Cannabis Withdrawal in the United States: Results From NESARC

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Objective: Although cannabis is the most widely abused illicit drug, little is known about the prevalence of cannabis withdrawal and its factor structure, clinical validity, and psychiatric correlates in the general population.

Method: National Epidemiologic Survey on Alcohol and Related Conditions participants were assessed, in 2001–2002, with structured in-person interviews covering substance history, DSM-IV Axis I and II disorders, and withdrawal symptoms after cessation of use. Of these, 2613 had been frequent cannabis users (≥ 3 times/week), and a "cannabis-only" subset (N = 1119) never binge-drank or used other drugs ≥ 3 times/week.

Results: In the full sample and subset, 44.3% (SE = 1.19) and 44.2% (SE = 1.75), respectively, experienced ≥ 2 cannabis withdrawal symptoms, while 34.4% (SE = 1.21) and 34.1% (SE = 1.76), respectively, experienced ≥ 3 symptoms. The symptoms formed 2 factors, one characterized by weakness, hypersomnia, and psychomotor retardation and the second by anxiety, restlessness, depression, and insomnia. Both symptom types were associated with significant distress/impairment ($p < .01$), substance use to relieve/avoid cannabis withdrawal symptoms ($p < .01$), and quantity of cannabis use (among the cannabis-only users $p < .05$). Panic ($p < .01$) and personality ($p \leq .01$) disorders were associated with anxiety symptoms in both samples, family history of drug problems was associated with weakness symptoms in the subset ($p = .01$), and depression was associated with both sets of symptoms in the subset ($p < .05$).

Conclusion: Cannabis withdrawal was prevalent and clinically significant among a representative sample of frequent cannabis users. Similar results in the subset without polysubstance abuse confirmed the specificity of symptoms to cannabis. Cannabis withdrawal should be added to DSM-V, and the etiology and treatment implications of cannabis withdrawal symptoms should be investigated.

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Cannabis is the most widely abused illicit drug in the United States. In the last decade, cannabis use disorders have become more prevalent,[1] the potency of cannabis available in the United States has strengthened,[1,2] and the proportion of substance abuse patients whose primary drug is cannabis has increased.[3] Additionally, current cannabis use is projected to increase in the next decade among aging baby boomers.[4] Given these developments, an improved multidisciplinary understanding of this significant U.S. public health problem is essential to guide treatment and prevention efforts. An important aspect of the cannabis problem for which epidemiologic information is lacking is cannabis withdrawal.

For most diagnoses of substance dependence in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), withdrawal is 1 of 7 criteria that jointly reflect dependence as a combination of physiologic and psychological processes.[5,6] In DSM-IV, withdrawal is defined as symptoms occurring after cessation of regular, heavy use of a substance. While withdrawal is not required to make a DSM-IV dependence diagnosis, withdrawal symptoms predict poorer prognosis among both alcohol- and drug-dependent individuals.[7,8] With-

drawal is also included in DSM-IV as a separate diagnosis, with specific withdrawal criteria for most substance categories (e.g., stimulants, sedatives).

In 1994, when DSM-IV was published, symptoms of cannabis withdrawal had been described in earlier studies and case reports.[9–11] However, the evidence for the validity of a cannabis withdrawal syndrome was considered too weak to include cannabis withdrawal in DSM-IV. Since then, evidence has accumulated from animal,[12] inpatient laboratory,[13–15] prospective nonlaboratory,[16–18] clinical,[19,20] and other retrospective studies[21,22] indicating the occurrence of cannabis withdrawal symptoms, typically beginning within a few hours or days after cessation of cannabis use. Importantly, placebo-controlled laboratory studies show that administration of Δ^9-tetrahydrocannabinol (THC) suppresses cannabis withdrawal symptoms,[23,24] indicating the pharmacologic specificity of the cannabis withdrawal syndrome. Cannabis withdrawal symptoms commonly identified in these studies include anxiety, irritability, various types of physical discomfort, negative affect, and appetite and sleep changes.[25] A recent study based on a convenience sample of non–treatment-seeking cannabis users suggested that cannabis withdrawal symptoms clustered into 2 components, a physical and a psychological component.[22]

The accumulating evidence has developed a consensus on the validity of cannabis withdrawal and the need to include it in DSM-V.[22,25,26] However, the epidemiology of cannabis withdrawal in the general population remains entirely unknown. This information is important for several reasons. First, if cannabis withdrawal occurs only among a small minority of frequent cannabis users in the general population, then its public health significance is limited. However, if withdrawal is common among frequent cannabis users, this is important knowledge to disseminate to clinicians and to the general public. Second, some previous studies were based on clinic patients, who are often polysubstance abusers, so the withdrawal symptoms they attributed to cannabis may have been due to other drugs. Third, many studies of untreated cannabis users have been small (e.g., samples of 30,[16] 12,[17] and 18[18] subjects), potentially leading to unstable results. Fourth, while laboratory studies have provided the fundamental data identifying the cannabis withdrawal syndrome, it is possible that individuals willing to spend several days in an inpatient setting or to visit a laboratory every day for over a month may differ from the broader underlying population of frequent cannabis users in a manner that affects the study results.[27]

