



Published in final edited form as:

*Exp Clin Psychopharmacol.* 2015 December ; 23(6): 415–421. doi:10.1037/pha0000053.

## Sex differences in cannabis withdrawal symptoms among treatment-seeking cannabis users

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### Abstract

Over 300,000 individuals enter treatment for cannabis use disorders (CUDs) in the U.S. annually. Cannabis withdrawal is associated with poor CUD treatment outcomes, but no prior studies have examined sex differences in withdrawal among treatment-seeking cannabis users. Treatment-seeking cannabis users (45 women and 91 men) completed a Marijuana Withdrawal Checklist (MWC) at treatment intake to retrospectively characterize withdrawal symptoms experienced during their most recent quit attempt. Composite Withdrawal Discomfort Scale (WDS) scores were calculated using the 14 items on the MWC that correspond to valid cannabis withdrawal symptoms described in DSM-5. Demographic and substance use characteristics, overall WDS scores, and scores on individual WDS symptoms were compared between women and men. Women had higher overall WDS scores than men, and women had higher scores than men on six individual symptoms in two domains, mood symptoms (irritability, restlessness, increased anger, violent outbursts) and gastrointestinal symptoms (nausea, stomach pain). Follow-up analyses isolating the incidence and severity of WDS symptoms demonstrated that women generally reported a higher number of individual withdrawal symptoms than men, and that they reported experiencing some symptoms as more severe. This is the first report to demonstrate that women seeking treatment for CUDs may experience more withdrawal than men during quit attempts. Prospective studies of sex differences in cannabis withdrawal are warranted.

### Keywords

Cannabis; Withdrawal; Sex Differences

### Introduction

Cannabis is the most widely used illicit drug worldwide (World Health Organization, 2014). In the U.S., about 9 percent of the population meets lifetime criteria for cannabis use disorder (CUD; Haberstick et al., 2013; Stinson et al., 2006). CUD is associated with a

variety of other problems, including mental illness, decreased school performance and lifetime achievement, negative effects on brain development, and respiratory problems (Volkow et al., 2014). Over 300,000 individuals enter treatment for CUDs in the U.S. annually, and treatment outcomes are generally poor (Substance Abuse and Mental Health Services Administration, 2014; Budney et al., 2007; Benyamina et al., 2008). Emerging evidence suggests that cannabis withdrawal is a highly specific indicator of incidence and severity of CUDs (Allsop et al., 2011), and that more severe withdrawal experiences are associated with functional impairment during abstinence and relapse (Budney et al., 2008; Haney et al., 2013).

A significant amount of scientific effort has been devoted to characterizing cannabis withdrawal; laboratory and clinical outpatient studies have established the reliability, validity, and time course of the syndrome. Individuals who abruptly quit heavy, frequent cannabis use often experience mood-related symptoms (depressed mood, irritability, nervousness/anxiety, restlessness, increased aggression, increased anger, violent outbursts), gastrointestinal symptoms (nausea, decreased appetite, stomach pain), physiological symptoms (shakiness, sweating, chills), sleep disturbance (sleep difficulty, strange/wild dreams), and craving to smoke cannabis (American Psychiatric Association, 2013). Withdrawal symptoms generally onset within the first 2–4 days of quitting, peak within the first week of abstinence, and resolve within 2–3 weeks of quitting, with the exception of strange dreams, which may persist for 30 days or longer (Kouri and Pope, 2000; Budney et al., 2003). Studies have also demonstrated that cannabis withdrawal is similar to nicotine/tobacco withdrawal with respect to the type and severity of symptoms (Budney et al., 2008; Vandrey et al., 2008), suggesting it is an important factor that may both promote continuous heavy cannabis use among individuals with CUDs and may influence treatment outcomes.

