



Published in final edited form as:

Drug Alcohol Depend. 2010 September 1; 111(1-2): 120–127. doi:10.1016/j.drugalcdep.2010.04.010.

Cannabis Withdrawal Symptoms in Non-Treatment-Seeking Adult Cannabis Smokers

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Abstract

Background—Cannabis withdrawal is not recognized in DSM-IV because of doubts about its clinical significance.

Objectives—Assess the phenomenon of cannabis withdrawal and its relationship to relapse in non-treatment-seeking adults.

Subjects—Convenience sample of 469 adult cannabis smokers who had made a quit attempt while not in a controlled environment.

Methods—Subjects completed a 176-item Marijuana Quit Questionnaire collecting information on sociodemographic characteristics, cannabis use history, and their “most difficult” cannabis quit attempt.

Results—42.4% of subjects had experienced a lifetime withdrawal syndrome, of whom 70.4% reported using cannabis in response to withdrawal. During the index quit attempt, 95.5% of subjects reported ≥ 1 individual withdrawal symptom (mean [SD] 9.5 [6.1], median 9.0); 43.1% reported ≥ 10 . Number of withdrawal symptoms was significantly associated with greater frequency and amount of cannabis use, but symptoms occurred even in those using less than weekly. Symptoms were usually of \geq moderate intensity and often prompted actions to relieve them. Alcohol (41.5%) and tobacco (48.2%) were used more often than cannabis (33.3%) for this purpose. There was little change during withdrawal in use of other legal or illegal substances.

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Contributors

Authors Gorelick, Levin, Copersino, and Heishman designed the study and wrote the protocol. Author Levin was responsible for data collection oversight and data base management. Authors Liu and Levin performed the statistical analyses. Authors Levin and Gorelick wrote the first draft of the manuscript. Authors Copersino, Kelly, and Boggs reviewed the manuscript for substantive intellectual content. All authors reviewed and approved the final manuscript.

Conflict of interest

No conflict declared.

Conclusions—Cannabis withdrawal is a common syndrome among adults not seeking treatment. The intention to relieve withdrawal symptoms can drive relapse during quit attempts, giving cannabis withdrawal clinical significance as a target of treatment.

Keywords

cannabis; marijuana; withdrawal; tolerance; relapse

1. Introduction

Cannabis is the most widely used illicit psychoactive substance in the world. An estimated 142–190 million people used cannabis in 2007 (3.3%–4.4% of the population aged 15–64 years), about 10% of whom were dependent (United Nations Office on Drugs and Crime 2009). In the United States, there were an estimated 15.2 million current (past month) cannabis users in 2008 (6.1% of the population 12 years or older), of whom 4.2 million met DSM-IV criteria for abuse or dependence (Substance Abuse & Mental Health Services Administration 2009). A majority of these current users have not sought treatment to stop their cannabis use (Stinson et al., 2006).

Research has now established withdrawal from cannabis as a distinct clinical phenomenon (Budney 2006; Budney and Hughes 2006). This research has used several approaches, including retrospective self-report studies (Copersino et al., 2006a; Hasin et al., 2008), prospective outpatient self-report studies (Budney et al., 2003; Kouri and Pope, Jr. 2000; Vandrey et al., 2008), prospective inpatient observational studies (Milin et al., 2008), and human laboratory studies of directly observed cannabinoid administration and abstinence (Haney et al., 1999; Jones et al., 1976; Jones et al., 1981; Nowlan and Cohen 1977). All these approaches demonstrate distinct withdrawal symptoms following abrupt cessation of cannabis use. Furthermore, these abstinence symptoms resolve with cannabinoid re-administration (Budney et al., 2007; Haney et al., 2004; Haney et al., 2008; Jones et al., 1981), a key characteristic of a drug withdrawal syndrome.

More than a dozen studies have retrospectively evaluated the prevalence of individual symptoms of cannabis withdrawal over a lifetime or past year. These studies fall into three general types. Four large-scale (sample sizes 739–1735) studies involved adults not in treatment: subsets of the National Epidemiologic Survey on Alcoholism and Related Conditions (NESARC) with current (Agrawal et al., 2008) or frequent peak lifetime cannabis use (Hasin et al., 2008); a subset of the Collaborative Study on the Genetics of Alcoholism (COGA) with more than minimal lifetime cannabis use (most with lifetime substance abuse and/or psychiatric comorbidity) (Wiesbeck et al., 1996); and one study involving a mixture of the general population and patients in treatment (Mennes et al., 2009). Seven smaller-scale (sample sizes 39–214) studies involved adolescents (Chung et al., 2008; Cornelius et al., 2008; Crowley et al., 1998; Mikulich et al., 2001; Vandrey et al., 2005) or adults (Arendt et al., 2007; Budney et al., 1999) in treatment, many with substance abuse or psychiatric comorbidity. Two smaller-scale studies (sample sizes 67 and 104) evaluated adult, non-treatment-seeking cannabis users without substance abuse or psychiatric comorbidity (Vandrey et al., 2008; Copersino et al., 2006a). Of these studies, none included less frequent (weekly or less) cannabis users and only one focused on a specific withdrawal episode (Copersino et al., 2006a) or reported on the time course of withdrawal symptoms (Copersino et al., 2006a) or changes in other substance use during withdrawal (Copersino et al., 2006b).