Without conducting research on cannabis withdrawal in a representative sample of frequent cannabis users, the extent to which sample biases have affected our understanding of cannabis withdrawal cannot be known. To our knowledge, such a study has never previously been conducted. Therefore, using data from a large, nationally representative survey that included frequent cannabis users, we investigated (1) the prevalence of cannabis withdrawal symptoms; (2) the factor structure of cannabis withdrawal symptoms; (3) whether cannabis withdrawal is accompanied by significant distress or impairment or by use of another substance to relieve/avoid withdrawal (important indicators of clinical significance); and (4) the demographic characteristics, psychiatric history, and cannabis use history associated with cannabis withdrawal. We addressed these questions in 2 groups. The first included all frequent cannabis users in the survey (N = 2613), regardless of use of other substances. Results from this group maximized representativeness, but left the possibility open that withdrawal symptoms due to other substances were erroneously attributed to cannabis. The second group, a subset of the first (N = 1119), never abused other substances. This group served the important function of ensuring that results on withdrawal symptoms attributed to cannabis were not actually due to another substance.

METHOD

Sample

Respondents were participants in the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC), a nationally representative U.S. sample of 43,093 civilian noninstitutionalized participants aged 18 and older. The sampling frame is detailed elsewhere.[28,29] The research protocol, including informed consent procedures, received full ethical review and approval from the U.S. Census Bureau and U.S. Office of Management and Budget. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) sponsored the study, conducted in 2001–2002 by the U.S. Bureau of the Census. Young adults, Hispanics, and African Americans were oversampled. The overall response rate was 81%. Data were adjusted for oversampling and nonresponse. The sample was then weighted to reflect the U.S. population from the 2000 Decennial Census. We included NESARC participants that used cannabis ≥ 3 times/week during their period of heaviest use. We further analyzed the subset of this sample that never drank ≥ 5 drinks/occasion or used other drugs ≥ 3 times/week (N = 1119) to ensure that withdrawal symptoms were due to cannabis rather than another substance.

Procedures

Professional interviewers from the U.S. Census Bureau experienced with health surveys administered the in-person interviews, after 10 days of centralized training supervised by the NIAAA. Regional supervisors recontacted a random 10% of all respondents to verify interviews. Further, 2657 randomly selected respondents were re-contacted and re-asked 1 to 3 sections of the interview, providing NESARC reliability data.[30] In the few cases

with uncertain accuracy, data were discarded and a supervisor repeated the interview.

Measures

All variables were assessed with the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV Version (AUDADIS-IV),[30,31] a computer-assisted interview with built-in skip, logic, and consistency checks designed for lay interviewers. Detailed withdrawal symptom information was obtained in the DSM-IV substance dependence module. Reliability and validity (including psychiatrist reappraisals) of substance dependence diagnoses and symptom items were good to excellent in U.S. and international clinical and general population studies.[30–35]

All withdrawal symptoms listed in DSM-IV were asked across all substances. Structured questions covered these symptoms after cessation of use, i.e., the morning after, or within the first few days. Eighteen symptoms were included in this study: anxiety, insomnia, vivid or unpleasant dreams, hallucinations, restlessness, shaking, depressed mood, hypersomnia, psychomotor retardation, and several symptoms of physical discomfort including feeling weak or tired, bad headaches, muscle cramps, runny eyes or nose, yawning, nausea, sweating, fever, and seizure.

Clinical significance was addressed with 2 variables. One was significant distress or impairment due to the cannabis withdrawal symptoms in social, occupational, or other important areas. The second was use of another substance to avoid or alleviate the withdrawal symptoms. We investigated the relationship of cannabis withdrawal to demographic characteristics (gender, age, race/ethnicity, marital status, and education) and to psychiatric and drug use history, including lifetime primary diagnoses of major depressive, generalized anxiety, and panic disorders, since these share symptoms with cannabis withdrawal. Substance-induced disorders were excluded. We also included personality disorders assessed in the NESARC (avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial). The reliability and validity of these diagnoses are fair to excellent,[31,36–38] comparing favorably to other research diagnostic interviews. Cannabis history variables included duration of period of heaviest use (≥ 1 year vs. others), usual number of joints smoked during period of heaviest use (≤ 1 vs. 2 [the median] or more), and age at onset of use < 16 years. Period of heaviest use was dichotomized as < 52 weeks (1st quartile) versus ≥ 52 weeks. Additional predictors included family history of drug problems (parent or sibling positive).

