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Cannabis Withdrawal in Patients With and Without Opioid Dependence

Emeline Chauchard, PhD^{a,b}, Oleg Goncharov, MD^c, Evgeny Krupitsky, MD PhD DMedSci^d, and David A. Gorelick, MD, PhD^{b,*}

^aCentre d'étude et de recherche en psychopathologie (CERPP), Université de Toulouse - Le Mirail, 5 allées Antonio Machado, 31058 Toulouse Cedex 9, France

^bIntramural Research Program, National Institute on drug Abuse, 251 Bayview Blvd., Baltimore, MD 21224, USA

^cDepartment of psychiatry, North-Western State Medical University named after I.I. Mechnikov, Kirochnaja street, 41, St-Peterburg 191015 Russia

^dDepartment of Addictions, St.-Petersburg Bekhterev Psychoneurological Research Institute, Bekhtereva street, 3, St.-Petersburg 192019, Russia

Abstract

Background—Cannabis use is common among opioid-dependent individuals, but little is known about cannabis withdrawal in this population.

Method—Thirty inpatients (57% men) completed the Marijuana Quit Questionnaire (MJQQ) after completing acute heroin detoxification treatment in St. Petersburg, Russia. The MJQQ collected data on motivations for quitting, withdrawal symptoms, and coping strategies used to help maintain abstinence during their most “userious” (self-defined) quit attempt made without formal treatment outside a controlled environment.

Results—At the start of their quit attempt, 70% of participants smoked cannabis at least weekly (40% daily), averaging [SD] 2.73 [1.95] joints daily; 60% were heroin-dependent. Subjects with heroin dependence were significantly older at the start of their quit attempt (22.9 [3.6] years vs. 19.1 [2.9] years), were significantly less likely to report withdrawal irritability/anger/aggression (22% vs. 58%), restlessness (0% vs. 25%), or physical symptoms (6% vs. 33%), or to meet diagnostic criteria for DSM-5 cannabis withdrawal syndrome (6% vs. 33%), and had shorter duration of abstinence (29.6 [28.7] months vs. 73.7 [44.1] months) than those without heroin dependence.

Conclusion—Cannabis users with opioid dependence are less likely to experience cannabis withdrawal, suggesting that opiate use may prevent or mask the experience of cannabis

*Correspondence should be addressed to David A. Gorelick, MD, PhD, Maryland Psychiatric Research Center, University of Maryland School of Medicine, PO Box 21247, Baltimore, MD 21228 USA. dgorelick@mprc.umaryland.edu.

AUTHOR CONTRIBUTIONS

Dr. Gorelick designed the study; Drs. Goncharov and Krupitsky collected the data and did initial data processing; Dr. Chauchard conducted the statistical analyses and wrote the first draft of the manuscript; and Dr. Gorelick reviewed the manuscript for major intellectual content. All authors reviewed and approved the final version of the manuscript

withdrawal. Results should be considered preliminary due to small convenience sample and retrospective data.

Keywords

cannabis; withdrawal; opioids

INTRODUCTION

Concurrent use of cannabis and opiates is common worldwide¹⁻⁵. Such use may be mediated by interaction between cannabinoid CB1 receptors and opioid receptors in the brain⁶⁻⁹, generating a reciprocal relationship between these two systems in the development of dependence and withdrawal⁸.

A cannabis withdrawal syndrome is now widely accepted¹⁰⁻¹³, but little is known about cannabis withdrawal in an opiate-dependent population. We are aware of only one study that investigated cannabis withdrawal symptoms, in a sample of 99 cannabis-dependent outpatients with or without concomitant opiate dependence¹⁴⁻¹⁵. That study reported no difference, with one exception, between the two groups in average number of withdrawal symptoms reported or the frequency and duration of symptoms, but only evaluated 6 symptoms: decreased appetite or weight loss, irritability, nervousness or anxiety, anger or aggression, restlessness, and sleep disturbance. The latter symptom was significantly more frequent in the outpatients with concomitant opiate dependence. That study did not evaluate motivations for quitting or coping strategies for maintaining abstinence.

