appropriate threshold for establishing a diagnosis, it was *a priori* required that two or more of these symptoms had clustered together during at least one reported withdrawal. DSM-IV requires two symptoms for a withdrawal syndrome from alcohol, sedative–hypnotics, amphetamines and cocaine, although thresholds of three or four items are required for withdrawal from opiates or nicotine (American Psychiatric Association, 1994).

The analyses presented in this paper explore the characteristics of subjects who reported a marijuana withdrawal syndrome (Group 4), contrasting these with repeat users who did not report a clustering of withdrawal phenomena when they stopped or cut back on cannabinoid use (Group 3). A χ^2 statistic was used for a comparison of categorical data, while a Student's *t*-test was invoked for a comparison of means. In order to place the Group 3 versus 4 comparisons in perspective, data are also offered regarding

Table 1. *Prevalence of possible marijuana withdrawal symptoms among frequent users[1] of marijuana, including 270 of those reporting a withdrawal cluster[2]*

	All frequent marijuana users ($n = 1735$)		Frequent users who reported a withdrawal cluster ($n = 270$)	
Withdrawal symptoms	*n*	(%)	*n*	(%)
Nervous, tense, restless	420	24.2	255	94.4
Sleep disturbance	235	13.5	204	75.6
Appetite increase or decrease	256	14.8	170	62.9
Tremble, twitch	63	3.6	56	20.7
Sweat, fever	46	2.7	40	14.8
Diarrhea, stomach problems	34	2.0	31	11.5
Nausea, vomiting	33	1.9	29	10.7

[1]Those who reported using marijuana at least 21 times in a single year.
[2]Users who reported two or more withdrawal symptoms during the same episode.

subjects who denied using marijuana (Group 1) and who reported less frequent use (Group 2). A logistic regression approach was used to evaluate the relative impact of several domains in predicting reports of withdrawal. Here, the dependent variable was Group 4 membership and the predictors were entered simultaneously.

Results

The 1465 Group 3 subjects reported having used cannabinoids a mean ($\pm$SD) of 522.1 ($\pm$416.58) times, while those in Group 4 reported 783.2 ($\pm$351.59) life-time uses ($t = -18.87$; df = 421; $p = 0.0001$). However, the SSAGA only allowed for coding up to 999 uses, making it important to note that this number was exceeded by 37.5% of Group 3 and 66.3% of Group 4 subjects ($\chi^2 = 77.37$; df = 1; $p < 0.0001$). More complete data were available on the longest period of consecutive months in which marijuana was used daily or nearly every day, with averages of 36.1 ($\pm$53.69) and 69.9 ($\pm$71.77) months of continuous use for Groups 3 and 4 ($t = -7.16$; df = 322; $p = 0.0001$). This included 65.3% and 93.0%, respectively, who had used daily for a month or more at a time ($\chi^2 = 82.67$; df = 1; $p < 0.0001$). Across Groups 3 and 4 49.1% and 83.0% had ever stayed high for an entire day ($\chi^2 = 105.30$; df = 1; $p < 0.0001$).

Table 1 relates the self-report for each of the seven potential withdrawal symptoms for the more frequent cannabis users. The first data columns offer information on subjects from Groups 3 and 4 combined, regardless of the total number of possible withdrawal symptoms that they reported, and independent of whether symptoms ever clustered together. The second set of data columns focuses only on the 270 Group 4 individuals who reported two or more symptoms of withdrawal clustering together. Using either approach, the marijuana-related symptoms most likely to be reported by either group after stopping use were nervousness, sleep disturbances or appetite change. The symptoms of tremor, sweating, diarrhea or nausea were observed relatively infrequently.

Tables 2 and 3 describe the demographic and substance related characteristics of the subjects in the four groups. While not shown in the tables, the ages across Groups 1 to 4 were 48.1 ($\pm$16.56), 35.7 ($\pm$11.42), 32.7 ($\pm$7.53) and 32.0 ($\pm$7.31) years, respectively, with no significant differences between Groups 3 and 4 ($t = 1.65$; df = 1,733; $p = 0.12$). The mean ($\pm$SD) for years of completed schooling were 12.9 ($\pm$2.62), 13.1 ($\pm$2.34), 12.7 ($\pm$2.10), and 12.2 ($\pm$2.08) years, with the latter two groups being significantly different ($t = 3.34$; df = 1,733; $p < 0.001$).