Data Analysis

Prevalences and standard errors were estimated using SUDAAN (Version 8.1, Research Triangle Institute, Research Triangle Park, N.C.) to adjust for the complex sample design. Weighted correlations were produced in SAS (SAS Institute, Inc., Cary, N.C.). Weighted exploratory factor analysis was conducted using Mplus (Version 3.13, Muthen & Muthen, Los Angeles, Calif.) using Promax rotation, allowing correlated factors. Exploratory factor analysis results were used to construct observed cannabis withdrawal symptom count variables. To examine how indicators of clinical significance and aspects of predictors related to cannabis withdrawal as dependent variables, weighted negative binomial regression models were conducted with STATA (Version 9.1, StataCorp, College Station, Tex.). Demographic variables were included as needed based on association with clinical significance indicators and outcome variables. The regression coefficient for a predictor is the log ratio of the change in means in outcome for a unit change in the predictor. Therefore, the coefficients were exponentiated to provide ratio estimates interpreted similarly to an odds ratio.

RESULTS

Sample and Subsample Characteristics

Frequent cannabis users comprised 6.58% (N = 2613) of the NESARC. Most used cannabis 5–7 days a week during heaviest use (Table 1). Over half (57.2%) were diagnosed with DSM-IV cannabis abuse, while 16.2% were diagnosed with DSM-IV cannabis dependence (≥ 3 of 6 dependence criteria, not including withdrawal). Mean age at first cannabis use was 16.3 years (range, 5–53), and total mean years from first to most recent use of cannabis was 12.5 (range, < 1–53 years). Mean period of heaviest use was 5.2 years. Over two thirds smoked > 1 joint/day on days they smoked during their period of heaviest use; mean joints smoked/day was 3.9 (SE = 0.1). About one fifth had primary major depression, 8.8% had generalized anxiety disorder, 12.6% had panic disorder, and 39.4% had personality disorders.

The subsample of frequent "cannabis-only" users comprised 2.69% of the NESARC (N = 1119). Compared to polysubstance frequent cannabis users, these 1119 cannabis-only users were more likely to be female, Hispanic, younger, unmarried, and better educated; be less frequent cannabis users; and have a lower prevalence of cannabis use disorders, panic disorder, and personality disorders ($p < .02$ to $p < .001$).

Prevalence of Cannabis Withdrawal Symptoms

The most prevalent symptoms (Table 2) were feeling weak or tired, hypersomnia, yawning, psychomotor retardation, anxiety, and depressed mood. In the full sample of frequent cannabis users, 57.7% experienced ≥ 1 cannabis withdrawal symptom, 44.3% (SE = 1.19) experienced ≥ 2 symptoms, and 34.4% (SE = 1.21) experienced

Table 1. Characteristics of NESARC Participants Using Cannabis ≥ 3 Times/Week During Heaviest Period[a]

Characteristics	All Frequent Cannabis Users (N = 2613)	All Polydrug Cannabis Users (N = 1494)	Cannabis-Only Subset (N = 1119)	All Polydrug Cannabis Users vs. Cannabis-Only Subset		
				χ^2	df	p Value
Gender, % (SE)				34.1	1	< .001
Male	66.9 (1.2)	73.0 (1.3)	58.2 (2.0)			
Female	33.1 (1.2)	27.0 (1.3)	41.8 (2.0)			
Race/ethnicity, % (SE)				28.0	4	< .001
White	75.4 (1.2)	78.4 (1.4)	71.1 (1.7)			
Black	11.4 (0.9)	8.6 (0.8)	15.3 (1.4)			
Hispanic	7.3 (0.8)	6.4 (0.8)	8.6 (1.2)			
Asian/Pacific Islander/native Hawaiian	2.2 (0.4)	2.2 (0.5)	2.3 (0.5)			
Native American/Alaska native	3.7 (0.5)	4.3 (0.8)	2.7 (0.7)			
Age, % (SE)				16.1	3	.002
18–29 y	32.6 (1.1)	29.0 (1.5)	37.7 (1.5)			
30–44 y	41.4 (1.2)	44.1 (1.5)	37.7 (1.8)			
45–64 y	25.6 (1.1)	26.7 (1.5)	24.1 (1.5)			
65 y and older	0.4 (0.1)	0.3 (0.1)	0.6 (0.2)			
Marital status, % (SE)				16.3	2	< .001
Married/living with someone as if married	51.1 (1.1)	50.8 (1.5)	51.5 (2.1)			
Widowed/separated/divorced	17.5 (0.8)	20.0 (1.2)	13.9 (1.1)			
Never married	31.4 (1.1)	29.2 (1.4)	34.6 (1.9)			
Education, % (SE)				16.3	2	< .001
Less than high school	15.3 (0.9)	17.8 (1.2)	12.0 (1.2)			
High school	30.7 (1.3)	31.6 (1.5)	29.4 (1.8)			
Some college or higher	54.0 (1.4)	50.9 (1.7)	58.7 (1.9)			
Personal and family drug history						
Frequency of cannabis use, % (SE)				32.5	2	< .001
3–4 d/wk	24.2 (1.0)	18.5 (1.2)	32.5 (1.8)			
5–6 d/wk	18.9 (1.0)	18.8 (1.3)	18.9 (1.4)			
7 d/wk	56.9 (1.3)	62.7 (1.5)	48.6 (2.1)			
Lifetime DSM-IV cannabis diagnosis, % (SE)				21.1	1	< .001
Dependence	16.2 (1.0)	18.5 (1.2)	12.9 (1.3)			
Abuse	57.2 (1.1)	58.6 (1.5)	55.1 (1.7)			
No diagnosis	26.6 (1.1)	22.9 (1.3)	32.0 (1.7)			
Age at first use of cannabis, mean (SE), y	16.3 (0.1)	16.0 (0.1)	16.6 (0.1)	–3.1[b]	…	.003
Total cannabis use, mean (SE), y	12.5 (0.2)	13.8 (0.2)	10.8 (0.3)	9.5[b]	…	< .001
Duration of heaviest period of cannabis use, mean (SE), y	5.2 (0.2)	6.3 (0.2)	3.7 (0.2)	7.0[b]	…	< .001
> 1 joint/d during period of heaviest use vs 1 or less, % (SE)	70.6 (1.2)	74.7 (1.3)	64.5 (1.8)	21.1	1	< .001
Family history of drug problems (parent or sibling), % (SE)	34.4 (1.2)	35.8 (1.5)	32.3 (1.8)	2.4	1	.13
Other DSM-IV primary disorders, % (SE)						
Lifetime major depressive disorder	20.6 (1.0)	20.5 (1.3)	20.7 (1.4)	0.0	1	.92
Lifetime panic disorder	12.6 (0.8)	14.1 (1.1)	10.5 (1.1)	6.1	1	.02
Lifetime generalized anxiety disorder	8.8 (0.7)	9.5 (0.8)	7.8 (1.1)	2.1	1	.16
Any personality disorder	39.4 (1.3)	45.2 (1.6)	33.2 (1.8)	19.2	1	< .001

