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Gender differences among treatment-seeking adults with cannabis use disorder: Clinical profiles of women and men enrolled in the Achieving Cannabis Cessation – Evaluating N-acetylcysteine Treatment (ACCENT) study

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Abstract

Background and Objectives—Recent evidence suggests that women may fare worse than men in cannabis trials with pharmacologic interventions. Identifying baseline clinical profiles of treatment-seeking cannabis-dependent adults could inform gender-specific treatment planning and development.

Methods—The current study compared baseline demographic, cannabis use, and psychiatric factors between women (n = 86) and men (n = 216) entering the Achieving Cannabis Cessation – Evaluating N-acetylcysteine Treatment (ACCENT) study, a multi-site, randomized controlled trial conducted within the National Drug Abuse Treatment Clinical Trials Network.

Results—Women reported greater withdrawal intensity (p = 0.001) and negative impact of withdrawal (p = 0.001), predominantly due to physiological and mood symptoms. Women were more likely to have lifetime panic disorder (p = 0.038) and current agoraphobia (p = 0.022), and reported more days of poor physical health (p = 0.006) and cannabis-related medical problems (p = 0.023). Women reporting chronic pain had greater mean pain scores than men with chronic pain (p = 0.006). Men and women did not differ on any measures of baseline cannabis use.

Discussion and Conclusion—Cannabis-dependent women may present for treatment with more severe and impairing withdrawal symptoms and psychiatric conditions compared to cannabis-dependent men. This might help explain recent evidence suggesting that women fare worse than men in cannabis treatment trials of pharmacologic interventions. Baseline clinical profiles of treatment-seeking adults can inform gender-specific treatment planning and development.

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Declaration of Interest

All authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Scientific Significance—Cannabis-dependent women may benefit from integrated treatment focusing on co-occurring psychiatric disorders and targeted treatment of cannabis withdrawal syndrome.

Keywords

cannabis; gender; N-acetylcysteine; treatment; disorder; marijuana

1. Introduction

Cannabis remains the most commonly used illicit drug in the United States (US) with an estimated 22.2 million people aged 12 or older reported past month usage in 2014[1]. Of those who ever use cannabis, approximately 9% will meet lifetime criteria for cannabis use disorder (CUD), increasing to 16.6% for those who first use in adolescence[2,3]. Heavy cannabis use is associated with myriad physical and mental health consequences including cognitive impairment, psychotic disorders, structural and functional brain changes, and respiratory problems, particularly among those who begin using in adolescence[4]. As a result, in 2013 approximately 280,000 individuals in the US (16.8% of all substance use disorder treatment admissions) entered treatment with a primary diagnosis of CUD[5].

Men and women demonstrate differing behavioral, clinical, and neural correlates of cannabis use. While men are more likely to initiate cannabis use and be diagnosed with CUD, women have demonstrated a telescoping effect progressing from first use to disorder and treatment entry more rapidly[6,7]. Women show greater abuse-related potential[8] and report greater withdrawal severity including physiological and mood symptoms[9,10], which may contribute to relapse[11]. Women also experience higher rates of comorbid depression and anxiety, while men experience more comorbid antisocial personality disorder[7]. Likewise, quantity of daily cannabis use (joints per day) more negatively impacts mental health quality of life among women compared to men[12]. In addition, preclinical studies suggest greater vulnerability to anxiogenic, reinforcing, and sedative effects among female compared to male rodents[13,14].

To date, behavioral treatments for cannabis cessation have shown the greatest effectiveness, yet outcomes remain modest and decline over time[15]. Pharmacologic interventions for cannabis cessation have fared poorly, but they have shown promise in treating cannabis withdrawal[15]. Of note, although behavioral studies have not found gender differences in treatment outcome at follow-up[16,17], a recent study of buspirone suggests that women show worse cannabis outcomes than men in the context of pharmacotherapy trial[18].