Similar to other drugs of abuse (e.g., nicotine, opioids and alcohol), several studies have indicated that there are sex differences in the development and presentation of CUDs. Women begin to use cannabis at a later age than men, but progress more quickly to cannabis dependence and treatment entry (“telescoping;” Hernandez-Avila et al., 2004; Ehlers et al., 2010; Khan et al., 2013). Despite having similar patterns of cannabis use, women seeking treatment for CUDs have higher Severity of Dependence Scale scores than men (Copeland et al., 2001). To our knowledge, only two studies have examined sex differences in cannabis withdrawal (Agrawal et al., 2008; Copersino et al., 2010). Agrawal and colleagues (2008) examined symptoms of cannabis withdrawal among individuals who reported cannabis use during the past 12 months using data from the National Epidemiologic Survey on Alcohol and Related Disorders. Women were more likely to report experiencing nausea, while men were more likely to report goosebumps/pupil dilation (Agrawal et al., 2008). Copersino and colleagues examined retrospective reports of quit attempts among non-treatment-seeking cannabis users, and indicated that women were more likely to report nausea during the quit attempt, while men were more likely to report craving for cannabis (Copersino et al., 2010).

The current study improves upon designs of the two prior studies that examined sex differences in cannabis withdrawal. First, both prior studies only reported on the incidence of cannabis withdrawal symptoms (i.e., the percentage of women and men who experienced a given symptom), without examining overall withdrawal or individual symptom severity

(i.e., how uncomfortable or disruptive experienced symptoms were). Data indicate that symptom severity predicts higher levels of functional impairment and that treatments tailored to target specific withdrawal symptoms may be useful (Allsop et al., 2012). Thus, characterizing sex differences in overall withdrawal and in the incidence and severity of individual withdrawal symptoms among treatment-seeking cannabis users has the potential to inform the development of sex-specific treatments for CUDs. Second, the two prior reports provide little data on the frequency and intensity of use of cannabis and other substances among the study samples. This is important because other studies have documented differences in use of cannabis and of other drugs that may influence withdrawal symptoms between women and men (e.g., men may use more cannabis, have more alcohol problems, and smoke more tobacco than women; Copeland et al., 2001; Khan et al., 2013), which could have tempered results. To address this issue, the current study utilized samples of men and women who were well characterized regarding recent cannabis use, and excluded individuals who met DSM-IV-TR criteria for alcohol or other drug use disorders, allowing us to better isolate relations between sex and cannabis withdrawal. Finally, since treatment seeking cannabis users report more withdrawal symptoms than non-treatment seeking users (Pacek and Vandrey, 2014), the current study examined whether the sex differences in withdrawal reported previously (Agrawal et al., 2008; Copersino et al., 2010) generalize to cannabis users seeking treatment.

The aim of this study is to thoroughly characterize sex differences in cannabis withdrawal among treatment-seeking cannabis users. Here, we examine the incidence and severity of cannabis withdrawal symptoms that women and men retrospectively reported experiencing during their most recent quit attempt. Women and men in this sample are comparable in terms of recent cannabis use and other factors (e.g. alcohol use) that may influence withdrawal symptoms.

## Methods

### Participants

Participants were frequent cannabis users presenting for treatment at an outpatient research clinic that was conducting a clinical trial examining an investigational pharmacotherapy for treatment of CUD. Participants were recruited for the trial via flyers, radio ads, newspaper ads, online classifieds ads (craigslist), and word-of-mouth referrals. Participants were recruited for the parent trial and included in the present study if they met the following criteria: 1) were between 18 and 55 years old, 2) reported using cannabis on at least 50 of the past 90 days, 3) were not using cannabis for medical reasons as prescribed by a physician, 4) were interested in quitting cannabis use within the next month, 5) reported that cannabis helps them sleep better at night or that they have had trouble sleeping in the past when abstaining from cannabis, 6) reported making at least one voluntary attempt to quit cannabis in their lifetime, 7) did not report any current major medical problems (e.g., heart failure), 8) reported drinking less than 20 standard drinks/week, 9) did not meet DSM-IV-TR abuse or dependence criteria for any substances other than cannabis, tobacco, or caffeine, 10) did not meet DSM-IV-TR criteria for any current major psychiatric problem

(e.g. major depression, psychosis), and 11) were not enrolled in another treatment study or taking investigational drugs.