[a]Participants included in these analyses are all frequent cannabis users (N = 2613); we subset these individuals to additionally examine the subset of "cannabis-only" users (N = 1119) who never drank 5 drinks/occasion or used other drugs ≥ 3 times/week.
[b]T test.
Abbreviations: DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; NESARC = National Epidemiologic Survey on Alcohol and Related Conditions.
Symbol: … = not applicable.

≥ 3 symptoms. Among the subset of frequent cannabis users that did not abuse other substances, 59.4%, 44.2% (SE = 1.75), and 34.1% (SE = 1.76) experienced ≥ 1, ≥ 2, and ≥ 3 cannabis withdrawal symptoms, respectively. Thus, a large proportion of frequent cannabis users experienced 1 or more of these symptoms, with little difference seen between those that used and did not use other substances. From a different perspective, among the entire NESARC sample, the prevalence of being a frequent cannabis user who experienced ≥ 3 cannabis withdrawal symptoms was 2.1% (SE = 0.1). All symptoms were tested for differences in prevalence by age, sex, ethnicity, and education. Only scattered symptoms were found to differ by these characteristics; in light of the number of tests run and the exploratory nature of the tests, the few significant results did not appear to contribute substantially to our understanding of these symptoms.

Association of Cannabis Withdrawal Symptoms With Cannabis Dependence Criteria and Clinical Characteristics

Among all frequent cannabis users, the correlation between the number of cannabis withdrawal symptoms and the number of DSM-IV cannabis dependence criteria (range, 0–6) was 0.54 ($p < .001$), while the corresponding correlation among frequent cannabis-only users was 0.64

Table 2. Lifetime Prevalence of Cannabis Withdrawal Symptoms Among Frequent Cannabis Users and the Cannabis-Only Subset

Symptom	All Frequent Cannabis Users (N = 2613), % (SE)[a]	Cannabis-Only Subset (N = 1119), % (SE)[b]
Hypersomnia	24.5 (0.98)	26.4 (1.52)
Feeling weak or tired	28.1 (1.04)	31.1 (1.63)
Depressed mood	16.7 (0.95)	15.9 (1.47)
Nausea	4.4 (0.45)	4.8 (0.73)
Yawning	25.0 (1.02)	26.6 (1.72)
Runny eyes or nose	5.8 (0.58)	6.4 (1.23)
Anxiety	16.3 (1.06)	19.3 (1.72)
Muscle aches	3.1 (0.49)	2.1 (0.82)
Fever	1.1 (0.27)	0.7 (0.35)
Restlessness	7.6 (0.74)	6.4 (1.17)
Psychomotor retardation	21.1 (1.00)	24.6 (1.55)
Sweating	9.0 (0.70)	8.8 (1.12)
Vivid dreams	7.4 (0.60)	7.0 (0.94)
Hallucination	5.9 (0.65)	6.5 (0.96)
Tremors	3.6 (0.51)	3.8 (0.96)
Insomnia	6.1 (0.64)	6.3 (1.16)
Seizure	0.7 (0.18)	0.9 (0.32)
Bad headaches	8.0 (0.69)	7.9 (0.96)
Any withdrawal symptom	57.7 (1.22)	59.4 (1.78)

[a]All participants using cannabis ≥ 3 times/week during heaviest use.
[b]Never drank ≥ 5 drinks of alcohol/occasion or used other drugs ≥ 3 times/week.