Relief of withdrawal symptoms has long been considered a negative reinforcer for continued use of substances such as alcohol and opiates (Schuster 1975; Thompson and Pickens 1975; Cicero 1980). Several studies based on retrospective self-report found cannabis users reporting

use to relieve or avoid cannabis withdrawal symptoms, suggesting that cannabis withdrawal can also serve as a negative reinforcer for cannabis use (Chung et al., 2008; Coffey et al., 2002; Cottler et al., 1995; Crowley et al., 1998; Copersino et al., 2006a; Gillespie et al., 2007; Mikulich et al., 2001; Swift et al., 1998; Swift et al., 2001). However, a prospective study of 36 cannabis-dependent outpatients who had not used other drugs or abused alcohol in the prior month found that total withdrawal severity (product of number of withdrawal symptoms \times symptom severity [on 4-point Likert scale]) was not significantly associated with relapse over an average 2-year follow-up period (Arendt et al., 2007). Most of these studies involved patients in treatment for cannabis abuse/dependence, and none evaluated the use of cannabis in association with specific withdrawal symptoms; only one evaluated changes in use of other psychoactive substances during the withdrawal period (Copersino et al., 2006b).

The present study used a more detailed version of the Marijuana Quit Questionnaire used previously by this research group (Copersino et al., 2006a) to evaluate the experience of cannabis withdrawal by retrospective self-report in a convenience sample of 469 adults. Subjects provided information about their lifetime withdrawal experience, as well as detailed information about withdrawal during their single most difficult quit attempt outside a controlled environment. Compared to prior published studies, our study provides a more comprehensive evaluation of a specific withdrawal episode in a large sample of non-treatment-seeking, adult cannabis users without current substance abuse or psychiatric co-morbidity. This information addresses some issues relevant to the development of DSM-V (Budney, 2006; Budney and Hughes, 2006): How often does cannabis withdrawal occur in nondaily users of cannabis? What is the co-occurrence of cannabis withdrawal and cannabis tolerance? Does cannabis withdrawal evoke changes in cannabis and other substance use?

2. Methods

2.1 Subjects

Subjects were a convenience sample of 500 non-treatment-seeking cannabis smokers in the Baltimore, MD area recruited from the community by advertising (49.7% print, 14.5% television, 0.6% radio, 0.6% internet), word-of-mouth (20.0%), and referral from other agencies (1.7%) (12.7% unknown). Eligible subjects were 18 years or older, able to read English at an 8th grade level, and had made at least one attempt to stop all cannabis use without formal treatment while not in a controlled environment. All subjects were primarily cannabis users with no other current substance use disorder except nicotine dependence (based on response to telephone screening questions).

This study was approved by the Institutional Review Board of the National Institute on Drug Abuse Intramural Research Program. Subjects gave written informed consent while not acutely intoxicated or in withdrawal and were paid for their study participation.

2.2 Procedures and Instruments

The Marijuana Quit Questionnaire (MJQQ) is a self-report questionnaire that collects information in three domains: sociodemographic characteristics, history of cannabis use (including any associated problems), and characteristics of subjects' "most difficult" (self-defined) quit attempt outside a controlled environment, including reasons for quitting, coping strategies to help quit, withdrawal symptoms, and substance use before and during the quit attempt. The questionnaire has five modules:

1. sociodemographic information
2. cannabis use history
3. cannabis-associated problems

4. cannabis quitting experience during their most difficult quit attempt outside a controlled setting, including withdrawal symptoms, quitting strategies, and reasons for quitting
5. cannabis craving at time of interview (Heishman et al., 2009)

Questions were adapted from relevant prior published studies:

1. reasons for quitting and resuming cannabis use (Adamson and Sellman, 2003; American Psychiatric Association, 2000; McBride et al., 1994; Selden et al., 1990)
2. cannabis-related problems (Adamson and Sellman, 2003; American Psychiatric Association, 2000)
3. coping strategies used during the quit attempt (Sobell et al., 2000; Walters, 2000)
4. withdrawal symptoms experienced during the quit attempt (Budney et al., 2004; Haney et al., 1999; Jones et al., 1981; Smith, 2002; Wiesbeck et al., 1996)
5. changes in other substance use (both licit and illicit) during the quit attempt (O'Farrell et al., 2003)

The list of lifetime cannabis-related problems allowed generation of proxy diagnoses for lifetime cannabis abuse or dependence. These included tolerance (“Have you ever found that you needed to use a lot more marijuana to get high than you did when you first started using it?”), withdrawal (“Has stopping or cutting down on marijuana use ever made you feel sick or given you withdrawal symptoms?”), and withdrawal relief (“After not using marijuana for a while, did you ever use it again to keep yourself from feeling sick or getting withdrawal symptoms?”). Subjects who endorsed lifetime experience of at least one problem from among the abuse criteria in DSM-IV were considered to have cannabis abuse. Subjects who endorsed lifetime experience of at least three problems from among the dependence criteria in DSM-IV were considered to have cannabis dependence. These must be considered proxy or tentative diagnoses because the DSM-IV criterion that the criteria occur within a 12-month interval was not assessed.

Subjects received a list of 40 possible withdrawal symptoms. If the symptom had been experienced, subjects indicated the number of days after last using cannabis that the symptom first appeared, its maximum intensity (on a 5-point Likert scale from “very little” to “very high”), the time of maximum intensity, the time that the symptom disappeared, and what, if anything, was done to relieve the symptom.

The MJQQ was presented on a computer monitor and took 30–45 minutes to complete.

2.3. Statistical Analyses

To minimize recall bias, only withdrawal symptoms with onset within one month of the start of the quit attempt were included in the analyses. To avoid potential censoring of time course data, subjects interviewed less than one month after the start of their quit attempt were not included in the analysis of onset, peak intensity, time of peak intensity, and duration of withdrawal symptoms (Table 1). Comparisons among subject groups used the chi-square test for categorical variables and the t-test or ANOVA for continuous variables. Bivariate logistic regression analysis was used to evaluate the association between continuous cannabis use variables and likelihood of experiencing lifetime cannabis withdrawal or the severity of withdrawal (number of withdrawal symptoms reported) during the index quit attempt. Multivariate linear regression analysis was used to evaluate the association between demographic and cannabis and tobacco use variables and severity of withdrawal during the index quit attempt. Because number of withdrawal symptoms was not normally distributed,

this variable was log transformed (with 0.5 added to zero values to allow log transformation). Pearson's *r* statistic was used to evaluate the correlation between frequency of cannabis use and number of withdrawal symptoms. All statistical analyses were performed with SAS statistical software version 9.1 (SAS Institute, Cary, NC). The two-tailed alpha level was set at 0.05.

