



Cannabis withdrawal in chronic cannabis users with schizophrenia

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ABSTRACT

Background: Chronic users of cannabis often report withdrawal symptoms after abstinence from use, but little is known about cannabis withdrawal in people with schizophrenia.

Methods: Cannabis use patterns and withdrawal symptoms in adults with schizophrenia who had at least weekly cannabis use before attempting to quit without formal treatment were assessed with the Marijuana Quit Questionnaire (MJQQ), a 176-item, semi-structured questionnaire.

Results: 120 participants, predominantly African–American (62.5%) and male (76.7%), met inclusion criteria. 20.1% reported that their first regular cannabis use (median age 15 years [range 8–48]) preceded their age at first psychotic symptoms (20 [4–50] years). Twenty (16.7%) participants met lifetime criteria for cannabis abuse; 98 (81.7%) met surrogate criteria for lifetime cannabis dependence. Withdrawal symptoms were reported by 113 (94.2%) participants, with 74.2% reporting ≥ 4 symptoms. The most frequently reported withdrawal symptoms were craving for cannabis (59.2%), feeling anxious (52.57%), feeling bored (47.5%), feeling sad or depressed (45.8%), feeling irritable or jumpy (45.0%), feeling restless (43.3%), and trouble failing asleep (33.3%). One hundred-and-four (92.0%) participants took some action to relieve at least one of their withdrawal symptoms during their index-quit attempt, including 26 (23.0%) participants who reported resuming cannabis use.

Conclusion: Cannabis withdrawal is a clinically significant feature of cannabis use among people with schizophrenia, may serve as a negative reinforcer for relapse, and deserves greater attention in treatment and research. Clinical Trials registration NCT00679016.

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1. Introduction

Cannabis is the most commonly used illicit substance among people with schizophrenia (Green et al., 2005), with prevalence rates between 20 and 80% in various studies (Volkow, 2009). Use of cannabis (or other illicit drugs) is associated with earlier age of onset (Barnett et al., 2007; Veen et al., 2004), more frequent symptom exacerbation (Linszen et al., 1994), more severe positive symptoms (Foti et al., 2010; Grech et al., 2005; Hall et al., 2004; Talamo et al., 2006), poorer medication adherence (Owen et al., 1996), and a higher rate of violence (Bartels et al., 1991; Fulwiler et al., 1997). In people without serious psychiatric co-morbidity, a cannabis withdrawal syndrome (CWS) has now been well described (Budney and Hughes, 2006; Budney et al., 2004; Levin et al., 2010) and proposed

for inclusion in DSM-V (www.dsm5.org). It is associated with clinically significant withdrawal symptoms, which can trigger resumption of cannabis use, i.e., serve as negative reinforcement for relapse during a quit attempt (Copersino et al., 2006a; Levin et al., 2010). A study of 18 male outpatients with “serious mental illness” (88.9% with schizophrenia or schizoaffective disorder) and at least weekly cannabis use found that 55.6% reported a history of cannabis withdrawal symptoms, but did not report the nature or context of the symptoms (Sigmon et al., 2000).

This study reports on cannabis use and withdrawal characteristics in a sample of 120 people with schizophrenia who had a history of regular cannabis use. To our knowledge, this is the first systematic investigation of cannabis withdrawal symptoms in people with schizophrenia. In particular, we evaluated the extent to which withdrawal symptoms were associated with relapse to cannabis use.