We compare here the experience of cannabis withdrawal in a convenience sample of 30 cannabis-dependent patients either with or without heroin dependence at the start of their cannabis quit attempt, including evaluation of 40 withdrawal symptoms, motivations for quitting cannabis use, and coping strategies for maintaining abstinence.

METHODS

Subjects were recruited during 2009 from a 3-week, inpatient, medication-free opiate detoxification program in Saint Petersburg, Russia and interviewed after detoxification. Patients were screened for a history of an attempt to quit cannabis use without formal treatment while not in a controlled setting such as hospital or jail, resulting in a convenience sample of patients admitted for clinical detoxification.

The study protocol was approved by the I.P Pavlov Saint Petersburg State Medical University Ethics Committee and the Institutional Review Board of the National Institute on Drug Abuse Intramural Research Program. After screening to establish meeting the inclusion criteria, all participants gave written informed consent while not in acute withdrawal. All participants were informed that their participation in the study was voluntary and that refusal to participate would not influence the quality and extent of their treatment in the Leningrad Oblast Drug Addiction Clinic.

Participants completed the Marijuana Quit Questionnaire (MJQQ), a 176-item self-report instrument that collects information about the subject's "most serious" (self-defined) marijuana quit attempt. Cannabis withdrawal symptoms were assessed with a list of 40 withdrawal symptoms based on published literature¹⁶⁻¹⁹. Each symptom was rated as present or absent; if present, intensity was rated on a 5-point Likert scale and any actions taken to relieve that symptom were assessed. Cannabis withdrawal syndrome was diagnosed by DSM-5 criteria (> 3 symptoms from a list of 7; see Table 2), including only symptoms for which some action was taken to relieve, as a surrogate for the DSM-5 requirement that a symptom generate distress or disability¹³. Heroin dependence was diagnosed by ICD-10 criteria²⁰. If the onset of heroin dependence was prior to the start of the cannabis quit attempt and the duration of heroin dependence overlapped with the start of the quit attempt, then the subject was considered heroin dependent at the time of the quit attempt.

Characteristics of participants who were heroin-dependent and non-heroin-dependent at the time of their index quit attempt were compared with the chi-square test, Kruskal-Wallis test, or Mann-Whitney U test, as appropriate, for independent samples. Statistical significance was considered a two-tailed alpha value < 0.05.

RESULTS

Participants were largely young (age range 22 to 35 years), single men at the time of interview (Table 1). Cannabis use characteristics are presented in Table 1. Participants first used heroin at mean [SD] age 19.8 [4] years and first became heroin dependent at age 21 [4.0] years.

During the 6 months before their index quit attempt, 70% of participants smoked cannabis at least weekly, including 40% who smoked daily. Sixty percent were heroin-dependent at the time of their quit attempt. There were no significant differences between heroin-dependent and non-heroin-dependent patients on sociodemographic, cannabis use, or other substance use variables during these 6 months (Table 1), except that heroin-dependent subjects were less likely to drink caffeine weekly (72% vs 100%; $\chi^2=4$, $p=.05$).

The quit attempt occurred 1-12 years before the study interview, but significantly more recently for the heroin-dependent subjects than for the non-heroin-dependent subjects (Table 1). Heroin-dependent subjects were significantly older than non-heroin-dependent subjects at the start of their quit attempt and had a shorter duration of subsequent abstinence (Table 1).

Forty percent of subjects relapsed after their index quit attempt. There were no differences between heroin- and non-heroin-dependent subjects in relapse rate (Table 1), use of legal psychoactive substances during the quit attempt, motives to quit marijuana use, or coping strategies used to maintain abstinence (data not shown).