Examining clinical profiles of women and men at treatment entry may help inform gender-specific treatment development. Only one such study has been reported to date, which examined baseline gender differences in patterns of cannabis use, cannabis-related problems, and general psychopathology in a treatment-seeking sample of adults with CUD[16]. There were no differences in CUD severity or patterns of use, but women reported greater concern about their use than men and were more likely to have a cannabis-using partner, while men were more likely to have a cannabis-using social network, and to report cannabis-related legal convictions. In an effort to better understand gender differences upon entering treatment, the current study analyzed baseline data from Achieving Cannabis Cessation –

Evaluating N-acetylcysteine Treatment (ACCENT), a multi-site, randomized controlled trial conducted within the National Drug Abuse Treatment Clinical Trials Network. Given there is an indication that women show worse CUD treatment outcomes with pharmacologic treatment compared to men [18], we hypothesized that women would present with more severe psychiatric, quality-of-life, and cannabis-related symptoms, which are generally poor prognostic indicators. To our knowledge the current study is the first to examine gender differences at baseline among treatment-seeking adults in a pharmacotherapy trial for CUD.

2. Materials and methods

2.1 Study design

The ACCENT study was a 12-week, double-blind, placebo-controlled, multi-site trial of *N*-acetylcysteine (NAC) combined with abstinence-based contingency management and brief medication management for the treatment of cannabis dependence. A full description of the methods has previously been published[19]. Briefly, 302 participants meeting criteria for CUD were randomized to receive oral administered 1200 mg of N-acetylcysteine or placebo twice daily for 12 weeks. All participants received weekly medication management and twice weekly contingency management for self-report cannabis abstinence confirmed by negative urine cannabinoid tests (UCT). The primary outcome was cannabis use during active treatment.

2.2 Participants

Participants were recruited from six geographically and demographically diverse NIDA CTN settings: Behavioral Health Services of Pickens County (Pickens, SC), The APT Foundation (New Haven, CT), University of Kentucky Medical Center (Lexington, KY), University of California, Los Angeles Integrated Substance Abuse Programs (Los Angeles, CA), The University of Texas Health Science Center at San Antonio (San Antonio, TX), and CODA, Inc. (Portland, OR). Eligible participants were adults 1) age 18–50, 2) who were able to comprehend the study and give informed consent, 3) met DSM-IV criteria for cannabis dependence, 4) were treatment-seeking, 5) had a positive UCT at screening, and 6) for women of childbearing potential, agreed to use birth control. Exclusion criteria included: 1) allergy or intolerance to NAC, 2) pregnancy or lactation, 3) use of NAC or NAC-containing supplements, 4) use of hazardous concurrent medications, 5) currently enrolled in treatment for cannabis dependence, 6) use of synthetic cannabinoids, 7) other substance dependence, 8) positive urine toxicology other than cannabis at randomization (with the exception of amphetamines if the participant had a valid prescription), 9) buprenorphine or methadone maintenance, 10) recent history of asthma, 11) uncontrolled medical or psychiatric illness that could put participant at risk, and 12) current risk of homicide or suicide. Detailed rationale for all inclusion/exclusion can be found elsewhere[19].

2.3 Baseline assessments

2.3.1 Cannabis use—Cannabis use was assessed via self-report and urine drug screen. The Timeline Follow-Back (TLFB) procedure[20] was used to assess self-report cannabis and other substance use for the 30 days prior to screening. In order to account for different potencies and methods of cannabis use, participants were also asked to weigh out a surrogate

substance estimating the amount of cannabis used by different methods (e.g. blunts, bowls, pipes, etc.) as well as the dollar value estimate of that amount to reflect potency. This procedure is designed to provide more accurate estimates of cannabis use[21]. Additional cannabis-specific assessments, all of which are well-validated for cannabis use research, included the Cannabis Withdrawal Scale (CWS)[22] which includes the subscales Intensity and Negative impact; Marijuana Craving Questionnaire (MCQ)[23] which includes the subscales Compulsivity, Emotionality, Expectancy, and Purposefulness; and Marijuana Problems Scale (MPS)[24] which assesses withdrawal symptoms and medical problems. The Obsessive Compulsive Drug Use Scale [25] was adapted for cannabis and used to assess cannabis-related obsessive-compulsive symptoms.