2. Materials and methods

Participants were recruited from among patients undergoing treatment at psychiatric facilities in the Baltimore, Maryland area

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affiliated or collaborating with the Maryland Psychiatric Research Center, University of Maryland School of Medicine. Participants were referred by clinicians or approached by study staff. Those considered potentially eligible were screened and consented, after obtaining permission from their treating clinician. Eligibility criteria included age 18 years or older, able to read English at 6th grade level (removed as a criterion after about 100 participants were enrolled), ability to give valid informed consent based on the Evaluation to Sign Consent process (DeRenzo et al., 1998), current schizophrenia or schizoaffective disorder (DSM-IV criteria) based on clinical history and/or chart review, self-reported history of cannabis use, and making at least one “serious” (self-defined) attempt to quit cannabis use without formal treatment and while not living in a controlled environment. Subjects with more than one such quit attempt were asked to report on their “most difficult” (self-defined) attempt. In order to avoid mislabeling other symptoms as due to cannabis withdrawal, we restricted this analysis to participants with at least weekly cannabis use for the 6 months prior to their index quit attempt and at least 4 days of cannabis use in the prior month.

The Institutional Review Boards of the University of Maryland Baltimore, the Maryland Department of Health and Mental Hygiene, Sheppard Pratt Health System, and the National Institute on Drug Abuse Intramural Research Program approved this study. All participants gave written informed consent and were paid for their study participation.

Participants were interviewed using the Marijuana Quit Questionnaire (MJQQ) (Levin et al., 2010). The MJQQ is a 176-item, semi-structured questionnaire that collects information in three domains: sociodemographic characteristics, history of marijuana use (including any associated problems), and characteristics of participants’ “most difficult” (self-defined) quit attempt. Characteristics assessed for the quit attempt include reasons for quitting, coping strategies to help quit, withdrawal symptoms, and changes in substance use during the quit attempt. The assessment of cannabis-associated problems allows for a putative diagnosis of cannabis dependence, i.e., meeting 3 out of 7 criteria in the DSM-IV criteria set for substance dependence. A true diagnosis cannot be assigned because the requirement that the dependence criteria occur within the same 12-month period is not evaluated.

Forty specific withdrawal symptoms were evaluated, drawn from those mentioned in previously published experimental and retrospective self-report studies of cannabis withdrawal (Budney et al., 2004; Haney et al., 2004; Jones et al., 1981; Wiesbeck et al., 1996). These include 4 pairs of mutually exclusive symptoms: increased or decreased sleep, appetite, weight, and sex drive. These 4 pairs serve as an internal validity check, in that both the increased and decreased symptom cannot be experienced at the same time, suggesting that a participant who so reports is providing invalid responses.

Participants indicated whether or not they had experienced each of the 40 symptoms. Each ‘yes’ answer was followed with questions regarding the time after last cannabis use that the symptom first appeared, the maximum intensity of the symptom (on a scale of 1–5; lowest–highest), the time of maximum symptom intensity, the time of symptom resolution, and what actions, if any, were taken to relieve the symptom. Participants could choose from a list of 22 possible relief actions, drawn from the published literature on “spontaneous” (i.e., without formal treatment) quitting of alcohol or tobacco use (Walters, 2000). To insure that reported symptoms were likely due to withdrawal, any symptom with onset more than one week after last cannabis use was not counted as a withdrawal symptom. Because many participants could not recall the times of maximum symptom intensity or of symptom resolution, these variables were not included in the present analysis.

Additional information gathered from participants and/or their clinical chart included lifetime psychiatric diagnoses, age of onset of psychotic symptoms, and psychiatric medications used around the time of their index quit attempt ($n = 116$).

Due to the non-normal distribution of the data, descriptive statistics are reported as median (range), correlations used Spearman correlation coefficients, and group comparisons used Kruskal–Wallis test or Fishers exact test, as appropriate. All analyses were performed using SAS version 9 (SAS Institute, Inc.; Cary, NC), with two-tailed $\alpha = 0.05$.

3. Results

3.1. Enrollment

Over 500 patients were screened for the study. Of the 239 who enrolled, 158 had a diagnosis of schizophrenia or schizoaffective disorder (data on those with other psychiatric diagnoses will be presented elsewhere) and reported at least 1 cannabis quit attempt during their life. 123 met the minimum cannabis use requirements for the 6 months and 1 month prior to their index quit attempt. Three of these subjects were excluded from analysis because they gave inconsistent answers (more than one-year difference) to two separate questions on the duration of abstinence during the index quit attempt. The analyses presented here include the remaining 120 participants.