Seventy percent of subjects reported at least one of the 40 evaluated withdrawal symptoms; the 10 most commonly reported symptoms are shown in Table 2. Heroin-dependent and non-dependent subjects did not differ significantly in number of symptoms reported (3.7 [4.2] vs. 6.2 [6.5], $p=.36$). Heroin-dependent subjects reported significantly less irritability/

anger/aggression, restlessness, and physical symptoms than did non-heroin-dependent subjects, but did not differ significantly in intensity of any of the seven DSM-5 withdrawal symptoms (Table 2).

Heroin-dependent subjects were significantly less likely to meet full diagnostic criteria for the DSM-5 cannabis withdrawal syndrome than were non-heroin-dependent subjects, although syndrome intensity was not significantly different (Table 2).

DISCUSSION

This is the first study of which we are aware to compare the full experience of cannabis withdrawal, including prevalence of a cannabis withdrawal syndrome, among a heroin-dependent population, and only the second study to describe cannabis withdrawal symptoms in this population.

In our study, 42% of non-heroin-dependent and 39% of heroin-dependent subjects experienced at least two DSM-5 withdrawal symptoms. This is less than the proportion previously reported in an opioid-dependent population (62.5-65.1%)¹⁵ and in adults without major psychiatric or substance abuse co-morbidity (57.3%)¹³. Thirty-three percent of participants without heroin dependence met DSM-5 criteria for a cannabis withdrawal syndrome, comparable to the 40.9% prevalence previously reported among adults without substance abuse or psychiatric comorbidity¹³. However, subjects with heroin dependence had significantly lower prevalence of cannabis withdrawal syndrome (6%), suggesting that opiate use may prevent or mask the experience of cannabis withdrawal. This is also suggested by the finding that subjects with heroin dependence were significantly less likely to report irritability/anger/aggression, restlessness, or physical symptoms during withdrawal. In animals, cannabis withdrawal is associated with decreased mesolimbic dopamine function²¹, while in rat brain tissue slices, repeated exposure to morphine increases dopamine release²², although these findings have not been directly replicated in human brain imaging studies²³. These preclinical findings suggest that chronic opioid use could attenuate cannabis withdrawal.

Patients who were heroin dependent at the start of their quit attempt had a significantly shorter duration of subsequent abstinence than those who were not heroin dependent, despite having less cannabis withdrawal. This runs counter to the clinical expectation that the experience of substance withdrawal is associated with greater risk of relapse²⁴. This finding may be due to the absence of significant group differences in the intensity of individual DSM-5 withdrawal symptoms or the overall withdrawal syndrome.

Subjects with heroin dependence did not report more insomnia, not confirming a previous study in an opiate-dependent sample^{14,15}. Feeling bored was the third most common withdrawal symptom (one-third of subjects), consistent with the proportion (50%) in a previous study of subjects without psychiatric or substance use comorbidity¹¹.

This study has several limitations. First, all data were collected by retrospective self-report, with no external corroboration. However, evidence exists that non-treatment cannabis users give reliable retrospective self-report about their cannabis use histories^{25,26} and withdrawal

symptoms^{11, 27}. Second, the MJQQ used to assess cannabis withdrawal is not psychometrically validated, in contrast to the recently developed Cannabis Withdrawal Scale²⁸. However, it has been used successfully in studies of cannabis smokers with schizophrenia²⁹ and without any psychiatric or substance abuse comorbidity¹¹. Third, no information was collected on heroin use during the index quit attempt, limiting the ability to evaluate in detail the relationship between opioid use and cannabis withdrawal. Fourth, the small sample size from a single site limits the external validity (generalizability) of these results.

These findings suggest that opiate dependence may reduce the prevalence of some cannabis withdrawal symptoms and of a full withdrawal syndrome, suggesting that opiate dependence may attenuate cannabis withdrawal. Future research with larger samples and contemporaneous data collection is needed to confirm these findings and improve our understanding of the relationship between cannabis and opiate dependence.

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TABLE 1

Sociodemographic characteristics, cannabis use history, motives to quit marijuana use, and strategies used to maintain abstinence among 30 adult cannabis users with (18) or without (12) heroin dependence at the time of quit attempt.