($p < .001$), indicating strong associations. To place these results in context, the corresponding correlation for alcohol withdrawal symptoms and number of DSM-IV alcohol dependence criteria (range, 0–6) among those ever drinking ≥ 5 drinks/day was 0.58, and the corresponding correlation for cocaine withdrawal symptoms and number of DSM-IV cocaine dependence criteria (range, 0–6) among those using cocaine ≥ 3 times/week was 0.76 ($p < .001$). Thus, the association of withdrawal symptoms to other dependence criteria was similar for cannabis and alcohol and only slightly weaker than the corresponding association for cocaine.

Among all frequent cannabis users, those with ≥ 3 cannabis withdrawal symptoms reported a median duration of 105 weeks, compared to 157 weeks in those who experienced < 3 symptoms (nonparametric comparison of medians, $p < .01$). Those reporting 3 or more cannabis withdrawal symptoms had a higher quantity of cannabis use versus those with < 3 symptoms (mean = 4.3 joints/day vs. 3.6 joints/day, respectively; $t = 2.6$, $p = .01$). There was no statistically significant difference in the mean age at onset between those reporting ≥ 3 symptoms vs. < 3 symptoms (17 vs. 18 years, $p = .10$). Those with ≥ 3 symptoms were more likely to have a family history of drug problems than those with < 3 symptoms ($\chi^2 = 8.3$, $df = 1$, $p < .006$). Results were essentially the same in the subsample of cannabis-only users, except that those with ≥ 3 symptoms had a significantly younger age at onset than those with < 3 symptoms (15.9 vs. 17.4 years, $p = .04$).

Factor Analysis

In the 2613 frequent users, the final model (Table 3) included 12 symptoms. The fit statistics indicated that a 2-factor solution had the best model fit ($\chi^2 = 35.12$, $df = 23$, $p = .17$; root-mean-square error of approximation [RMSEA] = 0.01). The eigenvalues over 1.0 also indicated 2 factors; the first factor, termed *weakness*, and the second, termed *anxiety/depression*. The item loadings on the factors indicated that the symptoms within each factor comprised a homogeneous set that measured the factor well, with the weakness factor measured by weakness, hypersomnia, psychomotor retardation, and yawning (factor loadings, 0.54–0.99) and the anxiety/depression factor measured by anxiety, depression, sweating, nausea, muscle aches, restlessness, tremors, and insomnia (factor loadings, 0.52–0.88). The 2 factors were correlated (0.64).

In the cannabis-only subsample of 1119, a similar 2-factor model (Table 3) was obtained ($\chi^2 = 15.3$, $df = 16$, $p = .50$, RMSEA = 0.046). The weakness factor was measured by the same symptoms found in the larger group (factor loadings, 0.65–0.88), and the anxiety/depression factor was measured by the same symptoms excepting nausea, which was not retained (factor loadings, 0.55–1.00). The 2 factors were correlated (0.59).

Clinical Significance of Cannabis Withdrawal Symptoms

In examining the clinical significance of the weakness and anxiety/depression cannabis withdrawal symptoms, distress/impairment showed a strong and statistically significant relationship to the symptom count for both types of withdrawal symptoms in the full sample of frequent cannabis users (Table 4) and in the subsample (Table 5). Furthermore, a strong, significant relationship was found between use of a substance to relieve/reduce cannabis withdrawal and both the weakness and anxiety/depression withdrawal symptoms in the full sample of frequent cannabis users (Table 4) and in the subsample (Table 5).

In examining the relationship of demographic characteristics, psychiatric history, and cannabis use history to cannabis withdrawal symptoms in the full sample of frequent cannabis users (Table 4), gender was associated with both the weakness symptoms and the anxiety/depression symptoms. Duration of heaviest use (less than 1 year) was significantly related to both types of withdrawal symptoms. Major depressive disorder was associated with anxiety/depression symptoms but was unrelated to weakness symptoms. Generalized anxiety disorder was unrelated to cannabis withdrawal symptoms, panic disorder was associated only with anxiety/depression withdrawal symptoms, and personality disorder was associated with both types of withdrawal symptoms.

In examining the relationship of psychiatric and cannabis use history to cannabis withdrawal symptoms in the

Table 3. Exploratory Factor Analysis: Factor Loadings[a]

	All Frequent Cannabis Users (N = 2613), 2-Factor Solution		Cannabis-Only Frequent Users (N = 1119), 2-Factor Solution	
Symptom	Weakness	Depression/Anxiety	Weakness	Depression/Anxiety
Hypersomnia	**0.80**	0.03	**0.88**	–0.05
Feeling weak or tired	**0.99**	–0.05	**0.86**	0.12
Yawning	**0.74**	0.04	**0.65**	0.15
Psychomotor retardation	**0.54**	0.08	**0.79**	–0.15
Depressed mood	0.27	**0.57**	0.36	**0.55**
Sweating	0.10	**0.67**	0.16	**0.69**
Nausea	0.18	**0.52**	…	…
Anxiety	0.09	**0.75**	0.18	**0.66**
Muscle aches	0.01	**0.80**	–0.03	**0.90**
Restlessness	0.01	**0.88**	0.09	**0.81**
Tremors	–0.03	**0.88**	–0.05	**1.00**
Insomnia	–0.10	**0.85**	–0.07	**0.91**
Eigenvalues	6.81	1.37	7.08	1.57
Promax factor correlations	0.64		0.59	

[a]Bold type indicates items loading onto each factor.
Symbol: … = not applicable.

