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Prolonged Cannabis Withdrawal in Young Adults with Lifetime Psychiatric Illness

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Abstract

Young adults with psychiatric illnesses are more likely to use cannabis and experience problems from use. It is not known whether those with a lifetime psychiatric illness experience a prolonged cannabis withdrawal syndrome with abstinence. Participants were fifty young adults, aged 18–25, recruited from the Boston-area in 2015–2016, who used cannabis at least weekly, completed the Structured Clinical Interview for DSM-IV to identify Axis I psychiatric diagnoses (PD+ vs PD−), and attained cannabis abstinence with a four-week contingency management protocol. Withdrawal symptom severity was assessed at baseline and at four weekly abstinent visits using the Cannabis Withdrawal Scale. Cannabis dependence, age of initiation, and rate of abstinence were similar in PD+ and PD− groups. There was a diagnostic group by abstinent week interaction, suggesting a difference in time course for resolution of withdrawal symptoms by group, $F(4,46)=3.8$, $p=0.009$, controlling for sex, baseline depressive and anxiety symptoms, and frequency of cannabis use in the prior 90 days. In post hoc analyses, there was a difference in time-course of cannabis withdrawal. PD− had significantly reduced withdrawal symptom severity in abstinent week one [$t(46)=-2.2$, $p=0.03$], while PD+ did not report improved withdrawal symptoms until the second abstinent week [$t(46)=-4.1$, $p=0.0002$]. Cannabis withdrawal symptoms improved over four weeks in young people with and without a lifetime psychiatric diagnosis. However, those with a psychiatric illness reported one week delayed improvement in withdrawal symptom severity. Longer duration of cannabis withdrawal may be a risk factor for cannabis dependence and difficulty quitting.

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Keywords

Marijuana; Cannabis; Mental Health; Cannabis Withdrawal Syndrome; Abstinence; Depression; Anxiety

Introduction

Cannabis use is common among young adults[1], particularly among those with a current or lifetime psychiatric illness[2–6]. For example, national epidemiologic data indicate up to double the prevalence of cannabis use among those with a past year depressive episode versus those without[7]. This high prevalence of comorbidity may be clinically relevant as co-occurring mood and cannabis use disorders may complicate both substance use and mood disorder treatment.

The relationship between cannabis use and psychiatric illness is postulated to be bidirectional[8]. Cannabis use may precipitate or hasten the onset of psychotic[9,10], depressive[11,12], and anxiety disorders[13]. Cannabis use during adolescence and young adulthood has been associated with earlier onset[14–17] and greater severity of mood symptoms[18–20]. Conversely, comorbid psychiatric illness may increase risk for problem cannabis use. Those with more severe depressive symptoms have been shown in longitudinal studies to have higher rates of subsequent cannabis use[4,6], predicting an increase in frequency of weekly cannabis use by up to two-days per week from adolescence into young adulthood[8].

Little is known about the association between lifetime psychiatric illness and the course of cannabis withdrawal symptom severity during the first weeks of cannabis abstinence. Cannabis withdrawal has been identified as a key criterion of cannabis use disorder[21,22], impacting between 35% to 75% of adolescents and young adults with a use disorder attempting to reduce or discontinue use[23]. According to the DSM-V, the cannabis withdrawal syndrome involves the manifestation of three or more of the following six symptoms: irritability or anger; nervousness or anxiety; sleep difficulty (i.e., insomnia, disturbing dreams); decreased appetite or weight loss; restlessness; depressed mood; and at least one physical symptom causing discomfort (i.e., abdominal pain, shakiness/tremors, sweating, fever, chills, headache)[24–26]. Due to the long half-life of Δ9-tetrahydrocannabinol (THC) and its metabolites, the cannabis withdrawal syndrome may last for several days to weeks following last use. Importantly, the presence of withdrawal symptoms with abstinence has been found to be a marker for problematic cannabis use, predicting severity of use, rapid reinstatement of use during a quit attempt, and problems from use[21,26,27] In a sample of adolescent cannabis users followed over one year, greater withdrawal symptom severity was associated with fewer days abstinent[23]

In a separate sample of 110 treatment-seeking emerging adults who were heavy cannabis users, those with significant cannabis withdrawal had a 53% greater risk of earlier resumption of cannabis use than those who did not report significant withdrawal symptoms[28].