3. Results

3.1. Subjects

Of the 922 individuals initially screened by telephone, 60 were ineligible and 5 were not interested in participating. Among the remaining 857 individuals scheduled for study sessions, 357 did not appear for their appointment. Of the 500 subjects consented, 2 did not complete the study and 29 were discovered to be ineligible: 14 had never made a quit attempt and 15 had quit in a controlled environment such as jail or hospital. The remaining 469 subjects provided the data presented in this paper.

The 469 subjects were largely young adult (mean [SD] age 31.2 [10.3] years, range 18 to 65 years, 16.9% < 21 years old, 39.9% 21–29, 19.6% 30–39, 18.6% 40–49, 4.9% 50–65) African-Americans (79.5%), with 58% male and 42% female. The sample was generally of low socioeconomic status. Mean years of education was 11.8 [2.1]; almost one-third (30.1%) had not completed high school, almost half (47.5%) were high graduates, and less than one-quarter (22.6%) had any college. Half (49.9%) the subjects were unemployed, 35.4% were employed full or part-time, 6.6% were students, and the remainder were disabled, retired, or homemakers. Almost three-quarters (73.1%) were never married and 11.5% were married.

The sample was skewed towards frequent cannabis users. Only 6.4% reported lifetime use \leq 100 times; 22.4% had used 100–999 times, 43.3% 1,000–10,000 times, and 27.9% more than 10,000. Cannabis preparations used included marijuana (88.7%), blunts (62.9%), hashish (39%), and hashish oil (14.5%).

Almost all subjects (98.5%) met at least one lifetime criterion for DSM-IV cannabis dependence; 90.6% met at least 3 criteria, suggesting a likely lifetime diagnosis of cannabis dependence. Of these, 81.4% met criteria for physiological dependence (i.e., with tolerance [79.7%] or withdrawal [42.4%]).

At the time of interview, 397 (84.6%) subjects had used cannabis in the prior month and 266 (56.7%) in the prior week, including 81 (17.3%) subjects who used on the day of interview. Fifty-five (11.7%) subjects had been continuously abstinent since their quit attempt.

3.2. Characteristics of Quit Attempt

The index ("most difficult") quit attempt started 41.4 [70.1] months (median 12 months, range 2 days to 35 years) before the interview, and lasted 14.5 [41.8] months (median 2 months, range 1 day to 35 years). 37 subjects were interviewed less than one month after the start of their quit attempt (13 within one week). At the start of the quit attempt, subjects were 27.7 (9.1) years old (range 10–64 years) and had been using cannabis regularly (i.e., at least weekly) for 11.3 (8.8) years (range 0–42 years). Seven subjects were not yet using cannabis regularly at the time of their quit attempt. Almost all subjects were smoking blunts (57.1%) or marijuana (40.5%). Over the 6 months prior to the quit attempt, almost two-thirds of subjects (65.2%) averaged daily smoking; another 30.1% smoked at least weekly. Subjects used cannabis on 22.6 [10.4] days (median 30, range 1–31) in the month prior to the quit attempt, averaging 3.8 [4.5] (median 2.5, range 0–50) joints per occasion and 8.7 [10.5] (median 6, range 1–120) joints per day.

Most subjects used legal psychoactive substances over the 6 months prior to the quit attempt: 69.7% used caffeine (36.3% at least five days per week), 75.3% alcohol (15.3%), and 79.3% tobacco (62.0%). There was minimal use of medications or illegal drugs: 7.7% used sedatives (0.8% at least five days per week), 7.5% over-the-counter sleep medication (1.3%), 14.5% stimulants (2.7%), 14.1% prescription opioid pain medication (2.1%), 7.9% illegal opioids (2.5%), 33.7% non-opioid pain medication (1.7%), 8.7% hallucinogens (0%), 3.8% phencyclidine (0.4%), and 4.7% various other psychoactive drugs (0.4%).

3.3. Withdrawal Syndrome

One hundred and ninety-nine (42.4%) subjects reported a lifetime experience of cannabis withdrawal. Greater lifetime cannabis use was associated with significantly greater likelihood of experiencing withdrawal (chi-square = 21.3, $df = 9$, $p = 0.01$). For example, among subjects reporting at least 2,000 lifetime uses of cannabis, 49.1% experienced lifetime withdrawal, while only 37.1% of those with 100–1,999 lifetime uses and 13.3% of those with less than 100 lifetime uses reported lifetime withdrawal.

There was a similar positive association between preceding cannabis use and severity of the index withdrawal episode. Greater severity, as reflected in the number of withdrawal symptoms reported during the quit attempt, was associated with longer duration of regular (at least weekly) cannabis use ($r = 0.12$, $p = 0.01$), higher frequency of cannabis use over 6 months ($r = 0.20$, $p < 0.0001$) or one month ($r = 0.15$, $p = 0.0009$), or more joints smoked per day prior to the quit attempt ($r = 0.10$, $p = 0.04$). In the multivariate analysis, only sex and frequency of preceding cannabis use were significantly associated with withdrawal severity. Men had 19% fewer withdrawal symptoms than women, and cannabis use more frequently than weekly was associated with about 80% more withdrawal symptoms. Race, age at start of quit attempt, frequency of preceding tobacco use, and other cannabis use variables had no significant association with withdrawal severity.