2.3.2 Diagnostic and psychological assessments—Substance use disorders were assessed using the Diagnostic and Statistical Manual of Mental Disorders-IV checklist (DSM-IV)[26]. In order to align with DSM-5 criteria released just prior to commencement of the study, a question pertaining to craving was added and the DSM-IV withdrawal criterion was modified to pertain to cannabis. Co-occurring and lifetime psychiatric disorders were assessed using the Mini International Neuropsychiatric Interview Plus (M.I.N.I 6.0)[27].

Baseline anxiety and depressive symptomology was assessed using the Hospital Anxiety and Depression Scale (HADS)[28], and the Fagerström Test for Nicotine Dependence (FTND)[29] was administered to assess tobacco smoking and nicotine dependence. The quality of life (QOL) measures are pulled directly from the standardized Tier 1 PhenX toolkit designed for NIH clinical trials. Chronic pain was assessed as part of the medical history which assessed the presence of chronic pain lasting longer than past 6 months (yes/no), severity of pain (0–10), and duration of chronic pain (months).

2.4 Data analytic plan

The current study was a cross-sectional analysis of baseline data from a prospective trial of treatment-seeking cannabis dependent adults who were randomized to receive active treatment or placebo. Baseline demographic, clinical, cannabis use, and psychiatric variables were compared across gender for all randomized participants. Continuous and count characteristics are presented as means and associated standard deviations while categorical characteristics are presented as a proportion of the group or total sample size. Baseline demographic characteristics not a part of correlations between cannabis use characteristics, craving, and withdrawal measures were tabulated across the entire cohort and were noted as Spearman’s Rho.

When several measurements or responses are taken on the same participant, related measures can show strong correlations with each other. Many of the baseline characteristics measured during the ACCENT study may have a shared process leading to highly correlated scores. Univariate analysis of these correlated measures ignores the interdependence among the correlated outcomes and could obscure the correct conclusions regarding possible gender differences at study presentation. Due to these multiple correlated characteristics, outcome groups were created and jointly analyzed using multivariate generalized linear mixed effects models (mGLMM). Models were developed using restricted maximum likelihood estimation

and fit specifying a shared random intercept. Prior to multivariate modeling, preliminary univariate models were constructed to assess individual outcomes distributions and assumptions; i.e. is the Poisson or Negative Binomial more appropriate for count variables and are any transformations necessary for continuous variables to verify residual normality. Additional variables were then created to note the distribution and link function associated with each outcome. Covariance estimates between outcome measures were assumed to be consistent between characteristics within groupings and were modeled as compound symmetric. Results are reported as the overall effect of gender on each outcome grouping as well as model based estimates from each characteristic within the group.

Clusters of similar data measures were grouped together for modeling purposes using both clinical relevance and correlations coefficients (Spearman's Rho;). Within the cannabis use characteristics data, variables were grouped as recent 30 day use characteristics (amount of recent cannabis use, amount of cannabis per using day, and percent of days using cannabis)and craving and withdrawal (MCQ, MPS, CWS, and OCDUS scores), and itemized analyses were conducted to examine specific symptomatology. To assess psychiatric conditions and quality of life, data variables were grouped as MINI psychiatric diagnosis (any with at least 2 endorsements per group), drug abuse diagnosis (alcohol, cocaine, benzodiazepine), and quality of life measures (HADS Total, Anxiety and Depression scores and Quality of life measures). Measures of nicotine dependence and pain were each measured on sub-populations only (confirmed smokers and those who endorsed chronic pain) and were analyzed independently of other variables.

Although the parent study was not specifically powered to detect cross-sectional gender differences at baseline, the randomized sample of 302 participants consisting of 216 males and 86 females is sufficiently powered to detect clinically relevant differences at baseline. With the collected sample size, we have 80% power with a type 1 error rate of 5% to detect gender differences in continuous characteristics with Cohen's d of 0.27 or greater. Additionally, the collected sample size will allow for use to find an 11% or greater difference in proportions when the lower proportion is as low as 5% and an 18% or greater difference in proportions when the lower proportion is as high as 50%. Significant differences between genders for the statistical tests on multiple correlated outcomes measures would support the hypothesis that there are true differences present[30,31]. Thus, we did not adjust for multiple comparisons when testing between genders for these outcomes. However, post-hoc analysis of individual items on the CWS were considered statistically significant at a multiplicity adjusted $\alpha<0.003$[32]. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary NC, USA) and no corrections were made for multiple comparisons.