While associations have been reported between lifetime psychiatric diagnosis and cannabis use, and between cannabis withdrawal symptom severity and worse cannabis use outcomes, there are no reports to our knowledge of cannabis withdrawal trajectories by lifetime psychiatric diagnosis. It is plausible that those with a current or past psychiatric illness will have a more severe and prolonged cannabis withdrawal syndrome, as it is well known that psychiatric populations experience more intense withdrawal from other substances, such as nicotine[29–33].

We investigated the time course and severity of cannabis withdrawal symptoms during four weeks of incentivized abstinence, and hypothesized that a lifetime psychiatric diagnosis would be associated with a slower rate of withdrawal symptom improvement among young adults who used cannabis at least weekly.

Methods

Participants

Eligible participants were otherwise healthy young adults, aged 18–25, who reported using cannabis at least weekly, recruited via peer referral and advertisements in the community that sought potential participants 'who use marijuana and are between age 18 and 25.' Inclusion criteria, determined via phone screen, included cannabis use in the week prior to the baseline visit, English language fluency, and willingness to stop using cannabis for 30 days. There was no requirement that potential participants wish to permanently discontinue cannabis use.

Assessments

At baseline, current and lifetime diagnoses of Axis I disorders were assessed with the Structured Clinical Interview for DSM-IV (SCID-IV)[34]. For this study, the lifetime psychiatric diagnosis group (PD+) was comprised of participants meeting diagnostic criteria for any current or lifetime Axis I disorder, with the exception that current or prior substance use disorder was not adequate for inclusion. Additional baseline assessments included the Wechsler Test of Adult Reading (WTAR)[35] for predicted full-scale IQ, Mood and Anxiety Symptoms Questionnaire (MASQ)[36], Cannabis Use Disorder Identification Test – Revised (CUDIT-R)[37], and Alcohol Use Disorders Identification Test (AUDIT)[38]. Detailed interviews using a modified Timeline Followback method[39] were conducted at baseline to approximate quantity and frequency of past 90-day cannabis and alcohol use.

At each study visit, cannabis use was assessed with a quantitative urine toxicology assessment and self-report[40]. Cannabis withdrawal symptom severity was assessed using the Cannabis Withdrawal Scale (CWS)[26], a self-report assessment of severity of 19 cannabis withdrawal symptoms (e.g., headache, decreased appetite, irritability) over the past 24 hours using a 10-point Likert scale (0: Not at all to 10: Extremely). The total withdrawal intensity score was created by summing each item score to a maximum withdrawal intensity score of 190.

Intervention

This study was conducted between July and November 2016. A detailed description of procedures has been described previously[40]. All study procedures were approved by the Partners Healthcare Human Subjects Committee. Eligibility was confirmed and written informed consent was performed during this first in-person visit.

Participants were asked to arrive for the baseline assessment after overnight cannabis abstinence. Participants were also asked to refrain from using illicit drugs and alcohol on the day of all study visits. Following baseline assessments, participants began a contingency management (CM) program of financial incentives for four weeks of continuous abstinence[40]. Briefly, participants were enrolled in a four-week abstinence-based incentive program. Participants earned incentives based on a two-track system for attendance and abstinence, with escalating denominations for both attendance and abstinence to encourage study retention and achievement of longer periods of continuous abstinence. The first 35 participants earned $585 for 30 days of abstinence with full attendance ($405 for continuous abstinence and $180 for full attendance). Due to the overwhelming success of the CM paradigm at eliciting 30 days of cannabis abstinence, the payment schedule was reduced by approximately 30% for the final 15 participants ($315 for 30 days of continuous abstinence and $105 for full attendance). Incentives were distributed via reloadable credit cards through Clinical Trials Payer (CT Payer) on the day of the study visit for attendance and upon receipt of the quantitative urinalysis results confirming abstinence (described below).

