Journal of Psychiatric Research 47 (2013) 240–245

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Cannabis withdrawal in chronic cannabis users with schizophrenia

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ARTICLE INFO

Article history:
Received 18 April 2012
Received in revised form
12 September 2012
Accepted 17 October 2012

Keywords:
Schizophrenia
Marijuana
Co-morbidity
Cannabis
Withdrawal

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.

Published by Elsevier Ltd.

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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0022-3956/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jpsychires.2012.10.010

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)
Sociodemographic characteristic	
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%
Psychiatric characteristic	
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)