## Measures

**Demographics and substance use characteristics**—Participants completed a questionnaire that collected information about basic demographic variables (e.g., age, race, ethnicity, sex, educational attainment) and a Timeline Follow-Back (TLFB; Robinson et al., 2014; Sobell and Sobell, 1992) interview to assess frequency and intensity of substance use (e.g., cannabis alcohol, tobacco, opioids, etc.) during the 90 days prior to the assessment. Since cannabis is not often administered in standardized units (i.e., the amount of cannabis included in a “joint” or “blunt” can vary greatly from user to user), we utilized a cannabis substitute and digital scale in order to better estimate the quantity of cannabis in each consumption unit reported on the TLFB (Norberg et al., 2012). Participants also completed the Marijuana Quit Questionnaire (MJQQ; Boyd et al., 2005; Copersino et al., 2006a), which is a 176-item, individually administered, self-report questionnaire that collects data on demographic information, cannabis use history, and information about prior attempts to quit cannabis use (Copersino et al., 2006).

**Marijuana Withdrawal Checklist**—Participants who experienced at least one prior period of cannabis abstinence completed a 29-item Marijuana Withdrawal Checklist (MWC; Budney et al., 1999; 2003) at study intake to retrospectively assess withdrawal symptoms they experienced during their most recent voluntary quit attempt. The symptoms included in the MWC consists of a mixture of validated cannabis withdrawal symptoms and distractor items: depressed mood, irritability, nervousness/anxiety, restlessness, increased aggression, increased anger, violent outbursts, nausea, decreased appetite, stomach pain, shakiness, sweating, sleep difficulty, strange/wild dreams, craving to smoke cannabis, diarrhea/loose stools, dizziness, muscle spasms/aches, hiccups, stuffy nose, feverish feeling, hot flashes, chills, increased appetite, headaches, fatigue/tiredness, yawning, difficulty concentrating, and general physical discomfort. Participants could also write in a symptom they experienced, but that was not listed elsewhere on the questionnaire. Participants were given the following instructions:

“Please indicate whether or not you have experienced these symptoms and rate their severity the last time you stopped smoking marijuana”

Participants then rated each of the 29 symptoms on a four-point scale (0=none, 1=mild, 2=moderate, 3=severe). A composite Withdrawal Discomfort Score (WDS) was calculated as the sum of the MWC items known to be valid, reliable cannabis withdrawal symptoms (American Psychiatric Association, 2013): depressed mood, irritability, nervousness/anxiety, restlessness, increased aggression, increased anger, violent outbursts, nausea, decreased appetite, stomach pain, shakiness, sweating, sleep difficulty, strange/wild dreams, and general physical discomfort.

## Data Analysis

**Demographics and substance use characteristics**—Demographics were compared between women and men using independent-samples *t*-tests for continuous variables and

Fisher's exact tests for categorical variables. Substance use data (percentage reporting use of all substances, intensity of cannabis, tobacco, and alcohol use, and history of attempts to quit using cannabis) was extracted from the TLFBI interview and the MJQQ and were compared between women and men using *t*-tests/Fisher's exact tests.

**Overall withdrawal scores**—Composite WDS scores, scores on the 14 individual validated cannabis withdrawal symptoms, and scores on “desire or craving to smoke cannabis” were compared between women and men using *t*-tests. “Desire or craving to smoke cannabis” is not typically included in composite WDS scores because its acceptance as a valid symptom of cannabis withdrawal is controversial (Budney et al., 2003) and it is not included in the DSM-V as a symptom of cannabis use disorder. Data are included here as craving has been added a symptom for other drug use disorders, and may be relevant for future studies.

**Incidence of withdrawal symptoms**—The average number of WDS symptoms reported was compared between women and men using a *t*-test. The percentage of women and men reporting experiencing each validated withdrawal symptom at some level (i.e., reporting “mild”, “moderate”, or “severe” and not “none”), and “desire or craving to smoke cannabis” were compared using Fisher's exact tests.

**Severity of withdrawal symptoms**—Mean scores on each validated withdrawal symptom were calculated among the women and men who reported experiencing that symptom to provide a metric of severity. The average severity of all WDS symptoms that were reported and the average severity of individual symptoms reported were compared between women and men using *t*-tests. All analyses were performed using SPSS v.21 (IBM corp.), *t*-tests were 2-tailed, and statistical significance was determined at  $p < .05$ .