Urine samples were shipped by overnight courier to Dominion Diagnostics (Kingstown, RI, USA) for quantitative assessment of concentration the 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH) metabolite of THC, using liquid chromatography/tandem mass spectrometry (LC-MS/MS). Quantitative indices were tracked to determine if creatinine-adjusted THCCOOH levels decreased during the four-week monitoring period consistent with abstinence[41], validated using a statistical model developed by Schwilke and colleagues[42]. Cannabis withdrawal rating data from participants who did not attain four weeks of abstinence were included in the analysis from visits with biochemically confirmed abstinence, and were excluded from the analysis for all visits subsequent to self-report or biochemical evidence for non-abstinence.

Analytic Approach

Data were analyzed from baseline and the four consecutive weekly post-baseline ‘abstinence’ assessments using Stata 13.1 and SAS 9.4. We inspected data for non-normal distribution and outliers, and performed rank-based nonparametric procedures (Mann-Whitney U tests, Spearman’s rank order correlations) when assumptions of normality were violated. A marginal model was conducted to detect longitudinal change in cannabis withdrawal intensity across four weeks of monitored abstinence. In the preplanned analysis, the following predictors were entered into the model: history of psychiatric diagnosis (dichotomous: PD+ versus PD−; between-subject effect), study week (range: 0–4; within-subject effect), the interaction of PD group and study week, and any baseline demographic, psychiatric or drug use factors that were different between PD groups. A significant interaction was followed by comparing adjusted means of withdrawal severity after

controlling for baseline covariates, examining the effect of group at each study week as well as the pattern of change in withdrawal severity within each group. As exploratory analyses, correlations were conducted between levels of withdrawal intensity at the time point when PD groups were most different and parameters of cannabis use severity. Finally, sensitivity analyses using marginal models were conducted to evaluate the independent effect of covariates that differed between PD groups on level of cannabis withdrawal symptoms over time. Alpha was set at 0.05 for all statistical tests.

Results

Participant Characteristics

Forty-four of 50 (88%) participants maintained biochemically-confirmed continuous abstinence for the four-week CM protocol, 22 in the PD+ group and 22 in the PD− group. Data were included for all participants at all time points with verified abstinence (see Methods). Those in the PD+ group were more likely to be female and report greater baseline symptom severity on the MASQ Anxious Arousal and Anhedonic Depression subscales. Groups were otherwise comparable across assessed demographic, mood, and alcohol use indices, including frequency and amount of alcohol consumed in the 90 days prior to and during the intervention. The most frequent Axis I psychiatric diagnoses in the PD+ group were major depressive disorder (92%), generalized anxiety disorder (16%), posttraumatic stress disorder (12%), panic disorder (8%), and bulimia (8%). Thirty-two percent of the PD+ sample had more than one psychiatric diagnosis by SCID-IV criteria. Baseline characteristics of the samples are presented in the table.

Cannabis Use Severity

There was no group difference in reported age of cannabis initiation [15.96 (1.67) years for PD+, 15.96 (2.09) years for PD−; t=0, p=1.00) or number of symptoms of cannabis dependence [CUDIT scores: 14.32 (4.49) for +PD, 13.96 (6.29) for −PD; t=−0.23, p=0.82]. Those in the PD+ group reported using cannabis more frequently in the three months prior to enrollment [63.52 (22.53) days for PD+, 44.1 (22.5) days for PD−; t=−3.04, p=0.004].

Trajectories of Withdrawal during Four Weeks of Cannabis Abstinence

The figure illustrates the mean raw withdrawal scores by diagnostic group at each time point.