3. Results

3.1 Demographics

The study sample (N = 302) was 28.5% (n=86) female and on average 30.3 years of age (SD = 9.0). The racial and ethnicity breakdown was 64% Caucasian, 28.5% African American, 7.9% other, and 21.5% Hispanic. A majority of the sample (51.3%) were employed, 30.1% were unemployed, and 11% were students and most participants reported drinking alcohol at

some time in the past month (72.2%). Women and men did not differ significantly on any of these variables [all p > 0.2; Table 1]. Women did report higher educational attainment compared to men [$X^2_3 = 8.0$, p = 0.046] with over 73% reporting some college or college degree, while only 56% of men reported achieving that level. Each demographic variable was independently added as a covariate to the multivariate models. Covariates were retained in adjusted models when 1) they were significantly associated with the jointly modeled outcome variables or 2) show evidence of a confounding effect between gender and the jointly modeled outcomes.

Initially each mGLMM was adjusted for educational attainment, age, race, employment, and recent drinking behavior; covariates that provided no evidence of significance or confounding with gender in each model were removed.

3.2 Cannabis use, craving, and withdrawal

Amount and frequency of cannabis use was significantly (positively) correlated with cannabis craving (MCQ), obsessive-compulsive drug use (OCDUS), and cannabis withdrawal (CWS) scores [all p < 0.01; Table 2]. Similarly, the MCQ, CWS, marijuana problem scale (MPS), and OCDUS were also all positively correlated within the sample [p < 0.01]. The relationship between the cannabis use, craving, and withdrawal variables was similar in men and women for most measures. However, in women the CWS scores (both intensity and negativity) were positively correlated with the amount and frequency of cannabis use [Rho > 0.25] while the relationship was attenuated in the male subgroup [Rho < 0.16].

The total amount and frequency of cannabis use in the 30 days prior to study baseline as well as baseline cannabis withdrawal and craving were tabulated and compared between women and men (See Table 3). Men and women did not have differing patterns of use in the 30 days prior to study entry [$F_{1,298}$=0.7; p=0.644]. There were no significant differences in total amount of use [t_{296}=−0.6; p=0.532], the number of using days [t_{296}=0.4; p=0.357], or the amount of use per using day [t_{296}=0.0; p=0.974]. However, men and women did differ on withdrawal and craving measures [$F_{1,298}$=37.8; p<0.001]. Women had greater Total [t_{276}=8.7; p<0.001], Intensity [t_{276}=4.2; p<0.001] and Negative Impact [t_{276}=4.5; p<0.001] scores on the CWS, and endorsed withdrawal symptoms [t_{276}=2.2; p=0.031] and medical problems [t_{276}=2.3; p=0.023] on the MPS more often compared to men. Total craving (via MCQ) and subscale scores as well as the OCDUS did not differ by gender. Secondary itemized analysis of the CWS was done to elucidate what symptomology influenced gender difference in both withdrawal and negative impact scores; the analysis revealed greater symptom severity in women on hot flashes [1.9(3.2) vs. 0.5(1.7), p = 0.001], and numerically greater (though not statistically-significant based on the adjusted cutoff of p < 0.003) symptom severity on headaches [2.6(3.3) vs. 1.4(2.6), p = 0.005], mood swings [3.0(3.6) vs. 1.8(2.6), p = 0.017], and felt irritated [3.3(3.6) vs. 2.1(2.9), p = 0.021]. Similarly, women also reported greater negative impact compared to men on headaches [2.4(3.2) vs. 1.3(2.6), p = 0.001] and hot flashes [1.7(3.1) vs. 0.4(1.4), p = 0.001], and numerically greater negative impact on felt nauseous [1.4(2.8) vs. 0.7(1.8), p = 0.039], mood swings [2.8(3.4) vs. 1.7(2.6), p = 0.017], felt irritated [3.2(3.5) vs. 2.0(2.8), p = 0.017], woke

up early [3.3(3.7) vs. 2.3(3.3), p = 0.029], stomach ache [1.8(2.9) vs. 1.0(2.1), p = 0.022], and nightmares/strange dreams [1.7(3.1) vs. 0.8(2.0), p = 0.009].