## Results

### Participant demographics/substance use

A total of 136 participants (45 women and 91 men) completed the screening interview, met inclusion criteria, and were included in the present analyses. Participant demographics and substance use characteristics are displayed in Table 1. Women and men significantly differed on age of first cannabis use (16.0 years among women vs. 14.2 years among men,  $p = 0.01$ ) and the number of days in the past 90 days that they used cannabis (85.1 days among women vs. 80.0 days among men,  $p = 0.03$ ). Women and men did not differ in amount of cannabis used in the last 90 days or in percentage that met DSM-IV criteria for cannabis dependence. On average, both women and men reported several prior attempts to quit using cannabis in their lifetime, and about three-fourths (i.e., 77% women, 70% men) reported making at least one quit attempt within the past year. About three-fourths of women and men reported using alcohol and tobacco at least once during the past 90 days, but were generally light and infrequent users of these substances. A minority of participants reported sporadic use of other substances (e.g., opioids, MDMA, etc.) in the past 90 days.

## Marijuana Withdrawal Checklist

**Overall withdrawal scores**—Average scores on individual items and composite WDS scores are displayed in Table 2. Women had significantly higher composite WDS scores than men (mean scores of 14.9 vs. 10.6, respectively,  $p < 0.01$ ). Women had significantly higher scores than men on six individual items. These items were in two domains, mood symptoms (irritability, increased anger, restlessness, violent outbursts), and gastrointestinal symptoms (nausea, stomach pain).

**Incidence of withdrawal symptoms**—Incidence of withdrawal symptoms and the average number of symptoms reported among women and men are displayed in Table 3. Overall, women reported experiencing more withdrawal symptoms than men (7.9 symptoms vs. 6.2 symptoms, respectively;  $p < 0.01$ ). A greater proportion of women reported experiencing irritability, violent outbursts, and nausea during their last quit attempt when compared with men.

**Severity of withdrawal symptoms**—Symptom severity ratings among women and men who reported experiencing each withdrawal symptom are displayed in Table 4. The average severity of symptoms reported did not differ between women and men (mean severity ratings of 1.81 vs. 1.66, respectively;  $p = 0.10$ ). However, women who reported experiencing nervousness/anxiety, restlessness, or increased aggression during their last quit attempt reported that these symptoms were more severe compared with men who also reported these symptoms.

## Discussion

To our knowledge, this report is the first examination of sex differences in cannabis withdrawal among treatment-seeking cannabis users, and the first to examine sex differences in both the incidence and severity of cannabis withdrawal symptoms. Women and men were, in general, well-matched on cannabis and other substance use characteristics that may have affected withdrawal. Total withdrawal discomfort was over 40 percent higher (more than half a standard deviation) among women compared with men, and women reported more severe withdrawal than men on six individual symptoms, which clustered in two areas, mood symptoms (irritability, restlessness, increased anger, and violent outbursts), and gastrointestinal symptoms (nausea, stomach pain). Women were more likely to report experiencing an increase in irritability, violent outbursts, and nausea during cannabis abstinence than men, and reported more symptoms in total during their last period of abstinence compared with men. Regarding symptom severity, women who experienced nervousness/anxiety, restlessness, and/or increased aggression reported experiencing these symptoms more severely than men.

It is interesting that withdrawal severity was greater among women though they reported very similar patterns of cannabis use to men, and a significantly later onset of cannabis use compared with men. The neurobiological mechanism for this finding is somewhat uncertain, but recent animal studies suggest a differential expression of the endocannabinoid system by sex (e.g., Castelli et al., 2013; Craft et al., 2013) an influence of sex hormones on cannabinoid receptor binding (Riebe et al., 2010; de Fonseca et al., 1994), and recent human

laboratory research suggests that women are more sensitive to acute cannabis effects than men (Cooper and Haney, 2014). These studies provide some evidence suggesting that sex differences in cannabis withdrawal may be biologically-mediated. However, human brain imaging studies in this area are lacking and few controlled prospective studies evaluating the acute and repeated effects of cannabis exposure have been adequately powered to evaluate sex differences.