3.2. Participant characteristics

Participant sociodemographic, psychiatric, and cannabis use characteristics are presented in Tables 1 and 2.

3.3. Lifetime cannabis use disorders and withdrawal symptoms

Twenty (16.7%) participants met putative DSM-IV diagnostic criteria for cannabis abuse based on the MJQQ; 98 (81.7%) met putative surrogate criteria for cannabis dependence. Two (1.7%) participants did not meet criteria for either cannabis use disorder.

Sixty participants (50%) reported a lifetime history of cannabis withdrawal syndrome, i.e., feeling “sick” when “stopping or cutting

Table 1

Sociodemographic and psychiatric characteristics of 120 people with schizophrenia and chronic cannabis use.

	% or mean (range)
<i>Sociodemographic characteristic</i>	
Male (%)	76.7%
Race or ethnicity (%)	
White	30.8%
African–American	62.5%
Other	6.7%
Age at interview (years)	41.5 (21.3–63.3)
Education; years	11.4 (3–18)
Current employment status (%)	
Employed	14.2%
Unemployed	40.0%
Disabled	45.8%
Current marital status (%)	
Never married	79.2%
Married	1.7%
Divorced or separated	17.5%
Widowed	1.7%
<i>Psychiatric characteristic</i>	
Outpatient status at interview (%)	75.0%
Age at 1st psychotic symptom (years) ($n = 107$)	20.5 (4–50)
Duration of psychotic illness at interview (years) ($n = 107$)	21.5 (0.8–47.7)

Table 2
Cannabis use characteristics of 120 participants with schizophrenia and chronic cannabis use.

Cannabis use characteristic	% or median (range)
Time since last use at interview (years)	1.3 (1 day–37)
Age at 1st use (years)	14 (8–23)
Age at 1st regular ^a use (years)	16 (8–48)
Age at index quit attempt (years)	29.3 (15.4–59.1)
Interval between index quit attempt & interview (years)	9 (1 day–37)
Number of lifetime quit attempts	4 (1–100)
Cannabis preparation ever used	
Marijuana	97.5%
Blunts	75.8%
Hashish	71.7%
Hashish oil	21.7%
Other	2.5%
Cannabis preparation used at time of quit attempt	
Marijuana	67.5%
Blunt	30.9%
Hashish	0.8%
Hashish oil	0.8%
Frequency of use during 6 months prior to index quit attempt	
More than once a day	43.3%
Once a day	9.2%
Four to six days a week	20.0%
Two to three days a week	20.0%
Once a week	7.5%
Days of use in month before index quit attempt	30 (4–31)
Number of “joints” smoked per day in month prior to index quit attempt	4 (1–80)
Number of “joints” smoked the month prior to index quit attempt	93 (4–2480)
Used cannabis before onset of schizophrenia (<i>n</i> = 107)	29.0%
Regular ^a use of cannabis before onset of schizophrenia (<i>n</i> = 107)	20.6%

^a Regular = at least weekly use.

down on marijuana use.” Fifty-seven (47.5%) participants reported resuming cannabis use to prevent withdrawal symptoms at some time during their lives. Eighty-three (69.2%) participants reported developing tolerance to cannabis, i.e., needing to use more than previously to get high, at some time during their lives.

3.4. Characteristics of index quit attempt

A majority of participants were smoking either marijuana (81, 67.5%) or blunts (37, 30.8%) at the start of their index quit attempt (Table 2); two people reported using other preparations.

Sixty-eight percent (78/114) of participants were taking prescribed psychotropic medications during their index quit attempt, including clozapine 2 (1.7%), other second-generation antipsychotics 41 (36.0%), first generation antipsychotics 31 (27.2%), selective serotonin reuptake inhibitors 16 (14.0%), other antidepressants 4 (3.5%), anticonvulsants 16 (14.0%), lithium 11 (9.7%), benzodiazepines 9 (7.9%), stimulants 2 (1.7%), and sleep aids 12 (10.5%). 57 (50%) reported taking multiple medications.