3.3 Psychiatric conditions

Overall, women were more likely to have a positive diagnosis on the M.I.N.I. as compared to men [$F_{1,301}$=4.83; p=0.029; See Table 4]. Specifically, women were more likely to be diagnosed with lifetime panic disorder [t_{279}=2.1; p = 0.038] and current agoraphobia [t_{291}=2.31; p = 0.022] on the MINI. Women had significantly lower quality of life ratings compared to men [$F_{1,301}$=11.4; p<0.001]. Women were more likely to have increased HADS total scores compared to men [t_{288}=3.3; p = 0.001]; primarily driven by higher scores on the anxiety portion of the questionnaire [t_{288}=2.3; p = 0.020]. Women also noted a greater number of days that their “physical health was not good” [t_{288}=2.8; p = 0.006]. However, women did not note an increase in number of days that their “mental health was not good” or days that they were “kept from their usual activities” compared to men.

3.4 Other drug use

Although men showed numerically higher rates of substance abuse, there was no statistical difference in the overall rate of endorsement [$F_{1,301}$=0.3; p=0.593; See Table 4]. Women were less likely to have co-occurring alcohol abuse than men (14.0% vs. 24.3%), but the relationship failed to achieve statistical significance [t_{301}=1.9; p = 0.054]. However, among participants reporting having at least 1 drink in the past 30 days, women reported significantly fewer total standard drinks than men [15.1(18.7) vs. 27.0(35.3), p = 0.013]. Neither nicotine dependence as assessed by the FTND [p = 0.303], nor cigarette smoking frequency [p = 0.862] or quantity [p=0.346] differed by gender.

4. Discussion

The current study investigated baseline gender differences in treatment-seeking cannabis-dependent adults in a pharmacotherapy trial. Clinical profiles varied significantly by gender with women having a more severe presentation than men in several domains. Women reported greater total withdrawal severity and negative impact of withdrawal symptoms than men. More specifically, women had higher severity scores on physiological (headaches, hot flashes) and mood symptoms (irritability, mood swings), and greater negative impact scores on physiological (headaches, nausea, stomach ache, hot flashes), mood (mood swings, irritability), and sleep symptoms (waking up early, nightmares). These findings replicate and extend existing evidence. Copersino and colleagues[9] assessed withdrawal symptoms during a serious quit attempt in 104 non-treatment seeking cannabis users and found greater likelihood of a physical withdrawal symptom (upset stomach) among women. A recent study of 136 treatment-seeking cannabis users found that women reported greater withdrawal severity during their most recent quit attempt compared to men, specifically on mood and gastrointestinal symptoms, as well as greater incidence of irritability, violent outbursts, and nausea [10]. Our results provide new evidence that the negative impact of withdrawal is greater on women compared to men, especially in physiological and mood domains. To note, our assessment timeframe was “past 24 hours,” rather than “most recent” or “most serious” past quit attempt. Given this limited timeframe, it is possible that the symptoms reported

represented current state discomfort not related to cannabis withdrawal; however, the significant differences in responses still suggest that such symptoms (physiological, mood, sleep-related) are important therapeutic targets, particularly for women.

Results from the current study show greater co-occurrence of anxiety and anxiety disorders in women compared to men. Women reported significantly more anxiety symptoms and had greater likelihood of being diagnosed with agoraphobia (current) and lifetime panic disorder. Findings from the largest treatment study to date, the Marijuana Treatment Project (N = 450), found that baseline anxiety was associated with more marijuana-related problems at 4- and 9-month follow-up among women compared to men [33]. However, change in anxiety score over time was more strongly associated with cannabis use outcomes among men. While it appears women are more prone to co-occurring anxiety disorders, how those disorders impact treatment is unclear. It may be that anxiety symptoms are more specific to cannabis use among men, while more generalized in women, thus contributing to cannabis-dependence being more treatment refractory in women, as some evidence suggests[18,34].