Table 4. Negative Binomial Regression Results, All Frequent Cannabis Users (N = 2613)

	Cannabis Withdrawal Symptom: Depression/Anxiety			Cannabis Withdrawal Symptom: Weakness		
Predictor	Ratio, Mean No. of Symptoms	Regression Coefficient (SE)	p	Ratio, Mean No. of Symptoms	Regression Coefficient (SE)	p
Clinical significance						
Withdrawal caused significant distress/ impairment	3.53	1.26 (0.12)	< .01	2.09	0.74 (0.08)	< .01
Substance used to relieve/avoid symptoms	3.13	1.14 (0.12)	< .01	1.85	0.62 (0.08)	< .01
Cannabis use and family drug history						
Smoked > 1 joint/d, heaviest period	1.15	0.14 (0.10)	.18	1.16	0.15 (0.07)	.08
Cannabis use onset < age 16 y	0.97	–0.03 (0.13)	.80	1.05	0.05 (0.07)	.48
Duration, heaviest period of use (< 52 wk)	1.68	0.52 (0.12)	< .01	1.29	0.25 (0.08)	< .01
Family history of drug problems (parents or siblings)	0.92	–0.08 (0.11)	.44	1.04	0.04 (0.07)	.59
Lifetime psychiatric history						
Major depressive disorder	1.24	0.22 (0.11)	.05	1.11	0.11 (0.07)	.11
Generalized anxiety disorder	1.09	0.08 (0.15)	.57	0.98	–0.02 (0.11)	.84
Panic disorder	1.40	0.33 (0.12)	< .01	1.02	0.02 (0.09)	.82
Personality disorder[a]	1.73	0.55 (0.15)	< .01	1.30	0.26 (0.07)	< .01
Demographics						
Age	1.13	0.12 (0.10)	.19	1.02	0.02 (0.07)	.73
Gender	1.94	0.66 (0.22)	< .01	1.86	0.62 (0.16)	< .01

[a]Avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial disorders (remaining personality disorders were assessed in the National Epidemiologic Survey on Alcohol and Related Conditions Wave 2 and will be reported later).

subsample of frequent "cannabis-only" users (Table 5), age was associated with both anxiety/depression symptoms and weakness symptoms, while gender was associated with depression/anxiety symptoms only. Quantity of cannabis was significantly related to both types of withdrawal symptoms. Duration of heaviest use (less than 1 year) was associated with anxiety/depression withdrawal symptoms but not weakness symptoms, while family history of drug problems was associated with weakness but not anxiety/depression withdrawal symptoms. Major depressive disorder and personality disorders were associated with both types of withdrawal symptoms, generalized anxiety disorder was not associated with either type, and panic disorder was associated with only the anxiety/depression withdrawal symptoms.

DISCUSSION

The results of this study indicate that cannabis withdrawal symptoms are highly prevalent among frequent cannabis users in the U.S. general population. The most common withdrawal symptoms were feeling weak/tired, hypersomnia, psychomotor retardation, yawning, depression, and feeling nervous or anxious, similar to symptoms found in volunteers in inpatient laboratory studies[13,14,26] and in patients.[19,20] Further, cannabis withdrawal, consistently identified by 12 symptoms, differentiated into 2 factors, one characterized by weakness and the other characterized by anxiety and depression. The findings are based on the largest and most representative sample of frequent cannabis users studied to date.

Table 5. Negative Binomial Regression Results, Cannabis-Only Frequent Users (N = 1119)

Predictor	Cannabis Withdrawal Symptom: Depression/Anxiety			Cannabis Withdrawal Symptom: Weakness		
	Ratio, Mean No. of Symptoms	Regression Coefficient (SE)	p	Ratio, Mean No. of Symptoms	Regression Coefficient (SE)	p
Clinical significance						
Withdrawal caused significant distress/ impairment	1.96	0.67 (0.20)	< .01	1.92	0.65 (0.12)	< .01
Substance used to relieve/avoid symptoms	3.07	1.12 (0.21)	< .01	2.14	0.76 (0.11)	< .01
Cannabis use and family drug history						
Smoked > 1 joint/d, heaviest period	1.33	0.29 (0.14)	.04	1.24	0.22 (0.10)	.03
Cannabis use onset < age 16 y	0.98	–0.02 (0.18)	.90	1.18	0.17 (0.10)	.11
Duration, heaviest period of use (< 52 wk)	1.48	0.39 (0.17)	.02	1.13	0.13 (0.11)	.23
Family history of drug problems (parents or siblings)	0.91	–0.10 (0.17)	.57	1.24	0.21 (0.08)	.01
Lifetime psychiatric history						
Major depressive disorder	1.39	0.33 (0.15)	.03	1.24	0.22 (0.09)	.02
Generalized anxiety disorder	1.14	0.13 (0.25)	.60	0.85	–0.16 (0.18)	.34
Panic disorder	1.66	0.50 (0.16)	< .01	1.19	0.18 (0.16)	.26
Personality disorder[a]	1.86	0.62 (0.24)	.01	1.23	0.20 (0.10)	.05
Demographics						
Age	2.50	0.92 (0.34)	.008	1.84	0.61 (0.21)	.004
Gender	1.38	0.32 (0.13)	.02	1.14	0.14 (0.09)	.13