As shown in Table 2, compared with Group 3, Group 4 subjects were more likely to have been male alcohol-dependent probands, and fewer were employed full-time. Also, the proportion of married subjects was significantly lower in Group 4 ($\chi^2 = 7.53$; df = 1; $p < 0.01$). As shown in Table 3, Group 4 subjects were significantly

Table 2. *Demography across four groups based on cannabis use and withdrawal among 5611 males and females (%)*

Demography	Group 1, never used marijuana ($n = 2300$) (41.0%)	Group 2, used marijuana < 21 times in a year ($n = 1576$) (28.1%)	Frequent marijuana users ($n = 1735$) Group 3, never withdrawal cluster ($n = 1465$) (26.1%)	Group 4, had withdrawal cluster ($n = 270$) (4.8%)	χ^2 Group 3 versus Group 4 (df = 1)
Subject group					
Proband from alcohol treatment	5.6	10.5	23.3	43.7	48.11, $p < 0.0001$
Relative of proband	74.0	75.9	69.8	52.9	29.16, $p < 0.0001$
Control family member	20.4	13.4	6.8	3.3	4.72, $p < 0.05$
Gender male	37.7	40.6	61.9	68.9	4.76, $p < 0.05$
Race/ethnicity					✓0.64, NS
Caucasian	78.1	75.2	72.4	71.1	
Black	13.6	15.1	18.7	20.4	
Hispanic	5.3	7.0	5.8	5.9	
Other	3.0	2.7	3.2	2.6	
Marital status					✓✓9.52, $p < 0.05$
Married	63.1	50.4	39.2	30.4	
Separated	3.3	5.7	6.8	9.6	
Divorced	10.5	12.8	15.9	15.6	
Widowed	5.7	1.4	0.9	1.1	
Never married	17.4	29.7	37.1	43.3	
Employed full-time	45.4	55.9	53.9	45.9	5.75, $p < 0.05$

The df for most comparisons is 1, except for ✓ which is 3 and ✓✓ which is 4.

more likely to have fulfilled criteria for dependence on other drugs and to be ASPD. Group 4 subjects were also more likely than those in Group 3 to have been treated for alcohol or other substance dependence, but were not more likely to have close relatives with substance use disorders or ASPD.

Thus, while the data indicate consistent differences between Groups 3 and 4 subjects on measures of the intensity of use of marijuana, those in Group 4 were also more likely to have used and to have become dependent on alcohol and drugs other than marijuana. To test the possibility that reports of marijuana withdrawal might have reflected the influence of other substances, a logistic regression analysis was performed on the subjects in Groups 3 and 4. Clustering of two or more withdrawal symptoms (i.e. Group 4 vs. Group 3 membership) was the dependent variable, while the independent variables included two measures of marijuana use (the longest period of continuous daily marijuana use and the number of times of marijuana use), a diagnosis of ASPD and the presence or absence of a diagnosis of dependence on alcohol or the four other categories of drugs in Table 4. These eight predictor variables yielded a model that significantly described marijuana withdrawal ($\chi^2 = 172.25$; df = 8; $p = 0.0001$; Hosmer & Lemeshow GOF = 8.60; $p = 0.38$). Within this model, the longest period of daily marijuana use, the number of times this drug was taken, sedative/hypnotic dependence, alcohol dependence and ASPD added significant unique contributions to predicting a marijuana withdrawal syndrome. The largest odds ratios, indicating the increased likelihood of reporting marijuana withdrawal as a function of the presence of the predictor, were observed for sedative/hypnotic dependence (2.34) and alcohol dependence (2.03). However, even though the odds ratio for the longest period of daily use was only 1.005, it is important to remember that this is a continuous variable and the unit is each month of use.