Health-related quality of life and measures of physical well-being were assessed as indices of daily functioning in cannabis-dependent adults in this study. Compared to men, women had more days of poor physical health. Likewise, women with chronic pain reported higher pain levels than men with chronic pain, and significantly more cannabis-related medical problems. The analgesic properties of cannabis have been widely studied in clinical trials showing efficacy in decreasing pain sensitivity and tolerance [35], and reducing neuropathic pain [36,37]. Women may therefore be at greater risk for using cannabis to manage chronic pain.

The significant differences in clinical characteristics between treatment seeking men and women suggest that gender-tailored interventions for cannabis use may be needed. Since female cannabis users show elevated rates of anxiety disorders compared to males, integrated care targeting anxiety is one area of investigation. In a small trial, de Dios and colleagues (2014) explored the utility of a motivational and mindfulness intervention targeting anxiety in young adult female cannabis users, and reported some improvements in cannabis use outcomes. Given our results, women may also benefit from interventions targeting both physical and psychological cannabis withdrawal symptoms, chronic pain, as well as sleep. For example, a trial of zolpidem alone or zolpidem in combination with nabilone during cannabis withdrawal (N = 11) found improved withdrawal-related sleep disruptions in both conditions, and decreased cannabis self-administration in the combination condition (Herrmann et al., 2016). Larger trials of this nature would allow investigation of gender as a potential moderator.

Although this is one of the largest studies of treatment-seeking cannabis dependent adults, there are limitations worth noting. Inclusion/exclusion criteria limit the generalizability of these findings, as potentially important and common issues (e.g., other substance dependence, serious psychiatric comorbidities) were exclusionary. In addition, this study is an analysis of baseline differences, not treatment outcomes, between treatment seeking women and men. However, understanding clinical profiles upon treatment entry is important to consider when interpreting clinical outcomes.

5. Conclusions

The current study examined gender differences in clinical profiles of treatment-seeking cannabis-dependent adults in a pharmacotherapy trial. We replicated previous findings including greater co-occurrence of anxiety disorders and more severe withdrawal symptoms in women, and provided new evidence on the negative impact of withdrawal symptoms, higher levels of chronic pain, and more cannabis-related medical problems in women. Furthermore, we provide a profile of treatment seeking cannabis-dependent women. Compared to men, women appear to enter treatment under especially challenging circumstances involving severe withdrawal symptoms, co-occurring psychiatric disorders, and poor overall quality of life. These important gender differences can inform gender-specific treatment planning, such as women potentially benefitting from integrated treatment focused on co-occurring psychiatric disorders and targeted interventions for cannabis withdrawal syndrome.

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Table 1

Basic Demographics

	Overall Sample (N = 302)	Male (n = 216)	Female (n = 86)	p-value
	M(SD)	*M(SD)*	*M(SD)*	
Age	30.3(9.0)	30.2(9.0)	30.4(9.1)	0.804
Alcohol Drinks in Past 30 Days *	5(20)	6(24)	5(13)	0.271
	%	*%*	*%*	
Any Alcohol Drinks Past 30 Days	72.2	72.2	72.1	0.982
Race				0.322
Caucasian	63.6	66.2	57.0	
African-American	28.5	26.4	33.7	
Other	7.9	7.4	9.3	
Education				***0.046***
Some college	35.4	33.8	39.5	
College Degree	25.8	22.7	33.7	
Employment Status				0.662
Employed	51.3	50.5	53.5	
Unemployed	30.1	30.1	30.2	
Students	11.6	13.0	8.1	

* Data shown as median and quartile range due to preponderance of zeros.

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Table 2

Correlations of continuous outcome variables; correlations are noted as Spearman Rank Order Correlation Coefficients.