Most participants were using legal psychoactive substances before their quit attempt: 109 (89.2%) caffeine [94 (78.3%) at least weekly], 100 (83.7%) alcohol [78 (65.0%) at least weekly], and 111 (92.5%) tobacco [109 (90.8%) at least weekly]. About three-quarters (74.2%) of participants used one or more illegal drugs or non-prescribed medications during the 6 months prior to their index quit attempt, with 40.8% using at least weekly: 29 (24.2%) stimulants [18 (15.0%) at least weekly], 20 (16.7%) sedatives [14 (11.7%) at least weekly], 16 (13.3%) sleeping aids [16 (13.3%) at least weekly], 11 (9.2%) hallucinogens [1 (0.8%) at least weekly], 12 (10.0%) phencyclidine [3 (2.5%) at least weekly], 67 (55.8%) non-opiate pain

medications [20 (16.7%) at least weekly], 11 (9.2%) opiates for recreation [7 (5.8%) at least weekly], and 6 (5.0%) opiates for pain [4 (3.3%) at least weekly].

Many regular (at least weekly) users of legal psychoactive substances changed their use pattern during the quit attempt. Caffeine use increased in 41 (43.6%) participants and decreased in 4 (4.26%). Alcohol use increased in 33 (42.3%) participants and decreased in 23 (29.5%). Tobacco use increased in 54 (49.5%) participants and decreased in 14 (12.8%). One person reported that he started tobacco use during his quit attempt.

3.5. Cannabis withdrawal symptoms during index quit attempt

94.2% (113) of participants reported experiencing at least one of the 40 individual cannabis withdrawal symptoms (range 1–33) (Table 3). Almost three-quarters (74.2%) reported at least 4 symptoms. The most frequently reported categories of withdrawal symptoms were mood (75.8%), craving for cannabis (59.2%), sleep problems (60.0%), physical symptoms (51.7%), and appetite change (52.5%) (Table 3). The most frequently reported individual withdrawal symptoms were craving for cannabis (59.2%), feeling anxious (52.5%), feeling bored (47.5%), feeling sad or depressed (45.8%), feeling irritable or jumpy (45.0%), feeling restless (43.3%), and trouble failing asleep (33.3%) (Table 3).

There was a significant association between total number of withdrawal symptoms and the mean number of joints smoked on each smoking occasion during the month prior to the quit attempt ($r = 0.23, p = 0.01$). There was no significant association between total number of withdrawal symptoms and the total number of joints smoked during the prior month ($r = 0.15, p = 0.11$), the average cannabis use over the 6 months prior to the quit attempt ($r = -0.14, p = 0.12$), the number of days cannabis was used in the prior month ($r = 0.08, p = 0.36$), the number of joints typically smoked in 24 h ($r = 0.14, p = 0.14$), or the type of cannabis preparation used ($t = 0.69, p = 0.49$).

3.6. Use of cannabis to relieve withdrawal symptoms

104 (92.0%) participants took some action to relieve at least one of their withdrawal symptoms, including 26 (23.0%) participants who reported resuming cannabis use.

3.7. Outcome of quit attempt

Almost two-thirds of participants 76 (63.3%) relapsed after their index-quit attempt. The median time to relapse was 182 days (range: 1 day–10 years). No measured subject characteristic was significantly associated with success of the quit attempt or the time to relapse (data not shown).

3.8. Internal validity

All but one of the 480 pairs of mutual exclusive withdrawal symptoms received consistent responses. One participant reported both increased and decreased sleep during withdrawal.