Table 3. *Personal and family substance use and psychiatric diagnoses in 5611 men and women with/without marijuana use and withdrawal (%)*

Substance use and psychiatric history	Group 1, never used marijuana ($n = 2300$)	Group 2, used marijuana <21 times in a year ($n = 1576$)	Frequent marijuana users ($n = 1735$)		
			Group 3, never withdrawal cluster ($n = 1465$)	Group 4, had withdrawal cluster ($n = 270$)	χ^2 Group 3 versus Group 4 (df = 1)
Ever used drugs 11 + times					
Cocaine	1.7	26.1	73.6	85.9	17.05, $p < 0.0001$
Amphetamines	1.8	20.2	54.2	71.5	27.70, $p < 0.0001$
Sedative/hypnotics	2.3	11.7	43.9	65.9	44.04, $p < 0.0001$
Opiates	1.1	7.7	35.0	61.9	67.42, $p < 0.0001$
Primary DSM-III-R psychiatric diagnosis					
Alcohol dependence	15.7	26.9	25.5	16.7	26.28, $p < 0.0001$
Other substance dependence	0.6	3.4	22.5	28.5	4.24, $p < 0.05$
Antisocial personality disorder	1.4	6.2	18.6	36.3	39.66, $p < 0.0001$
Anxiety disorder	2.3	2.0	2.0	2.2	NS
Major depressive disorder	16.3	18.5	11.1	11.1	NS
No psychiatric diagnosis	63.2	42.2	19.7	4.4	15.60, $p < 0.0001$
DSM-III-R dependencies (includes primary and secondary diagnoses)					
Marijuana	0	0	41.6	97.8	288.12, $p < 0.0001$
Alcohol	19.7	39.7	66.5	87.8	49.04, $p < 0.0001$
Cocaine	0.6	6.9	32.7	57.8	61.81, $p < 0.0001$
Amphetamines	0.4	3.1	15.1	34.4	57.64, $p < 0.0001$
Sedative/hypnotics	0.5	2.3	6.7	26.7	102.95, $p < 0.0001$
Opiates	0.3	2.0	7.5	24.9	74.54, $p < 0.0001$
Ever treated for alcohol problems (among users)	15.4	20.6	39.5	64.4	56.63, $p < 0.0001$
Ever treated for substance use (among users)	32.7	34.9	39.5	63.9	42.21, $p < 0.0001$
Proportion of first-degree relatives with					
Alcohol dependence	15.9	19.1	20.0	22.9	NS
Substance dependence	11.4	13.3	14.5	14.4	NS
Antisocial personality disorder	7.1	9.8	10.3	10.5	NS

The increase in the value of this predictor by a single unit, 1 month, has a far less impact on the occurrence of marijuana withdrawal than the increase by a single unit (i.e. from "no" to "yes") of a categorical variable such as sedative or alcohol dependence, but because of the large number of months of use this variable was an important predictor. The same explanation applies to the low odds ratio (1.001) of the second continuous variable, the number of times of marijuana use.

Several additional steps were taken to probe for evidence of a marijuana withdrawal syndrome even after controlling for the impact of other drugs. The first was to evaluate if marijuana use patterns still contributed to Group 4 membership when additional *withdrawal phenomena* to other drugs were considered. Therefore, a second logistic regression was carried out, but in this case substituting a diagnosis of withdrawal rather than a diagnosis of dependence on each of the other drugs. The results were quite similar to those displayed in Table 4 ($\chi^2 = 202.3$; df = 8; $p = 0.0001$; GOF = 6.29; $p = 0.61$). Reported withdrawal syndromes from sedatives/hypnotics and alcohol had significant unique contributions to predicting Group 4 membership within this model. Importantly, even after taking into account withdrawal from those drugs, both assessments of marijuana use ("longest period of daily use" and "number of times of use") still significantly contributed to Group 4 member-

Table 4. *Logistic regression with "marijuana withdrawal syndrome" (Group 4) as dependent variable and several predictor variables*

Predictor variable	χ^2 (df = 1)	p	Odds ratio
Longest period of continuous marijuana use	17.99	< 0.001	1.005
Number of times of marijuana use	8.13	< 0.01	1.001
Cocaine dependence	1.48	NS	1.22
Amphetamine dependence	2.88	NS	1.35
Sedative/hypnotic dependence	14.02	< 0.001	2.34
Opiate dependence	2.35	NS	1.42
Alcohol dependence	10.47	< 0.01	2.03
Antisocial personality disorder	5.55	< 0.05	1.10

ship, with the same odds ratios as reported earlier.