	All	Heroin dependence before quit attempt		
		N=30	No N=12	Yes N=18
Sociodemographic				
Male	67 % (20)	40 % (8)	60% (12)	
Single	47 % (17)	47.1% (8)	52.9% (9)	
Age	27.7 ±3.02	16.7 ±2.2	28.2 ±3.4	
Cannabis use				
Age of first use	15.8 ±2.10	15.6 ±1.5	16.1 ±2.4	
Age of regular use	16.1 ± 1.94	15.4 ±1.6	16.6 ±2.0	
Cannabis use at least once a day	40 % (12)	41.7% (5)	58.3% (7)	
Join smoke/day	2.73 ±1.95	2.3 ±1.7	3 ±2.1	
Cannabis quit attempt				
Quit attempt occurred (years ago)	6.17 ±3.2	7.6 ±2.5	5.2 ±3.3	
Age at the time of the quit attempt	21.4 ±3.8	19.1 ±2.9	22.9 ±3.6	
Duration of the quit attempt (months)	47.3 ±41.3	73.7 ±44.1	29.6 ±28.7	
Relapse	40% (12)	25% (3)	75% (9)	
Motives to quit marijuana use^(a)				
I could get praise from people I am close to	60% (18)	50% (6)	67% (12)	
I could feel in control of my life	57% (17)	58% (7)	59% (10)	
Using marijuana did not fit who I want to be	57% (17)	50% (6)	61% (11)	
To save money	57% (17)	67% (8)	50% (9)	
I do not want to be a bad example for children	53% (16)	42% (5)	61% (11)	
To show myself that I could quit	50% (15)	42% (5)	56% (10)	
I would like myself better if I quit	50% (15)	42% (5)	56% (10)	
The people I am close to would stop nagging at me	50% (15)	42% (5)	56% (10)	
I noticed symptoms that marijuana was hurting my health	50% (15)	58% (7)	44% (8)	
To have more energy	50% (15)	50% (6)	50% (9)	

	All N=30	Heroin dependence before quit attempt		<i>p</i>
		No N=12	Yes N=18	
Coping strategies used to maintain abstinence ^(b)				
Got rid of my marijuana	57% (17)	67% (8)	50% (9)	
Stopped going to places where marijuana is smoked	53% (16)	67% (8)	44% (8)	
Stopped associating with people who smoke marijuana	40% (12)	50% (6)	33% (6)	
Encouragement from family	33% (10)	42% (5)	28% (7)	
Got rid of my marijuana paraphernalia	33% (10)	50% (6)	22% (4)	
Encouragement from friends	23% (7)	25% (3)	22% (4)	
Religious support, prayer	20% (6)	25% (3)	17% (3)	
Saw a physician	10% (3)	17% (2)	6% (1)	
Attended a self-help group	7% (2)	0% (0)	11% (2)	

Note. Data presented as % (n) or mean±SD.

^(a) 26 items, based on three questionnaires studying motives to quit in treatment context and tobacco motives cessation^{32,33}.

^(b) 16 items, based on question from studies assessing alcohol, tobacco and other drug quit strategies^{32,33}.

TABLE 2
Cannabis withdrawal symptoms reported by 30 adults with (18) or without (12) heroin dependence during their quit attempt