4. Discussion

In this study of 120 people with schizophrenia and chronic cannabis use (86.5% meeting surrogate criteria for lifetime cannabis dependence), 94% reported experiencing at least one cannabis withdrawal symptom during a “serious” quit attempt, with 74.2% reporting at least 4 symptoms. Although the high frequency of cannabis use among people with schizophrenia is well known (Volkow, 2009), this study is the first of which we are aware to show

Table 3

Prevalence and intensity of self-reported cannabis withdrawal symptoms in 120 participants with schizophrenia and chronic cannabis use.

Symptom	n (%)	Onset after quitting (Days)	Peak intensity: 1–5 (Lowest–Highest)	n (%) taking action to relieve
		Mean ± SD	Mean ± SD	
Mood symptom	91 (75.8%)			
Feeling anxious, “nervous”	63 (52.5%)	1.7 ± 1.9	4.0 ± 1.1	60 (95.2%)
Feeling bored	57 (47.5%)	2.0 ± 2.1	3.8 ± 1.1	52 (91.2%)
Feeling sad, depressed	55 (45.8%)	2.0 ± 2.3 ^b	3.8 ± 1.0	46 (85.2%)
Feeling irritable, “jumpy”	54 (45.0%)	1.7 ± 1.9	4.0 ± 1.2	43 (79.6%)
Feeling restless	52 (43.3%)	2.2 ± 2.3	3.6 ± 1.3 ^b	46 (88.5%) ^b
Craving for marijuana	71 (59.2%)	1.4 ± 1.7	4.0 ± 1.2 ^b	67 (94.4%)
Sleep problem	72 (60.0%)			
Trouble falling asleep	40 (33.3%)	1.9 ± 2.1	3.7 ± 1.2	36 (90.0%)
Sleep less than usual	36 (30.0%)	2.1 ± 2.1	3.7 ± 1.2	30 (83.3%)
Waking up during the night	35 (29.2%)	2.6 ± 2.2	3.7 ± 1.2	31 (88.6%)
Vivid dreams	33 (27.5%)	2.2 ± 2.2	4.3 ± 1.1	19 (57.6%)
Strange dreams	29 (24.2%)	2.3 ± 2.3	4.5 ± 0.8 ^b	16 (55.2%)
Waking up earlier than usual	28 (23.3%)	2.7 ± 2.4	3.7 ± 1.2	18 (66.7%)
Sleep more than usual	19 (15.8%)	2.7 ± 2.8	3.1 ± 1.0	11 (57.9%)
Other sleep problem	1 (0.8%)	1.3	4	1 (100%)
Physical symptom	62 (51.7%)			
Headaches	28 (23.3%)	2.0 ± 2.1	4.2 ± 1.2	21 (77.8%)
Weight gain	21 (17.5%)	4.5 ± 2.6	3.6 ± 1.2	15 (71.4%) ^b
Sweating	17 (14.17%)	1.6 ± 1.7	3.7 ± 1.5	11 (68.7%)
Stomach pains	15 (12.5%)	2.0 ± 1.9	3.8 ± 1.1	12 (80.0%) ^b
Chills	13 (10.8%)	1.6 ± 1.2	2.8 ± 1.3	8 (61.5%)
Tremor, shakiness	13 (10.8%)	1.3 ± 1.0	3.5 ± 1.2	10 (76.9%)
Upset stomach	11 (9.2%)	2.1 ± 2.1	3.9 ± 1.1	10 (90.9%)
Muscle twitches	10 (8.3%)	1.3 ± 1.2	3.1 ± 1.7	5 (50.0%)
Nausea	10 (8.3%)	2.2 ± 1.9	3.3 ± 1.2	9 (90.0%)
Weight loss	8 (6.7%) ^a	2.0 ± 2.2	3.0 ± 1.4	3 (37.5%) ^b
Physical discomfort	8 (6.7%)	2.5 ± 1.9	4.3 ± 0.9	6 (75.0%)
Vomiting	6 (5.0%)	1.5 ± 1.4	4.0 ± 0.9	4 (66.7%)
Diarrhea	6 (5.0%)	3.0 ± 2.3	3.7 ± 1.8	5 (83.3%)
Appetite change	63 (52.5%)			
Increase in appetite	35 (29.2%)	2.5 ± 2.1 ^b	4.0 ± 1.0	26 (74.3%) ^b
Decrease in appetite	28 (23.3%)	1.9 ± 2.0	3.1 ± 1.2	16 (57.1%)
Verbal/physical aggression	45 (37.5%)			
Feeling angry	34 (28.3%)	1.9 ± 2.3	3.8 ± 1.3	23 (67.6%)
Feeling aggressive	22 (18.3%)	1.8 ± 2.0	4.2 ± 0.9	15 (68.2%)
Insulted, yelled or swore at a person	21 (17.5%)	2.5 ± 2.5	4.0 ± 1.0	11 (61.1%)
Threw or broke something	10 (8.3%)	2.8 ± 2.3	4.0 ± 1.3	3 (30.0%)
Punched or kicked a person	9 (7.5%)	1.9 ± 2.2	4.7 ± 0.5	4 (50.0%)
Physically attacked a person	7 (5.8%)	2.0 ± 2.4	4.6 ± 0.8	5 (71.4%)
Pushed, grabbed, or slapped a person	6 (5.0%)	1.5 ± 1.2	4.2 ± 1.6	2 (33.3%)
Pulled a knife, gun, or other weapon	2 (1.7%)	1.0 ± 1.4	3.5 ± 2.1	1 (50.0%)
Sex drive change	25 (20.8%)			
Increase in sex drive	14 (11.7%)	3.2 ± 3.0	4.3 ± 0.6	8 (57.1%)
Decrease in sex drive	11 (9.2%)	2.1 ± 1.9	3.5 ± 1.2	4 (40.0%)
Improved memory	19 (15.8%)	2.7 ± 2.2	3.8 ± 1.0	4 (21.0%)
Other	6 (5.3%)			