The results of this study parallel the findings of prior research conducted on cannabis withdrawal and on other substance use disorders. Overall WDS scores and scores on individual items observed here are comparable to the peak withdrawal scores reported during periods of abstinence in prospective laboratory studies of cannabis withdrawal (e.g., Budney et al., 2003). This suggests that recall of withdrawal severity in this study was valid. Further, the observation that women reported more severe cannabis withdrawal is consistent with other reports on sex differences in withdrawal from alcohol (Stewart & Brown, 1995) and tobacco (Hatsukami et al., 1995; Leventhal et al., 2007). This is potentially important for treatment planning as findings from the larger substance abuse literature suggest women and men differ in both withdrawal and treatment response. For example, evidence suggests nicotine replacement therapy (e.g. Cepeda-Benito et al., 2004; Collins et al., 2004; Hatsukami et al., 1995; Perkins, 2001; Wetter et al., 1999) and varenicline/bupropion combination therapy (Rose & Behm, 2014) may be more effective for men than women, while bupropion alone (Collins et al., 2004) and varenicline alone (Rose & Behm, 2014) may be equally effective in both sexes. Since amelioration of withdrawal symptoms is assumed to drive the efficacy of many pharmacotherapies for substance use disorders, data on sex differences in withdrawal could be used to prospectively inform the development of sex-specific pharmacotherapies.

That said, research on sex differences in CUD treatment response is lacking. A recent Cochrane Review examined 14 studies of various pharmacotherapies for the treatment of CUD (Marshall et al., 2014). Nine out of these 14 used cannabis withdrawal as an outcome measure. Only one of these studies reported on the results of a formal comparison of outcomes by sex (Cornelius et al., 2010). The fact that 13/14 of these studies did not compare outcomes based by sex may at first seem surprising, however, 10/14 had sample sizes of  $N=81$  or less, and more than half of the trials were conducted with samples that were 75% or more male. Thus, it is likely that the vast majority of studies examining pharmacotherapies for CUD are not powered to detect sex differences in treatment response. Given the sex differences in withdrawal reported here, and the sex differences observed in response to pharmacotherapy for other substance use disorders (e.g., nicotine dependence; Hatsukami et al., 1995; Rose & Behm, 2014), studies examining pharmacotherapies for CUD should be appropriately powered to examine sex differences in treatment response.

This study must be considered in light of limitations. First, the study design (retrospective, self-report) limits the conclusions that can be drawn. It is impossible to determine if the sex differences in withdrawal we observed are true differences in withdrawal, or just differences in the way women and men report previously experienced withdrawal symptoms (see Pomerleau et al., 1994). Second, we did not ask women about menstrual cycle phase during their most recent quit attempt. This may have influenced results because symptoms of

cannabis withdrawal overlap with many symptoms women may experience during premenstrual and menstrual phases of the cycle. Third, it is possible that women experienced higher levels of mood and gastrointestinal symptoms than men for reasons unrelated to cannabis withdrawal. Women may experience greater levels of life stress than men (e.g., Klonoff et al., 2000), which could lead to higher levels of mood disturbances (e.g. Fernandez-Guasti et al., 2012) and gastrointestinal disturbances (Mayer et al., 2001). Future studies could partially ameliorate the three above-mentioned limitations by: 1) collecting withdrawal data from participants while they are using cannabis as usual to characterize baseline symptomatology, 2) prospectively examining gender differences in cannabis withdrawal symptoms that occur during biochemically-verified periods of abstinence, and 3) characterizing and/or controlling for menstrual phase during early abstinence. Fourth, the majority of our sample was African American and resided in an urban environment. It is not known if these findings will generalize to treatment-seeking cannabis users with different ethnic, racial, or environmental backgrounds. Though most of the participants in the present study reported use of other substances, mainly alcohol and tobacco, there were no gender differences in the current pattern of other substance use in this sample. Thus, it is unlikely that tobacco, alcohol, or other substance use impacted the study outcomes.

In summary, this study provides preliminary evidence that, among treatment-seeking cannabis users, women experience a greater incidence and severity of mood-related and gastrointestinal cannabis withdrawal symptoms compared with men. These findings extend those of a prior study examining sex differences in cannabis withdrawal among non-treatment-seeking users (Copersino et al., 2010). If the observed sex differences in cannabis withdrawal reported here are validated by prospective studies that employ both objective biological (e.g., neuroimaging, polysomnography) and subjective measures of withdrawal, then the investigation of sex-specific therapeutic interventions is warranted.