	Percent of Days Using	Total Cannabis Use	Amount per Using Day	MCQ TS	MCQ Comp	MCQ Emot	MCQ Exp	MCQ Purp	Obs. Compl. Use	CWS Total	CWS Int	CWS Neg
Percent of Days Using	-											
Total Cannabis Use	***0.639*** *	-										
Amount per using Day	***0.458*** *	***0.958*** *	-									
MCQ TS	***0.197*** *	***0.330*** *	***0.328*** *	-								
MCQ Compulsion	***0.152*** ‡	***0.330*** *	***0.338*** *	***0.752*** *	-							
MCQ Emotionality	***0.204*** ‡	***0.274*** *	***0.260*** *	***0.870*** *	***0.526*** *	-						
MCQ Expectancy	***0.134*** ‡	***0.237*** *	***0.240*** *	***0.848*** *	***0.468*** *	***0.746*** *	-					
MCQ Purposefulness	***0.172*** ‡	***0.273*** *	***0.267*** *	***0.767*** *	***0.489*** *	***0.524*** *	***0.562*** *	-				
Obs. Compl. Use	0.089	***0.276*** *	***0.295*** *	***0.482*** *	***0.501*** *	***0.409*** *	***0.349*** *	***0.341*** *	-			
CWS Total Score	0.061	***0.169*** ‡	***0.180*** ‡	***0.496*** *	***0.425*** *	***0.477*** *	***0.399*** *	***0.289*** *	***0.501*** *	--		
CWS Intensity	0.030	***0.150*** ‡	***0.169*** ‡	***0.504*** *	***0.412*** *	***0.482*** *	***0.409*** *	***0.314*** *	***0.494*** *	***0.955*** *	-	
CWS Negativity	0.082	***0.165*** ‡	***0.171*** ‡	***0.443*** *	***0.385*** *	***0.444*** *	***0.365*** *	***0.238*** *	***0.463*** *	***0.948*** *	***0.829*** *	-
MPS	0.020	0.067	0.058	***0.332*** *	***0.338*** *	***0.328*** *	***0.228*** *	**0.136**	***0.476*** *	***0.589*** *	***0.577*** *	***0.539*** *

Percent of Days Using, Total Cannabis Use, and Amount per Using Day: Noted as taken from the TLFB for 30 days prior to study entry.

Age at First Use: Self-reported age at first cannabis use

Years to Abuse and Years to Dependence: Difference in self-reported Age of Abuse/Dependence and self-reported Age at First Use.

MCG TS: Marijuana Craving Questionnaire Total Score

Obs. Compl. Use: Obsessive Compulsive Drug Use Scale

CWS: Cannabis Withdrawal Scale

MPS: Marijuana Problems Scale.

‡ P<0.05

* P<0.001

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Table 3

Cannabis Use and Cannabis Withdrawal. Data are shown as means and standard deviations for continuous characteristics and percentages for dichotomous characteristics. Aggregate data are presented for women, men and the entire cohort. Global model p-values are shown for each model as well as comparisons for each measure across gender.

Model	***Dependent Variables***	**Overall (N = 302)**	**Men (n = 216)**	**Women (n = 86)**	**p-value**
		M(SD)	***M(SD)***	***M(SD)***	
Amount/Frequency of MJ Use[1]					0.417
TLFB (past 30 days)	Percent of days using	86.8(20.7)	86.6(21.1)	87.2(19.8)	0.269
	Total cannabis use (grams)	79.1(152.4)	83.4(174.4)	68.1(70.4)	0.357
	Amount per using day (grams)	2.9(5.2)	3.1(6.0)	2.5(2.3)	0.964
Withdrawal and Craving[2]					***<0.001***
	MCQ – Total Score	50.7 (17.1)	49.2 (17.1)	52.3 (17.1)	0.376
	Compulsive	9.2 (5.2)	9.0 (5.0)	9.4 (5.6)	0.917
	Emotionality	11.8 (5.7)	11.6 (5.6)	12.1 (5.8)	0.883
	Expectancy	14.0 (5.1)	13.5 (5.0)	14.5 (5.3)	0.776
	Purposefulness	15.2 (5.0)	14.7 (5.2)	15.6 (4.4)	0.796
	Obsessive Compulsive Drug Use Scale	21.7 (9.1)	21.1 (9.3)	22.2 (8.4)	0.742
	Cannabis Withdrawal Scale – Total Score	86.3 (68.0)	71.4 (59.7)	101.3 (81.8)	***0.001***
	Intensity	46.6 (34.9)	39.5 (31.1)	53.6 (41.6)	***0.001***
	Negative Impact	39.5 (35.4)	31.7 (31.2)	47.3 (42.5)	***0.001***
	Marijuana Problem Scale	7.1 (3.9)	7.1 (3.9)	7.0 (4.0)	0.961
		%	%	%	
	Withdrawal Symptoms	50.2	45.1	62.8	***0.031***
	Medical Problems	9.3	6.5	16.3	***0.023***