Prevalence data in bold represent the number (%) of people reporting at least one symptom within that category of symptoms.

^a n = 119.^b One person did not respond to the question.

that a substantial proportion of such individuals experience withdrawal symptoms, if not a full-blown withdrawal syndrome, when trying to quit cannabis use without formal treatment.

Several factors suggest that our findings reflect true cannabis withdrawal, rather than the chance occurrence of isolated, non-specific symptoms. First, there was frequent co-occurrence of multiple symptoms. Second, tobacco withdrawal, which has substantial symptom overlap with cannabis withdrawal (Vandrey et al., 2008), is unlikely to have been a significant confound. While the majority of participants (90.8%) were using tobacco at least weekly at the start of their quit attempt, only 13% decreased their tobacco use during the quit attempt, putting them at risk for concurrent tobacco withdrawal.

The type and frequency of cannabis withdrawal symptoms reported by participants with schizophrenia in this study is roughly comparable to that reported in previously published studies of cannabis users without serious psychiatric co-morbidity (Allsop

et al., 2011; Budney et al., 2004; Copersino et al., 2006a; Hasin et al., 2008; Levin et al., 2010). The most commonly reported symptoms were psychological, e.g., cannabis craving, anxiety, depression, irritability, and insomnia (Table 3), with physical symptoms (e.g., headache, tremor, nausea, diarrhea) much less common, and many participants experiencing multiple symptoms. These findings support the need for clinicians to monitor for withdrawal symptoms in people with schizophrenia and recent regular cannabis use.

A substantial number of participants (29.2%) reported increased appetite during withdrawal, with 17.5% reporting weight gain. By comparison, only 23.3% of participants reported decreased appetite and 6.7% reported weight loss, symptoms more commonly associated with cannabis withdrawal in non-comorbid samples (Budney et al., 2004; Copersino et al., 2006a; Levin et al., 2010). Some studies of non-clinical samples without serious psychiatric co-morbidity also reported substantial minorities of subjects experiencing increased appetite or weight gain (Copersino et al., 2006a; Levin