	Withdrawal symptom frequency				Withdrawal symptom intensity ^(g)		
	All		Heroin dependence before quit attempt		All	Heroin dependence before quit attempt	
	% (n)	No	Yes	Chi ² value <i>p</i>	Mean (n) ±SD	No	Yes
Withdrawal symptoms ^(a)							
Feeling sad, depressed	43(13)	50 (6)	39 (7)		3.45 (11) ±1.04	4.00 (4) ±0.82	3.14 (7) ±1.07
Increase in appetite	40 (12)	50 (6)	33 (6)		3.64 (11) ±0.92	4.17 (6) ±0.75	3.00 (5) ±0.71
Feeling bored	33 (10)	25 (3)	39 (7)		3.30 (10) ±0.95	3.67 (3) ±0.58	3.14(7) ±1.07
Strange dreams	27 (8)	33 (4)	22 (4)		3.50 (8) ±1.41	4.25 (4) ±0.96	2.75 (4) ±1.50
Feeling irritable, jumpy	27 (8)	42 (5)	17 (3)		3.00 (8) ± 0.76	3.00 (5) ±0.71	3.00 (3) ±1.00
Trouble falling asleep	23 (7)	25 (3)	22 (4)		2.43 (6) ±1.40	3.30 (3) ±1.53	1.75 (4) ±0.96
Vivid dreams	23 (7)	33 (4)	17 (3)		3.86 (7) ±0.90	4.25 (4) ±0.96	3.33 (3) ±0.58
Waking up during the night	20 (6)	25 (3)	17 (3)		2.17 (6) ±0.98	2.67 (3) ±0.58	1.67 (3) ±1.15
Sleep more than usual	20 (6)	33 (4)	11 (2)		2.83 (6) ±0.75	3.00 (4) ±0.82	2.50 (2) ±0.50
Cravings for MJ	20 (6)	17 (2)	22 (4)		1.83 (6) ±0.76	1.00 (2) ±0	2.25 (4) ±1.89
DSM-5 symptoms ^(b)							
Irritability, anger, or aggression	37 (11)	58 (7)	22 (4)	0.044**	3.18 (11) ±0.87	3.00 (7) ±0.58	3.50 (4) ±1.29
Nervousness or anxiety	23 (7)	33 (4)	17 (3)		2.43 (7) ±0.98	300 (4) ±0	1.67 (3) ±1.15
Insomnia ^(c)	37 (11)	42 (5)	33 (6)		3.36 (11) ±1.21	4.00 (5) ±1.00	2.83 (6) ±1.17
Decreased appetite or weight loss	17 (5)	8 (1)	22 (4)		3.00 (5) ±0	3.00 (1)	3.00 (4) ±0
Restlessness	10 (3)	25 (3)	0	0.025**	4.00 (3) ±1.00	4.00 (3) ±1.00	0 (0)
Depressed mood	43 (13)	50 (6)	39 (7)		3.45 (11) ±1.04	4.00 (4) ±0.82	3.14 (7) ±1.07
Physical symptoms ^(d) (at least one)	17 (5)	33 (4)	6 (1)	0.046**	2.80 (5) ±0.45	2.75 (4) ±0.5	3.00 (1)
DSM-5 Withdrawal syndrome							
Three symptoms ^(e)	17 (5)	33 (4)	6 (1)	0.046**	3.35 (5) ±0.49	3.44 (4) ±0.52	3.00 (1)
Two symptoms ^(f)	40 (12)	42 (5)	39 (7)		2.99 (12) ±0.77	3.52 (5) ±0.58	2.62 (7) ±0.68*

Note.

(a) 10 most frequently experienced withdrawal symptoms from a list of 40 withdrawal symptoms based on published literature (Budney et al., 2008; Haney et al., 1999; Jones et al., 1981; Smith, 2002; Wiesbeck et al., 1996).

(b) Symptom included only if it elicited some action to relieve it, as surrogate for DSM-5 requirement that symptom cause discomfort or disability.

(c) Strange dreams, trouble falling asleep, or waking up during the night.

(d) Stomach pain, shakiness/tremors, sweating, fever, chills, or headache.

(e) Full diagnostic criteria < 3 out of 7 symptoms. Intensity rating for the syndrome is the mean of the ratings of the individual component symptoms

(f) 2 out of 6 symptoms, i.e., without physical symptoms. Intensity rating for the syndrome is the mean of the ratings of the individual component symptoms.

(g) Intensity measured on 5-point Likert scale (1-5). Intensity rating for each DSM-5 symptom is the highest rating for any of its individual component symptoms.

** Cramer V effect size = moderate association between independent and dependent variables (between 0.3 and 0.5)

* p = 0.05 (Mann-Whitney U test) for group difference in withdrawal intensity