Lifetime cannabis withdrawal was significantly associated with lifetime cannabis tolerance (chi-square = 14.4, $df = 1$, $p = 0.0001$). Almost half (46.8%) of subjects experiencing tolerance also reported withdrawal, compared with 25.3% of those not experiencing tolerance. Conversely, the majority (87.9%) of subjects experiencing withdrawal also reported tolerance. Subjects reporting a cannabis “hangover” (“ever needed to use marijuana in the morning to get yourself going after a heavy session of using marijuana?”) or lifetime cannabis-associated problems were also more likely to experience withdrawal: 52.9% vs. 25.3% (chi-square = 34.5, $df = 1$, $p < 0.0001$) and 47.9% vs. 33.5% (chi-square = 9.4, $df = 1$, $p = 0.002$), respectively. No other subject characteristic, including type of cannabis preparation used, was significantly associated with withdrawal. There was a non-significant trend for women and African-Americans to be more likely than other subjects to experience withdrawal: 47.2% (men) vs. 39.0% (women) (chi-square = 3.2, $df = 1$, $p = 0.075$) and 45.0% (among African-Americans) vs. 31% (among whites) vs. 36% (among others) (chi-square = 5.3, $df = 2$, $p = 0.07$), respectively.

3.4. Individual Withdrawal Symptoms

95.5% of all subjects experienced at least one of the 40 individual withdrawal symptoms during their index quit attempt (Table 1). Among subjects reporting any withdrawal symptom, the mean number of symptoms was 9.5 [6.1] (median 9.0, range 1–38). Almost all subjects reported more than one symptom: 91.3% reported at least two, 85.1% at least three, 79.1% at least four, 73.6% at least five, and 43.1% ten or more. The commonest symptoms were psychological: cannabis craving (75.7%), mood changes (33.7%–50.1%), sleep disturbances (21.8%–46.9%), and decreased appetite (38.8%) (Table 1). The commonest physical symptoms were weight

gain (23.5%) and headache (23.2%). Except for weight loss (15.1%) and upset stomach (13%), no other physical symptom occurred in more than 10% of subjects (Table 1).

The onset of acute symptoms (i.e., excepting improved memory and weight change) ranged from one day to one week after the start of the quit attempt, with peak symptom intensity two days to two weeks thereafter (Table 1). The duration of withdrawal symptoms was highly variable, ranging from 1.5 weeks to more than one year (Table 1). Physical symptoms and aggressive behaviors tended to have quicker onset, quicker peak intensity, and shorter duration than sleep disturbances or mood changes (Table 1).

Mean peak intensity ratings ranged from 2.7 to 4.2 across the 40 symptoms (Table 1). At least half the subjects gave one of the two highest intensity ratings (4 or 5 out of 5) for 22 of the symptoms (data not shown). Every symptom had at least one-quarter of subjects assign one of the two highest ratings. Physical symptoms tended to have the lowest mean intensity ratings (Table 1) and the lowest proportions of subjects assigning high intensity ratings (data not shown).

At least half the subjects reporting a withdrawal symptom took action to relieve that symptom, with the exception of improved memory (probably not a true withdrawal symptom), strange or vivid dreams, and decreased appetite or sex drive (Table 1).

3.5. Relapse in Response to Withdrawal

One hundred and forty subjects (70.4% of those experiencing a lifetime withdrawal syndrome) reported cannabis use in response to withdrawal. There were no significant associations between such relapse and lifetime cannabis use, tolerance, cannabis “hangover,” or cannabis-associated problems.

The proportion of subjects who reported using cannabis to relieve a withdrawal symptom during their index quit attempt varied from 0%–25.5% for physical symptoms (median 14.7%) to 13.3%–22.8% (median 16.6%) for mood symptoms and 7.8%–33.3% (median 13.3%) for sleep symptoms (Table 2). There was no obvious association between any specific withdrawal symptom and cannabis use (Table 2).

3.6. Other Substance Use in Response to Withdrawal Symptoms

Subjects were more likely to use alcohol or tobacco, rather than cannabis, to relieve most withdrawal symptoms, except for physical symptoms (Table 2). Overall, 186 (41.5%) subjects reported using alcohol to relieve at least one withdrawal symptom; 216 (48.2%) used tobacco to relieve a symptom. Sedatives, stimulants or anti-depressants were used by less than 5% of subjects (Table 2). During the quit attempt, a minority of subjects increased their existing use of substances without necessarily attributing it to withdrawal relief: 16.8% increased their use of caffeine, 33.7% alcohol, and 37.7% tobacco. Less than 5% of subjects started or increased their use of illegal drugs or prescription medications; 7.9% increased their use of non-opioid pain medications.

Few subjects decreased existing use of substances during the quit attempt. 7.9% decreased use of caffeine, 12.6% alcohol, 10.2% tobacco, 0.9% sedatives, 1.5% over-the-counter sleep medication, 4.7% stimulants, 2.8% opioid pain medication, 2.6% illegal opioids, 3.2% non-opioid pain medication, 2.8% hallucinogens, 1.1% phencyclidine, and 0.9% other substances.

4. Discussion

This study found high rates (42.4%) of lifetime cannabis withdrawal, and of single (95.5%) and multiple (91.3%) withdrawal symptoms after the index quit attempt, in a convenience

sample of 469 non-treatment-seeking adults. Psychological symptoms, e.g., cannabis craving (75.7%) and mood changes (33.7%–50.1%), and sleep disturbances (20.1%–46.9%) were substantially more prevalent than physical symptoms (2.1%–13.0%), except for headache (23.2%) and weight gain (23.5%) (Table 1). Symptoms began within one day to one week of quitting, with physical symptoms tending to have quicker onset and shorter duration than other types of symptoms. More than two-thirds (70.4%) of those experiencing lifetime withdrawal, and up to one-third of those reporting specific withdrawal symptoms during the index quit attempt, reported cannabis use in response to withdrawal, suggesting that cannabis withdrawal can serve as a negative reinforcer for relapse. These findings confirm and extend previous results in smaller samples of treatment-seeking adolescents and adults.