Another attempt to probe for the validity of self-reports of a marijuana withdrawal syndrome was to identify a subgroup among the 270 individuals in Group 4 who reported marijuana withdrawal but who did not meet criteria for dependence on any drug other than marijuana. Thus, the marijuana-related syndrome could be studied without possible contamination by the impact of other drugs. Unfortunately, 237 of the 270 men and women in this category met criteria for alcohol dependence either alone or in the context of other drug dependencies, and 15 of the remaining 33 individuals met criteria for dependence on sedative/hypnotics, opiates or cocaine. Only 10 men and eight women reported a marijuana withdrawal syndrome in the absence of dependencies on other drugs. Although this sample is too small to generate meaningful conclusions, it is worth mentioning that the most frequently observed withdrawal symptoms for these 18 subjects ("nervous, tense, restlessness", "sleep disturbance" and "appetite change") were the same as those reported by the frequent users of Group 3 and 4 reported in Table 1.

Finally, it was hypothesized that if Group 4 subjects were accurately reporting a marijuana withdrawal syndrome there should be a relationship between the level of restrictiveness of the diagnostic criteria and measures of the use of marijuana. Thus, the patterns of marijuana use associated with a threshold of three of the seven possible withdrawal items in Table 1, and then four of the seven possible items were evaluated. Since the structured interview cut off the number of marijuana uses at 999 times during lifetime, the longest period (in months) of daily marijuana use was the focus of the analysis. Here, those with a cluster of *only two* possible withdrawal symptoms had a longest period of daily use of 62.9 ($\pm$71.22) months, while those with a cluster of three reported 76.7 ($\pm$65.53) months, and those with four or more noted 83.6 ($\pm$79.26) months. An analysis of variance (ANOVA) with the longest period of daily marijuana use (months) as the dependent variable and a cluster of 2, 3 or 4 and more withdrawal symptoms as grouping variables yielded no significant difference ($F_{(2;256)} = 1.88$; $p = 0.15$). However, when the group with two symptoms was compared to those with four, the difference was significant ($t = 1.71$; df = 197; $p = 0.045$). This result suggests that in Group 4 subjects an increase in the number of withdrawal symptoms that clustered together was associated with an increase in the length of time of daily marijuana use, but the effect was not very strong.

While the major focus of this work was to identify the prevalence and characteristics associated with the self-report of marijuana withdrawal among cannabinoid users, the data gave interesting information on the characteristics of users overall. To analyze this issue more closely, the non-users and the less-than-21-times per year users were combined (Group 1 + 2) and then compared with the more frequent marijuana users (Group 3 + 4). Statistical evaluation revealed that Group (1 + 2) differed significantly from Group (3 + 4) in almost every variable listed in Tables 2 and 3. More frequent marijuana users (Group 3 + 4), had a higher proportion with psychiatric diagnoses ($\chi^2 = 54.73$; df = 1; $p < 0.001$), and carried higher propor-

tions with dependence on marijuana ($\chi^2 = 2309.64$; df = 1; $p < 0.001$), alcohol ($\chi^2 = 874.76$; df = 1; $p < 0.001$), cocaine ($\chi^2 = 1152.19$; df = 1; $p < 0.001$), amphetamines ($\chi^2 = 536.62$; df = 1; $p < 0.001$), sedative/hypnotics ($\chi^2 = 237.63$; df = 1; $p < 0.001$) and opiates ($\chi^2 = 273.80$; df = 1; $p < 0.001$), compared with Groups 1 and 2 subjects. Group (3 + 4) also reported more treatment for alcohol ($\chi^2 = 581.23$; df = 1; $p < 0.001$) and drug problems ($\chi^2 = 801.07$; df = 1; $p < 0.001$). Additionally, membership in Group (3 + 4) was associated with a significantly higher number of first-degree relatives with alcohol dependence ($t = -8.48$; df = 2968.2; $p < 0.001$) and other substance dependencies ($t = -11.43$; df = 2,892.7; $p < 0.001$) or ASPD ($t = -7.09$; df = 2,790.1; $p < 0.001$). More frequent marijuana users (Group 3 + 4) were more often male, black ($\chi^2 = 17.57$; df = 1; $p < 0.001$), separated ($\chi^2 = 21.13$; df = 1; $p < 0.001$), divorced ($\chi^2 = 20.72$; df = 1; $p < 0.001$) or never married ($\chi^2 = 194.12$; df = 1; $p < 0.001$). On the other hand, Group (1 + 2) members were more likely to be female ($\chi^2 = 280.95$; df = 1; $p < 0.001$). white ($\chi^2 = 14.58$; df = 1; $p < 0.001$), married ($\chi^2 = 194.12$; df = 1; $p < 0.001$), or widowed ($\chi^2 = 35.51$; df = 1; $p < 0.001$), and were more often recruited as control family members ($\chi^2 = 125.78$; df = 1; $p < 0.001$) or relatives ($\chi^2 = 35.09$; df = 1; $p < 0.001$).