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**Table 1****Participant Demographics and Cannabis Use History**

Demographic and substance use characteristics among women (n=45) and men (n=91) included in withdrawal analyses. Data shown are group means ( $\pm$ SD) or % of subjects. Groups were compared using *t*-tests for continuous variables and Fisher's exact tests for categorical variables. Significant ( $p < 0.05$ ) sex differences are highlighted with **bold text**.

Characteristic	Women (n=45)	Men (n=91)	<i>p</i> -value
Demographics			
Age (years)	34.1 (11.1)	32.5 (10.0)	0.41
Race (% Black)	87	84	0.80
Ethnicity (% Hispanic/Latino)	7	4	0.69
Education (years)	12.9 (1.5)	12.4 (1.8)	0.14
Employed (% full-time, part-time, or student)	31	43	0.2
Marital Status (% Married)	2	6	0.66
Substance use			
Cannabis			
<b>Age first use (years)</b>	<b>16.2 (4.5)</b>	<b>14.2 (4.5)</b>	<b>0.01</b>
Years first use to regular use	2.2 (3.8)	2.5 (3.5)	0.67
<b>Days used in past 90 days</b>	<b>85.1 (9.6)</b>	<b>80.0 (14.1)</b>	<b>0.03</b>
Amount used per day in past 90 days (grams)	3.0 (2.9)	2.8 (2.6)	0.71
Cannabis dependent (%)	80	77	0.83
Number of lifetime quit attempts	5.9 (8.7)	8.1 (15.6)	0.39
Made quit attempt in past year (%)	78	70	0.42
Other substances used in past 90 days			
Tobacco (%)	76	71	0.86
Average cigarettes per day (among smokers)	5.9 (6.7)	5.9 (5.0)	0.99
Alcohol (%)	73	74	0.55
Average drinks per week (among drinkers)	4.2 (6.4)	4.6 (5.9)	0.74
Opioids (%)	2	11	0.10
MDMA (%)	7	5	1.00
Cocaine (%)	7	2	0.33
Hallucinogens (%)	2	0	0.33
Amphetamines (%)	0	1	1.00
Synthetic Cannabinoids (%)	0	1	1.00
Sedatives/Hypnotics (%)	0	0	-

*Note.* Cannabis dependence based on DSM-IV-TR criteria.

**Table 2**

## Mean Withdrawal Scores.

Mean ( $\pm$ SD) Withdrawal Discomfort Scale (WDS) scores and mean ( $\pm$ SD) scores on individual symptoms among women (n=45) and men (n=91). Scores were compared between women and men using t-tests.

Significant ( $p < 0.05$ ) sex differences are highlighted with **bold text**.

	Women (n=45)	Men (n=91)	<i>p</i> -value
<b>mean WDS score</b>	<b>14.9 (7.9)</b>	<b>10.6 (6.6)</b>	<b>&lt; 0.01</b>
depressed mood	1.2 (0.9)	1.0 (0.9)	0.20
<b>irritability</b>	<b>1.7 (0.9)</b>	<b>1.3 (1.0)</b>	<b>0.01</b>
nervousness/anxiety	1.0 (1.1)	0.8 (0.9)	0.25
restlessness	<b>1.8 (1.1)</b>	<b>1.3 (1.0)</b>	<b>&lt; 0.01</b>
increased aggression	1.0 (1.2)	0.7 (0.9)	0.07
<b>increased anger</b>	<b>1.2 (1.2)</b>	<b>0.7 (0.9)</b>	<b>&lt; 0.01</b>
<b>violent outbursts</b>	<b>0.7 (0.9)</b>	<b>0.4 (0.8)</b>	<b>0.02</b>
<b>nausea</b>	<b>0.6 (0.9)</b>	<b>0.1 (0.4)</b>	<b>&lt; 0.01</b>
decreased appetite	1.6 (1.2)	1.3 (1.1)	0.13
<b>stomach pain</b>	<b>0.3 (0.5)</b>	<b>0.1 (0.3)</b>	<b>0.02</b>
shakiness	0.3 (0.6)	0.2 (0.4)	0.11
sweating	0.5 (0.8)	0.4 (0.7)	0.25
sleep difficulty	2.3 (0.7)	2.1 (1.0)	0.05
strange/wild dreams	0.7 (0.9)	0.6 (0.9)	0.76
craving to smoke cannabis *	2.3 (0.7)	2.2 (0.9)	0.66

*Note.* WDS = 14-item Withdrawal Discomfort Scale. WDS sum scores range from 0 (no symptoms reported) to 42 (all 14 symptoms reported as severe). Scores on individual symptoms range from 0 (none) to 3 (severe).