The proportion of subjects experiencing cannabis withdrawal is somewhat greater than that in most other studies of non-treatment-seeking adults with frequent lifetime or current cannabis use (range 15.6%–40.9%) (Cottler et al., 1995; Schuckit et al., 1999; Swift et al., 1998; Swift et al., 2000; Wiesbeck et al., 1996) and smaller than that in two Australian studies of cannabis-dependent adults (95.5%, 88.8%) (Copeland et al., 2001; Swift et al., 2001). Differences in prevalence of true cannabis dependence and in substance abuse and psychiatric comorbidity among the various study populations may explain the discrepancy.

Our findings differ somewhat from those in the larger sample (1,119) of lifetime cannabis-using adults in the NESARC study (Hasin et al., 2008), which found fewer subjects reporting multiple withdrawal symptoms (59.4% at least one, 44.2% at least two, and 34.1% at least three) and a lower prevalence of mood changes (6.4%–19.3%) and sleep disturbances (6.3%–26.4%). These differences may be due to a low prevalence of lifetime cannabis dependence (12.9%) in the NESARC sample and to differences in the questionnaire used. The NESARC study asked about 18 withdrawal symptoms, fewer than the 40 symptoms used in this study, but comparable to the 16 or 18 symptoms used by Budney et al. (2008) or Copersino et al. (2006a). However, the questionnaire used in the NESARC study was designed for general use across all drug withdrawal syndromes; thus, it omitted some symptoms with high prevalence in other studies (e.g., cannabis craving, irritability) and included symptoms not associated with cannabis withdrawal (e.g., seizures, hallucinations, fever, runny eyes or nose, and yawning).

The time course of retrospectively reported withdrawal symptoms was broadly consistent with that reported in a smaller retrospective study of non-treatment-seeking adults (Copersino et al., 2006a). That study also found the onset of symptoms within one day to one week of quitting, with physical symptoms tending to have quicker onset and shorter duration than other types of symptoms. Two small prospective studies of non-treatment-seeking adults assessed daily for six weeks or four weeks found symptom onset within 1–3 days of quitting, peak intensity in 2–6 days, and symptom resolution within two weeks (Budney et al., 2003; Kouri and Pope, Jr., 2000). Similar to our results, one study found that physical symptoms tended to be less intense and to peak and resolve sooner than other symptoms (Budney et al., 2003). The other study found that some physical symptoms lasted the entire four weeks of the study (Kouri and Pope, Jr., 2000). We are not aware of other nonresidential studies that evaluated the time course of cannabis withdrawal symptoms over intervals longer than five days.

Our data suggest that subjects were experiencing a true cannabis withdrawal syndrome. The intensity of cannabis use (e.g., frequency of use, joints used per occasion or per day) prior to the quit attempt was positively correlated with the severity of withdrawal (as reflected in the number of withdrawal symptoms), as expected from the pharmacological relationship between substance use and withdrawal. Also consistent with this pharmacological relationship is the positive correlation between tolerance to cannabis and experiencing withdrawal. Almost all subjects reported multiple symptoms, suggesting that subjects were not reporting the scattered occurrence of nonspecific symptoms. Most symptoms had at least moderate mean peak

intensity (Table 1); many were rated high or very high in intensity; and many prompted subjects to take action to relieve them (Table 1). These characteristics suggest that many of the reported withdrawal symptoms met the DSM-IV withdrawal criterion of “clinically significant distress or impairment” (American Psychiatric Association, 2000).

A minority of subjects increased their use of alcohol, tobacco, or caffeine during their quit attempt, often to relieve specific withdrawal symptoms (Table 2). A smaller retrospective study of non-treatment-seeking adults also found up to one-third of subjects increasing legal substance use during their quit attempt (Copersino et al., 2006b). In contrast, a prospective study of 19 adult daily cannabis smokers who tried to reduce or quit their use without formal treatment found no change in alcohol or caffeine use over the one month of daily assessment (Hughes et al., 2008). A controlled clinical trial of psychosocial treatment in 450 adults with cannabis dependence also found no change in alcohol use associated with abstinence (Marijuana Treatment Project Research Group, 2004). Thus, whether subjects increase other substance use in response to cannabis withdrawal and abstinence remains unresolved.

Our findings have several implications for the treatment of cannabis dependence. Given that withdrawal symptoms may serve as negative reinforcement for relapse, patients should be monitored for withdrawal and significant symptoms promptly alleviated. We did not observe an obviously greater association between any specific symptoms and relapse, but the commonest symptoms (e.g., insomnia, depression, irritability, anxiety, restlessness) should clearly be a focus of clinical attention. Many cannabis users are concurrent users of alcohol, tobacco, and caffeine. They are at risk for increased use during a quit attempt, with consequent adverse health effects. Clinicians should monitor concurrent substance use and proactively work to forestall any increased use.

Our findings have several implications for the development of DSM-V. Cannabis tolerance and withdrawal were significantly associated, but 47.5% of subjects experienced just one or the other, supporting their continuance as two separate dependence criteria. We are not aware of any other study that evaluated the conjoint distribution of these two dependence criteria in cannabis users.

Cannabis withdrawal, although common in daily users, occurred in some weekly or less frequent users (a population not included in previous studies), suggesting that frequency of use should not limit the diagnosis of withdrawal. The initial proposed diagnostic criteria for DSM-V (www.dsm5.org, accessed March 19, 2010) require “cessation of cannabis use that has been heavy and prolonged.” Our findings suggest that a stringent interpretation of “heavy and prolonged” may exclude some individuals who are experiencing cannabis withdrawal. The proposed criteria also require experiencing three or more symptoms of withdrawal (from among a list of seven) within several days after cessation of use. These requirements are consistent with the experience of cannabis withdrawal in our study sample, as long as “several days” is broadly interpreted. 85.1% of our subjects experienced at least three withdrawal symptoms, and the mean onset after cessation of use was 3–5 days for mood symptoms, 3–6 days for insomnia, and 2–4 days for most physical symptoms.