[a]Avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial disorders (remaining personality disorders were assessed in the National Epidemiologic Survey on Alcohol and Related Conditions Wave 2 and will be reported later).

The largest early clinical study of cannabis effects, a study of 53 men hospitalized for 21–42 days,[9] indicated that in the week following cessation of cannabis use, symptoms commonly reported included sleep disturbance (89%), restlessness (89%), and irritability (62%). In more recent prospective outpatient and inpatient studies,[13–18] no cannabis withdrawal symptom emerged in all studies. However, symptoms commonly reported were anxiety (after low dose[13])[14,16,18] and symptoms of physical discomfort.[16–18] Irritability was also commonly found,[13–18] although in one study,[13] it was found only in the low consumption condition; in a second study,[14] only in the high consumption condition; and in a third study, evidence was only "moderate."[17] The anxiety/depression withdrawal symptoms found in these studies corresponded well to our second factor, providing important consistency between this large general population sample and previous prospective outpatient and inpatient studies. Weakness withdrawal symptoms were also found in lab studies[13,14] and in a clinical study of adolescents, especially males.[20] While fatigue was not found during cannabis withdrawal among cannabis users in their home environments,[17] the other studies in conjunction with the present findings indicate that these symptoms merit further investigation. Irritability and anxiety may receive greater clinical consensus as regular features of cannabis withdrawal because they are subjectively and clinically striking compared to fatigue and related symptoms. Varying emergence of weakness and depression/anxiety symptoms as part of cannabis withdrawal may also relate to varying levels of Δ^9-THC in cannabis and varying levels of other cannabinoids that, while weaker than Δ^9-THC, may interact with Δ^9-THC to alter its effects.[39]

Our results also indicated support for the validity of the cannabis withdrawal syndrome in the general population, as clinical distress/impairment and using to relieve or avoid symptoms were strongly related to both depression/anxiety and weakness in both samples. We did not find that age at onset of cannabis use predicted cannabis weakness or depression/anxiety withdrawal symptoms in either sample. This could be due to restricted variance of this variable, as early age at onset is highly associated with frequent cannabis use.[40,41] We also found that shorter duration of cannabis use predicted more withdrawal symptoms. This could be because shorter-term users were those that did not have innate tolerance to cannabis, making them initially more sensitive to adverse aftereffects that discouraged long-term use. These validators should be further addressed in future laboratory studies to establish more specific mechanisms. Finally, weakness/fatigue cannabis withdrawal symptoms in our study were associated with a family history of drug problems in the subset of frequent cannabis-only users, while the depression/anxiety withdrawal symptoms were not. Further evidence of the familial nature of these 2 types of symptoms would contribute important information toward understanding their etiology.

Budney and colleagues[19] showed that psychopathology measured on symptom scales was related to cannabis withdrawal in patients seeking treatment for marijuana problems, but no previous studies addressed the relationship of cannabis withdrawal to DSM-IV disorders. We studied primary major depression, generalized anxiety, and panic disorder because their symptoms partially overlap with cannabis withdrawal symptoms. We studied personality disorders because this has not been done

before and the high prevalence of personality disorders in "healthy" volunteers for research studies[27] may have influenced earlier findings. The association of primary panic disorder or major depression with cannabis depression/anxiety withdrawal symptoms suggests possible common vulnerability, meriting further investigation. The association of personality disorders with depression/anxiety but not weakness withdrawal symptoms in the subsample suggests further study of weakness symptoms in participants screened for personality as well as Axis I psychopathology, as weakness withdrawal symptoms may emerge more among individuals without personality disorders, and prior laboratory and prospective studies screened for Axis I psychopathology only.

We found that despite the high proportion of withdrawal symptoms in the sample, the prevalence of DSM-IV cannabis dependence was only 16%. While this may appear inconsistent, it is explained by the fact that the DSM-IV cannabis dependence diagnosis currently omits withdrawal as a criterion. If we had included withdrawal as a cannabis dependence criterion by requiring 2 or more withdrawal symptoms, the proportion of respondents with cannabis dependence would have been considerably higher, 32.3%. If we had included withdrawal as a criterion requiring 3 or more symptoms, the proportion with cannabis dependence would have been 30.1%. Thus, the use of 6 criteria instead of 7 and omission of the withdrawal criterion created an odd-looking imbalance between the proportion of respondents with withdrawal and the prevalence of cannabis dependence in the sample. Adding withdrawal to the cannabis dependence criteria would address this imbalance.