\* Craving is reported separately as it is not one of the symptoms included in the WDS total score.

**Table 3**

## Incidence of Withdrawal.

Mean number of WDS symptoms reported, and the percentage of women and men who reported experiencing each individual symptom among women (n=45) and men (n=91). Mean number of symptoms reported was compared between women and men using a t-test and percentage reporting individual symptoms were compared using Fisher's exact tests. Significant ( $p < 0.05$ ) sex differences are highlighted with **bold text**.

	Women (n=45)	Men (n=91)	<i>p</i> -value
<b>mean (<math>\pm</math>SD) number of WDS symptoms reported</b>	<b>7.9 (3.3)</b>	<b>6.2 (3.2)</b>	<b>&lt;0.01</b>
depressed mood	76	64	0.12
<b>irritability</b>	<b>89</b>	<b>73</b>	<b>0.05</b>
nervousness/anxiety	51	51	1.00
restlessness	84	74	0.20
increased aggression	51	43	0.46
increased anger	60	53	0.07
<b>violent outbursts</b>	<b>47</b>	<b>22</b>	<b>&lt;0.01</b>
<b>nausea</b>	<b>40</b>	<b>7</b>	<b>&lt;0.01</b>
decreased appetite	73	67	0.56
stomach pain	22	10	0.07
shakiness	22	14	0.33
sweating	31	26	0.69
sleep difficulty	100	90	0.03
strange/wild dreams	47	40	0.46
craving to smoke cannabis *	100	96	0.30

Note. WDS = 14-item Withdrawal Discomfort Scale,

\* Craving is reported separately as it is not one of the symptoms included in the WDS total score.

**Table 4**

Severity of Symptoms Among Individuals Who Endorsed Them.

Mean ( $\pm$ SD) severity of Withdrawal Discomfort Scale (WDS) symptoms that were reported, and mean severity scores on individual symptoms among women (n=45) and men (n=91). Scores were compared between women and men using t-tests. Significant ( $p < 0.05$ ) sex differences are highlighted with **bold text**.

	Women	Men	<i>p</i> -value
mean severity of any WDS symptoms reported	1.81 (.05)	1.66 (0.5)	0.10
depressed mood	1.5 (0.7)	1.5 (0.6)	0.75
irritability	1.9 (0.7)	1.7 (0.7)	0.21
<b>nervousness/anxiety</b>	<b>1.9 (0.8)</b>	<b>1.5 (0.7)</b>	<b>0.04</b>
<b>restlessness</b>	<b>2.2 (0.8)</b>	<b>1.8 (0.7)</b>	<b>0.02</b>
<b>increased aggression</b>	<b>2.0 (0.8)</b>	<b>1.6 (0.7)</b>	<b>0.05</b>
increased anger	1.9 (0.7)	1.6 (0.7)	0.06
violent outbursts	1.5 (0.7)	1.6 (0.8)	0.74
nausea	1.6 (0.9)	1.3 (0.5)	0.56
decreased appetite	2.2 (0.8)	1.9 (0.7)	0.11
stomach pain	1.2 (0.4)	1.0 (0.0)	0.17
shakiness	1.3 (0.5)	1.1 (0.3)	0.18
sweating	1.7 (0.5)	1.4 (0.7)	0.17
sleep difficulty	2.3 (0.7)	2.2 (0.7)	0.46
strange/wild dreams	1.5 (0.7)	1.6 (0.7)	0.66
craving to smoke cannabis *	2.3 (0.7)	2.3 (0.8)	0.63

Note. WDS = 14-item Withdrawal Discomfort Scale. Severity scores range from 1 (mild) to 3 (severe).

\* Craving is reported separately as it is not one of the symptoms included in the WDS total score.