et al., 2010). In those studies, the onset of these symptoms was generally later than the onset of decreased appetite or weight loss (Copersino et al., 2006a), suggesting that the increased appetite and weight might represent more of a post-withdrawal phenomenon. Participants in this study did not reliably report the time course of their withdrawal symptoms, so this issue cannot be addressed in these data. Another possible explanation for the difference could be the large number of individuals in this sample taking psychotropic medications as treatment for their schizophrenia. Because many antipsychotics (used by 59.8% of participants in the present study) cause increased appetite and/or weight gain (Bhuvanewar et al., 2009), medication effects could have counteracted the propensity to decreased appetite and weight loss in the CWS. In addition, divalproex, an anticonvulsant used as a mood stabilizer, increased appetite in non-psychotic individuals in a human laboratory study of CWS (Haney et al., 2004).

Our sample reported many similarities to cannabis users without serious psychiatric illness in other published cannabis withdrawal studies, although some differences were found. 47.5% of participants reported cannabis use to relieve withdrawal symptoms at some time in their lives, consistent with most (Budney et al., 2008; Copersino et al., 2006b; Cornelius et al., 2008), but not all (Arendt et al., 2007), prior published studies. 23.0% reported using cannabis for this purpose during their index quit attempt, similar to the one third (Levin et al., 2010) and one-fifth (Copersino et al., 2006a) reported in two previous studies that used the MJQQ. Only 63.3% of participants relapsed during their index quit attempt, substantially less than the 89% who relapsed in a prior study of 469 adult cannabis smokers without psychiatric co-morbidity (Levin et al., 2010). These differences may be due to psychiatric co-morbidity and psychiatric treatment in participants in the present study. While participants were not in drug abuse treatment during their quit attempt, the majority were in psychiatric treatment (as indicated by their taking prescribed psychoactive medication). It is possible that this psychiatric treatment participation, even if not targeted specifically at cannabis use, reduced the likelihood of relapse to cannabis use. Lower availability or affordability of cannabis, compared to those without serious psychiatric co-morbidity, may also be a factor. Finally, some currently unidentified factor in people with schizophrenia may make them more able than others to spontaneously stop using cannabis.

This study has several limitations, including small sample size ($n = 120$), data collection by retrospective self-report over a median interval of 9 years, and no collateral sources or objective confirmation. However, there is evidence that patients with severe mental illness can give valid retrospective self-report about their drug-using behavior (Carey et al., 2001) and that cannabis users not in treatment, and without serious psychiatric co-morbidity, do give reliable retrospective self-report about their cannabis withdrawal symptoms (Mennes et al., 2009). In addition, the high internal consistency rate for responses to mutually exclusive pairs of questions suggests that participants were giving valid responses. All participants lived in one metropolitan area at the time of study and all were receiving care from public or publically funded facilities; therefore, the external validity (generalizability) may be limited.

In conclusion, to our knowledge, this is the first study to report the occurrence of cannabis withdrawal symptoms in people with schizophrenia. These withdrawal symptoms warrant clinical attention because they are often associated with clinically significant behavior change, including relapse to cannabis use and increased tobacco use. Thus, our findings suggest that cannabis withdrawal is a clinically significant feature of cannabis use among people with schizophrenia, as it is among those without serious psychiatric illness, and deserves greater attention in treatment and

research. More research is needed to evaluate the effects of cannabis in people with schizophrenia and how withdrawal symptoms affect psychosis, relapse to cannabis use, and quality of life. Future studies would benefit from larger samples that prospectively characterize cannabis dependence and longitudinally measure objective symptoms of cannabis withdrawal.

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NIDA and NIMH had no role in study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

Authors Gorelick, Boggs, and Kelly designed the study and wrote the protocol. Authors Turner and Linthicum contributed to protocol design and were responsible for data collection oversight. Authors Liu, McMahon, and Schroeder performed the statistical analyses. Author Boggs wrote the first draft of the manuscript. Authors Gorelick and Kelly reviewed the manuscript for substantive intellectual content. All authors reviewed and approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

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