Although subjects were living in the community, rather than in a controlled environment, during their quit attempt, other substance use likely did not confound cannabis withdrawal. Most subjects were using legal substances (caffeine, alcohol, tobacco) prior to their cannabis quit attempt, but only 7.9%–12.6% decreased their use at the time, thereby putting themselves at risk for a concurrent withdrawal syndrome. In addition, tobacco use prior to the quit attempt was not significantly associated with number of withdrawal symptoms reported, as might be expected if concurrent nicotine withdrawal were confounding reporting of withdrawal symptoms. Few subjects were using illegal drugs or psychoactive medications (<15% in each

category); even fewer (<10%) were using at least 5 days per week (the average frequency of cannabis use in the month prior to the quit attempt), and few (<5% in each category) decreased their drug use during the quit attempt, making them at low risk for another drug withdrawal syndrome. Large-scale retrospective survey studies have found little or no difference in prevalence of cannabis withdrawal symptoms between subjects with or without other substance dependence (Agrawal et al., 2008; Hasin et al., 2008).

This study has several limitations. Data were obtained by retrospective self-report without external corroboration, as is true of most studies of cannabis quitting. There is evidence that cannabis users not in treatment give reliable retrospective self-report about their cannabis use histories (Fendrich and Mackesy-Amiti 1995; Ensminger et al., 2007) and withdrawal symptoms (Mennes et al., 2009). In addition, the pattern of responses to some withdrawal symptoms suggests that subjects were giving valid responses, rather than just responding from a generalized response set. There were four pairs of apparently mutually exclusive withdrawal symptoms. Only 25 (5.3%) subjects reported both increased and decreased sleep, 18 (3.8%) both increased and decreased appetite, five (1.1%) both increased and decreased sex drive, and five (1.1%) both weight gain and weight loss. This low rate of concurrent reporting of opposite symptoms suggests that subjects were giving valid self-reports. Among the eight sleep-related withdrawal symptoms, there was a two-fold range in prevalence and time of onset and a 2.5-fold range in time of peak effect and proportion taking action to relieve, suggesting that subjects were capable of making distinctions among symptoms.

Subjects were a convenience sample of cannabis users from one city in one country, which may limit the external validity of the findings. Compared with the 2000 US national household population of current (past 12 months) cannabis users without other current drug dependence (except tobacco) and no more than minimal use of other illegal drugs (Substance Abuse and Mental Health Services Administration, 2001), subjects in this study were of similar age and gender distribution, but more likely to be African-American (79.5% vs. 12.4%) and of lower socioeconomic status. Fewer study subjects were married (11.5% vs. 26.1%), employed (35.4% vs. 80.6%), or had college education (22.6% vs. 43.3%).

In summary, we found that cannabis withdrawal is a common, clinically significant syndrome among adult users not seeking treatment and without other substance abuse or psychiatric comorbidity. Withdrawal was experienced by those using cannabis less than daily. Cannabis withdrawal may trigger relapse to cannabis use and thus is a legitimate focus of treatment efforts.

Acknowledgments

The authors thank Ms. Janeen Nichels for testing participants, Mr. John Etter for testing participants and data management, and Dr. Susan Boyd for epidemiological comparison with the 2000 US national household population.

Role of funding sources

This study was supported by the Intramural Research Program, National Institutes of Health, National Institute on Drug Abuse, and NIDA Residential Research Support Services Contract HHSN271200599091CADB. The funding sources had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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Table 1
 Characteristics of cannabis withdrawal symptoms reported by 469 adult, non-treatment-seeking cannabis smokers

Withdrawal symptom	% (n) reporting	Onset after quitting* (days)	Peak intensity*	Time of peak intensity* (days)	Duration of symptom* (days)	% (n) taking action to relieve
Craving for cannabis	75.7% (355)	2.6 (5.2)	4.2 (1.1)	9.3 (28.2)	113.8 (656.0)	76.3% (271)
Improved memory	27.9% (131)	12.5 (11.2)	3.8 (1.2)	36.2 (63.7)	376.4 (1404.2)	12.2% (16)
Sleep						
Trouble falling asleep	46.9% (220)	2.7 (4.6)	3.6 (1.2)	6.3 (13.1)	756.1 (9291.1)	77.3% (170)
Waking up during the night	31.1% (146)	3.3 (5.8)	3.6 (1.1)	7.9 (14.8)	172.0 (966.5)	71.9% (105)
Waking up earlier than usual	35.6% (167)	4.2 (6.6)	3.4 (1.2)	8.8 (19.4)	213.2 (1144.3)	53.9% (90)
Sleep more than usual	27.1% (127)	5.9 (8.8)	3.4 (1.1)	19.6 (61.9)	123.8 (421.3)	52.7% (67)
Sleep less than usual	34.1% (160)	4.0 (6.2)	3.4 (1.1)	9.4 (22.5)	241.1 (1241.9)	61.9% (99)
Strange dreams	20.1% (98)	5.8 (7.4)	3.7 (1.3)	15.4 (36.6)	332.2 (1332.5)	39.8% (39)
Vivid dreams	21.8% (102)	6.5 (8.4)	3.8 (1.2)	13.0 (30.7)	128.8 (314.1)	31.4% (32)
Other sleep problem	3.8% (18)	4.9 (8.2)	3.9 (1.1)	7.4 (10.3)	49.6 (101.1)	83.3% (15)
Appetite						
Increase in appetite	29.2% (137)	5.6 (8.6)	3.9 (1.2)	11.5 (25.0)	130.4 (406.6)	69.3% (95)
Decrease in appetite	38.8% (182)	3.7 (5.9)	3.4 (1.2)	7.8 (14.1)	62.2 (155.8)	41.8% (76)
Verbal/Physical Aggression						
Feeling aggressive	24.1% (113)	3.9 (6.5)	3.6 (1.1)	10.7 (19.9)	52.0 (100.2)	78.8% (89)
Insulted, yelled or swore a person	28.8% (135)	3.4 (5.5)	3.8 (1.1)	11.4 (28.6)	70.9 (154.6)	72.6% (98)
Punched or kicked a person	1.92% (9)	5.9 (10.8)	3.3 (1.2)	5.1 (11.0)	45.9 (100.9)	100% (9)
Pushed, grabbed, or slapped a person	3.6% (17)	5.6 (10.1)	3.9 (1.2)	7.1 (10.4)	50.4 (95.5)	82.4% (14)
Pulled a knife, gun, or other weapon	1.1% (5)	2.4 (1.7)	3.6 (1.3)	3.4 (3.8)	17.2 (25.0)	100% (5)
Threw or broke something	14.7% (69)	6.3 (8.6)	3.3 (1.2)	9.0 (11.9)	217.8 (1367.3)	75.4% (52)
Physically attacked a person	1.5% (7)	1.2 (1.1)	3.5 (1.0)	1.9 (2.6)	146.4 (287.7)	100% (7)
Sex Drive						
Increase in sex drive	26.0% (122)	6.2 (8.6)	4.0 (1.1)	14.7 (25.1)	246.0 (1122.2)	71.3% (87)
Decrease in sex drive	15.6% (73)	7.2 (9.4)	3.4 (1.2)	9.5 (10.7)	63.3 (136.1)	46.6% (34)