Study limitations are noted. First, withdrawal symptoms were measured via retrospective structured self-report rather than observation. However, the coherence of our findings on the anxiety withdrawal symptoms with earlier studies adds strength to the aggregated literature on this aspect of cannabis withdrawal, while the finding on the weakness factor merits further investigation. Second, the symptoms analyzed included those listed for other substances in DSM-IV. While multiple symptoms of anxiety, physical discomfort, and negative affect were included, irritability was not. As noted above, a number of studies show irritability as a cannabis withdrawal symptom. While our factors might have been altered if we had included irritability, irritability tends to co-occur with anxiety, depression, and insomnia,[1,7,22] suggesting that the addition of irritability would not result in a major restructuring of the factors. However, future epidemiologic studies on cannabis withdrawal should clearly include irritability. Third, we did not have precise measures of the amount of Δ^9-THC ingested; cannabis potency and the efficiency of self-administration can vary considerably. Most of those in our sample appear to have been heavily exposed to cannabis during their period of heaviest use, but we cannot precisely quantify the relationship of cannabis ingested with the emergence of withdrawal symptoms on abstinence.

Fourth, information is lacking on whether those in the sample who used cannabis 3–4 times/week used cannabis on consecutive days. However, these respondents constituted a minority of the sample, and results of the factor analysis were virtually identical when the 3–4 times/week users were removed from the sample. Fifth, it is possible that individual symptoms we identified might be related to other conditions, e.g., that the individual symptom of weakness might reflect postural hypertension, a direct effect of cannabis use.[42] However, our wording of the question on the timing of the symptoms relative to cannabis use ("the morning after, or in the first few days after") in addition to the empirical clustering of symptoms found reduces the possibility that the full syndrome reported is a conglomeration of individual symptoms resulting from other diverse conditions.

Advantages of the study are also noted. The similarities between the full group and the subset suggested that withdrawal symptoms of cannabis were not being confused with other substances in the full group. First, the large and representative sample afforded a new vantage point on cannabis withdrawal. Further, the subset of respondents who did not abuse other substances provided an important opportunity to confirm that cannabis withdrawal symptoms reported by the larger group were not due to other substances they had used. Second, weighted factor analysis of the symptoms provided an organized quantitative method of arriving at a set of items that measured 2 aspects of cannabis withdrawal well. While replication of the factor structure is clearly needed, this study is the first to provide information from such analyses. Third, the measures included in the study enabled us to address important historical and psychiatric correlates of the 2 factors, contributing new and valuable information on clinical significance and associated aspects of psychiatric history.

In demonstrating a syndrome, some variability in its presentation does not negate its existence. For example, few would now argue against the existence of an alcohol withdrawal syndrome, despite well-recognized variability in its clinical features.[43] While such variability in the presentation of cannabis withdrawal may relate to the amount of the active substance ingested, it is also likely to be related to individual variation in the pharmacokinetics and pharmacodynamics of the psychoactive elements in cannabis. A better understanding of these processes appears important in understanding the development of cannabis disorders and their treatment. Additionally, we found gender and age effects on the number of depression/anxiety and weakness symptoms reported. Demographic differences in the presentation of withdrawal symptoms are not unique to cannabis,[43] but should be further investigated in future studies.

The findings of this study have several implications. First, the prevalence of cannabis withdrawal symptoms among frequent cannabis users in the U.S. general population indicates a problem national in scope that is not limited to patients or individuals who are willing to volunteer for inpatient laboratory studies. Given the projected increase in cannabis use in the coming decade,[4] the established increase in potency of the cannabis in general distribution in the United States,[2] and evidence that higher potency increases the reward properties of cannabis,[27] the prevalence of cannabis withdrawal among users highlights the importance of understanding such withdrawal better. Second, the findings suggest that clinicians should be aware of the potential for cannabis withdrawal symptoms in frequent cannabis users, even if the primary drug is a different substance. Due to the common use of marijuana among patients in substance abuse treatment, the occurrence of cannabis withdrawal may need closer attention than previously believed. Posthospital marijuana use predicts poor outcome of dependence on other substances,[45] and cannabis withdrawal symptoms may contribute to such poor outcome. Coverage of cannabis withdrawal symptoms in research evaluations can provide more information on this point, potentially assisting in identification of patients at risk for poor outcome due to these symptoms. Third, the study findings further support addition of cannabis withdrawal to DSM-V and ICD-11. Our analyses did not directly investigate a valid threshold, but a 3-symptom threshold would be consistent with other withdrawal categories in DSM-IV and would identify about one third of all frequent cannabis users. Lastly, the findings suggest that an understanding of the etiology of these symptoms would be worthwhile. Such an understanding should contribute to the development of better treatments for patients with cannabis use disorders, an increasing public health problem.

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