Discussion

Both animal and human research indicate that under some circumstances withdrawal symptoms develop following exposure to high levels of marijuana. However, after reviewing animal and human studies, it is not possible to either establish the prevalence or describe the profile of the more usual marijuana withdrawal phenomena in a non-drug clinic population. To approach this problem, the present study used data from a large cohort of individuals and addressed three major questions: (1) how prevalent was a marijuana withdrawal syndrome in a population not selected because of seeking treatment for marijuana-related problems? (2) what were the characteristics of the usual withdrawal syndrome? and (3) could marijuana withdrawal be disentangled from the intoxication or the withdrawal symptoms of alcohol or other drugs?

In the present analyses, the threshold for a withdrawal syndrome was set as two of seven potential items, a ratio chosen as being representative of most withdrawal syndromes in DSM-IV. Using this approach only 4.8% of the total sample, but 15.6% of the more frequent marijuana users, reported ever experiencing at least one withdrawal syndrome related to marijuana. The clinical symptoms reported were usually limited to feelings of nervousness, sleep disturbance or a change in appetite. This was consistent with the withdrawal profile reported by a small subsample of 18 subjects who were never dependent on drugs other than marijuana. There was no evidence that any individuals received treatment for their withdrawal, and none offered a history of significant morbidity associated with the syndrome.

There were several types of indication that what was being reported as a marijuana withdrawal syndrome might have been accurate. First, regarding intensity of use Group 4 subjects reported the highest average number of uses of marijuana, and gave a history of almost 70 months of daily or nearly daily self-administration of this drug. More than eight of 10 of the subjects in Group 4 reported ever having stayed high from marijuana for an entire day at a time. On each of these measures, the Group 4 subjects who reported at least one withdrawal syndrome in the past had significantly higher intensities of intake than Group 3 men and women. A second indication of the probable validity of the self-reports of a withdrawal syndrome comes from the two logistic regression analyses where the two measures of intensity of use (the number of times of marijuana intake and the longest period of daily use) remained robust predictors of Group 4 membership *even after considering* the potential impact of the diagnoses of dependence or of withdrawal syndromes on drugs other than marijuana. Finally, there was at least a trend whereby those individuals reporting a larger number of withdrawal symptoms were likely to have reported longer periods of daily use.

Of course, the present results must be considered in light of the methodologies employed. Unfortunately, the manner in which the data were collected did not allow for a direct analysis of the number of times marijuana was taken per month as a predictor of a withdrawal phenomenon. Thus, it is possible that had we been able to isolate a group with a larger number of administrations per day for an extended period of time,

the intensity of the withdrawal syndrome might have been higher. At the very least, the present data indicate that some level of withdrawal can occur after heavy marijuana consumption, even in a population not originally identified because they sought help for a marijuana-related problem.

In addition, all information was generated from retrospective self-reports, and many subjects had experience with multiple drugs. Thus, it is possible that a prospective study might have identified a larger proportion of subjects with withdrawal symptoms, or might have identified a different pattern of withdrawal phenomena. On the other hand, of the 270 Group 4 subjects who reported withdrawal, only 18 individuals did so in the absence of dependence on drugs other than marijuana. Thus, it is not possible from the present data to definitively establish that the withdrawal symptoms reported did not simply reflect symptoms related to actual withdrawal from alcohol, sedative/hypnotics or opiates. It is also possible that the experience of intoxication and potential withdrawal symptoms from these other classes of drugs might have facilitated the development of withdrawal symptoms related to marijuana.

Gathered from a very large sample of carefully interviewed subjects, the data suggest that some level of marijuana withdrawal not only occurs in the experimental literature, but is also experienced under realistic conditions of a self-chosen pattern of drug use. These data indicate that it may be helpful for clinicians to reassure their patients with a history of heavy marijuana use, that restlessness, insomnia and lack of appetite could be reflections of withdrawal discomfort, that these symptoms might impact on their desire to return to use of the substance, but are not likely to progress to a more severe syndrome that requires acute medical intervention.

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