Withdrawal symptom	% (n) reporting	Onset after quitting* (days)	Peak intensity* (days)	Time of peak intensity* (days)	Duration of symptom* (days)	% (n) taking action to relieve
Mood Symptoms						
Feeling sad, depressed	45.1% (211)	4.2 (6.3)	3.5 (1.3)	11.3 (24.6)	122.2 (489.6)	75.4% (159)
Feeling irritable, "jumpy"	45.0% (211)	3.9 (6.7)	3.7 (1.1)	14.2 (47.0)	113.0 (503.4)	69.2% (146)
Feeling anxious, "nervous"	50.1% (235)	2.9 (5.2)	3.5 (1.1)	10.2 (32.2)	94.8 (344.1)	79.6% (187)
Feeling bored	50.1% (235)	3.8 (7.2)	3.9 (1.2)	22.6 (150.1)	98.8 (438.6)	80.0% (188)
Feeling restless	33.7% (158)	3.6 (5.9)	3.6 (1.1)	11.8 (30.8)	107.3 (478.6)	71.5% (113)
Feeling angry	33.7% (158)	3.7 (6.4)	4.0 (1.1)	11.7 (26.7)	85.6 (232.2)	79.8% (126)
Physical Symptoms						
Physical discomfort	10.0% (47)	4.0 (7.7)	3.9 (1.1)	8.0 (15.8)	47.9 (83.8)	83.0% (39)
Tremor, shakiness	5.5% (26)	2.0 (1.9)	3.0 (1.2)	2.2 (1.9)	44.7 (150.3)	76.9% (20)
Muscle twitches	7.9% (37)	3.1 (4.1)	3.5 (1.3)	9.2 (19.4)	31.1 (70.8)	62.2% (23)
Nausea	8.3% (39)	2.8 (5.2)	3.4 (1.2)	4.9 (10.7)	49.1 (157.5)	59.0% (23)
Vomiting	2.1% (10)	8.2 (12.8)	2.7 (1.7)	11.6 (20.8)	60.1 (120.9)	70.0% (7)
Diarhea	4.3% (20)	1.1 (0.8)	3.3 (1.3)	1.5 (1.0)	8.9 (15.5)	65.0% (13)
Upset stomach	13.0% (61)	3.4 (6.0)	3.3 (1.3)	4.7 (9.9)	33.8 (76.6)	77.1% (47)
Stomach pains	9.6% (45)	2.2 (2.8)	3.6 (1.4)	3.7 (5.7)	24.1 (61.1)	73.3% (33)
Chills	6.0% (28)	2.8 (4.1)	2.7 (1.0)	5.6 (9.6)	43.2 (81.5)	57.1% (16)
Headaches	23.2% (109)	4.2 (6.6)	3.3 (1.2)	10.4 (27.2)	70.8 (171.0)	75.2% (82)
Sweating	7.5% (35)	4.2 (6.5)	3.7 (1.1)	8.6 (17.0)	49.2 (88.6)	68.6% (24)
Weight gain	23.5% (110)	16.2 (11.5)	3.3 (1.3)	34.0 (49.0)	118.8 (178.8)	54.6% (60)
Weight loss	15.1% (71)	12.4 (11.3)	2.7 (1.3)	30.2 (47.1)	100.4 (455.6)	50.7% (36)
Other	10.2% (37)	3.9 (5.9)	4.0 (1.0)	12.3 (33.9)	178.1 (426.4)	60.0% (12)

Data presented as % (n) or mean (standard deviation)

Peak intensity rated on 5-point Likert scale from 1 ("very little") to 5 ("very high")

* N = 432, excluding 37 subjects interviewed less than one month after start of their index quit attempt.