[1]Results adjusted for age reported at screening

[2]Results adjusted for current employment status

Table 4

Psychiatric conditions, quality of life, and other substance use. Data are shown as means and standard deviations for continuous characteristics and percentages for dichotomous characteristics. Aggregate data are presented for women, men and the entire cohort. Global model p-values are shown for each model as well as comparisons for each measure across gender.

		Overall (N = 302)	Male (n = 216)	Female (n = 86)	p-value
		%	%	%	
MINI Psychiatric Diagnosis[1]					***0.029***
	Any current diagnosis	36.8	33.8	44.2	0.152
	Any lifetime diagnosis	23.5	20.4	31.4	0.067
	MDD, Current	5.0	4.2	7.0	0.266
	MDD, Lifetime	19.9	17.1	26.7	0.084
	Panic Disorder, Current	1.7	0.9	3.5	0.112
	Panic Disorder, Lifetime	4.3	2.8	8.1	***0.038***
	Agoraphobia	15.2	12.0	23.3	***0.022***
	Social Phobia	4.0	4.2	3.5	0.891
	GAD	3.6	3.7	3.5	0.962
	ADHD – Inattentive	12.3	11.1	15.1	0.344
	ADHD – Hyperactive	4.6	4.2	5.8	0.463
	ADHD – Combined	4.6	4.6	4.7	0.890
	OCD	2.7	3.2	1.2	--
	PTSD	1.7	0.5	4.6	--
Drug Abuse Diagnosis[2]					0.593
	Alcohol Abuse	21.5	24.5	14.0	0.054
	Cocaine Abuse	2.7	1.9	4.7	0.176
	Amphetamine Abuse	1.3	1.4	1.2	--
	Opioid Abuse	1.0	0.9	1.2	--
	Benzodiazepine Abuse	1.4	1.4	2.3	0.542
Quality of Life[3]					***<0.001***
	HADS – Total	22.1 (3.4)	21.4 (3.5)	22.7 (3.1)	***0.001***

		Overall (N = 302)	Male (n = 216)	Female (n = 86)	p-value
		%	%	%	
	Anxiety	7.7 (3.2)	7.3 (3.3)	8.2 (3.0)	***0.020***
	Depression	14.3 (2.1)	14.1 (2.1)	14.5 (2.0)	0.328
	Quality of Life (past 30 days)				
	Days mental health not good	5.1 (7.4)	4.6 (7.1)	6.5 (8.0)	0.217
	Days physical health not good	2.8 (5.3)	2.5 (4.7)	3.7 (6.5)	***0.006***
	Days kept from usual activities	3.2 (5.1)	2.9 (6.7)	4.0 (5.9)	0.136
Nicotine Dependence	Fagerström Nicotine Dependence (n = 116)	3.08 (2.28)	3.21 (2.24)	2.75 (2.38)	0.303
Chronic Pain	Avg rating for chronic pain >6 months; n = 54)	4.5 (2.2)	3.9 (2.1)	5.7 (1.7)	***0.006***

Note: GAD = Generalized Anxiety Disorder, OCD = Obsessive-Compulsive Disorder, PTSD = Posttraumatic Stress Disorder, ADHD = Attention Deficit Hyperactivity Disorder. “—” indicates insufficient cell size to conduct analysis.

[1]No additional covariates included in the model

[2]Additionally adjusted for participant race

[3]Additionally adjusted for participant race and recent drinking intensity (past 30 days)