Table 2

Subjects reporting a cannabis withdrawal symptom who used a substance to relieve it

Withdrawal symptom (n)	Cannabis	Alcohol	Sedatives	Tobacco	Anti-depressants	Stimulants
Craving for marijuana (235)	23.1% (82)	30.7% (109)	3.1% (11)	39.2% (139)	1.1% (4)	1.1% (4)
Improved memory (131)	5.4% (7)	0.8% (1)	0% (0)	2.3% (3)	0% (0)	0% (0)
Sleep						
Trouble falling asleep (220)	14.6% (32)	31.4% (69)	14.1% (31)	30.9% (68)	1.8% (4)	1.8% (4)
Waking up during the night (146)	15.8% (23)	32.2% (47)	9.6% (14)	26.7% (39)	1.4% (2)	0% (0)
Waking up earlier than usual (167)	12.0% (20)	18.0% (30)	6.0% (10)	21.0% (35)	1.2% (2)	1.2% (2)
Sleep more than usual (127)	8.7% (11)	15.8% (20)	3.2% (4)	15.8% (20)	0.8% (1)	2.4% (3)
Sleep less than usual (160)	15.6% (25)	21.3% (34)	8.8% (14)	21.3% (34)	0.6% (1)	0.6% (1)
Strange dreams (98)	10.2% (10)	12.2% (12)	4.1% (4)	11.2% (11)	1.0% (1)	1.0% (1)
Vivid dreams (102)	7.8% (8)	7.8% (8)	2.0% (2)	8.8% (9)	0% (0)	1.0% (1)
Other sleep problem (18)	33.3% (6)	16.7% (3)	5.6% (1)	16.7% (3)	0% (0)	0% (0)
Appetite						
Increase in appetite (137)	8.0% (11)	11.0% (15)	1.5% (2)	19.0% (26)	0% (0)	0.7% (1)
Decrease in appetite (182)	9.9% (18)	6.6% (12)	2.2% (4)	11.5% (21)	0.6% (1)	1.1% (2)
Verbal/Physical Aggression						
Feeling aggressive (113)	18.6% (21)	28.3% (32)	5.3% (6)	34.5% (39)	3.5% (4)	3.5% (4)
Insulted, yelled or swore a person (135)	19.3% (26)	22.2% (30)	3.0% (4)	34.1% (46)	1.5% (2)	0% (0)
Punched or kicked a person (9)	11.1% (1)	33.3% (3)	33.3% (3)	44.4% (4)	11.1% (1)	0% (0)
Pushed, grabbed, or slapped a person (17)	23.5% (4)	11.8% (2)	11.8% (2)	23.5% (4)	5.9% (1)	0% (0)
Pulled a knife, gun, or other weapon (5)	0% (0)	20.0% (1)	0% (0)	40.0% (2)	0% (0)	20.0% (1)
Threw or broke something (69)	13.0% (9)	26.1% (18)	5.8% (4)	30.4% (21)	2.9% (2)	1.5% (1)
Physically attacked a person (7)	0% (0)	57.1% (4)	28.6% (2)	42.9% (3)	0% (0)	0% (0)
Sex Drive						
Increase in sex drive (122)	9.0% (11)	13.9% (17)	0.8% (1)	14.8% (18)	0% (0)	0.8% (1)
Decrease in sex drive (73)	15.1% (11)	19.2% (14)	2.7% (2)	15.1% (11)	1.4% (1)	1.4% (1)
Mood Symptoms						
Feeling sad, depressed (211)	19.9% (42)	27.5% (58)	4.3% (9)	32.2% (68)	7.1% (15)	3.8% (8)

Withdrawal symptom (n)	Cannabis	Alcohol	Sedatives	Tobacco	Anti-depressants	Stimulants
Feeling irritable, "jumpy" (211)	13.3% (28)	25.6% (54)	3.8% (8)	32.2% (68)	2.4% (5)	2.4% (5)
Feeling anxious, "nervous" (235)	18.3% (43)	32.3% (76)	4.3% (10)	40.9% (96)	2.1% (5)	2.1% (5)
Feeling bored (235)	14.9% (35)	28.9% (68)	2.6% (6)	28.1% (66)	0.9% (2)	1.7% (4)
Feeling restless (158)	14.6% (23)	20.3% (32)	4.4% (7)	27.2% (43)	1.9% (3)	2.5% (4)
Feeling angry (158)	22.8% (36)	28.5% (45)	5.7% (9)	36.7% (58)	3.8% (6)	3.2% (5)
Physical Symptoms						
Physical discomfort (47)	25.5% (12)	23.4% (11)	8.5% (4)	25.5% (12)	2.1% (1)	2.1% (1)
Tremor, shakiness (26)	30.1% (8)	26.9% (7)	0% (0)	38.5% (10)	0% (0)	0% (0)
Muscle twitches (37)	10.8% (4)	16.2% (6)	0% (0)	18.9% (7)	2.7% (1)	0% (0)
Nausea (39)	18.0% (7)	2.6% (1)	2.6% (1)	15.4% (6)	0% (0)	0% (0)
Vomiting (10)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Diarrhea (20)	10.0% (2)	5.0% (1)	0% (0)	0% (0)	0% (0)	0% (0)
Upset stomach (61)	23.0% (14)	8.2% (5)	0% (0)	13.1% (8)	0% (0)	0% (0)
Stomach pains (45)	13.3% (6)	8.9% (4)	0% (0)	11.1% (5)	0% (0)	0% (0)
Chills (28)	17.9% (5)	21.4% (6)	0% (0)	17.9% (5)	0% (0)	0% (0)
Headaches (109)	14.7% (16)	13.8% (15)	1.8% (2)	21.1% (23)	0% (0)	0.9% (1)
Sweating (35)	8.6% (3)	5.7% (2)	0% (0)	2.9% (1)	0% (0)	0% (0)
Weight gain (110)	6.4% (7)	2.7% (3)	0% (0)	5.5% (6)	0% (0)	0.9% (1)
Weight loss (71)	12.7% (9)	4.2% (3)	0% (0)	15.5% (11)	0% (0)	0% (0)
Other (37)	20.0% (4)	15.0% (3)	0% (0)	30.0% (6)	5.0% (1)	0% (0)