After controlling for sex, self rating of anxious arousal and anhedonic depression, and past 90 day cannabis use frequency, there was a main effect of time (study week) [$F(4,46) = 3.41$, $p = .02$], but not PD group [F(1,46) = 0.09, p = 0.77] on cannabis withdrawal symptom severity. There was a significant PD group by time (study week) interaction [$F(4,46) = 3.84$, $p = 0.009$], suggesting that the group effect was modified by study week. Groups were not different at baseline and weeks 2, 3, and 4 [p-values >0.32], and there was a trend for the PD + group to have higher withdrawal scores at week 1 [t(46)=1.87 p=0.07]. Additionally, there was significant reduction in withdrawal severity by 8.25 units from baseline to week 1 in the PD− group [t(46) = −2.24, p = 0.03], but no significant change from baseline to abstinent week 1 the PD+ group [t(46) = 0.27, p = 0.79]. From abstinent week 1 to 2, there was no

significant reduction in withdrawal severity in the PD− group [t(46) = 0.83, p = 0.41], but there was significant reduction in withdrawal symptom severity score from week 1 to week 2 in the PD+ group [12.89 units; t(46) = −4.13, p = 0.0002]. Pairwise comparisons for withdrawal symptom severity in weeks 2 to 3 and 3 to 4 in each group were not significant [p-values > 0.48].

Exploratory correlation analyses suggested that withdrawal symptom intensity at one week of abstinence, when PD groups were most different, was positively associated with number of symptoms of cannabis dependence [ρ=0.38, p=0.009], frequency of baseline cannabis use [ρ=0.34, p=0.02], and there was a trend for a negative association with age of first cannabis use [ρ=−0.27, p=0.06]. There was no association between withdrawal symptom intensity at week 1 and amount of cannabis used in the 90 days prior to baseline [ρ=0.23, p=0.12].

Sensitivity Analyses

More frequent cannabis use and more severe self-rated symptoms of anhedonic depression prior to abstinence were associated with more severe withdrawal in the full sample [frequency of cannabis use $F(1,48) = 4.41$, $p = 0.04$; anhedonic depression symptoms: $F(1,48) = 12.24$, $p = 0.001$]. However, neither the effect of frequency of cannabis use nor depressive symptoms was modified by time [cannabis use frequency by time interaction: $F(4,48) = 1.06$, $p = 0.39$; anhedonic depression by time interaction: $F(4,48) = 0.53$, $p = 0.71$], suggesting that neither explained why withdrawal symptoms were changing differently over time among ±PD groups. Sex was neither associated with withdrawal severity [$F(1,48) = 0.49$, $p = 0.49$], nor time-course [$F(4,48) = 0.46$, $p = 0.76$]. In contrast, more severe baseline anxious arousal was associated with more symptoms of cannabis withdrawal [$F(1,48) = 11.48$, $p = 0.001$], and this effect varied with time [$F(4,48) = 3.72$, $p = 0.01$]. At baseline, each unit increase in anxious arousal severity predicted a 2.25 unit increase in cannabis withdrawal symptom severity at baseline [t(48)=3.92, p=0.0003], and this effect remained significant at weeks 1 and 2 [week 1 effect size=2.34, t(48)=3.67, p=0.0007; week 2 effect size=1.91, t(48)=4.50, p=<0.0001]. The effects of anxious arousal on cannabis withdrawal were not significant at weeks 3 and 4 [effect size= 0.54, t(48) = 0.83, p = 0.41 and effect size= 0.56, t(48) = 1.02, p = 0.31, respectively].

Discussion

Though the prevalence of psychiatric illness among young adult regular cannabis users is high, little is known about the impact of psychiatric illness on the time-course of the cannabis withdrawal syndrome. In this sample of 50 young adults who use cannabis regularly, lifetime psychiatric illness was associated with more persistent cannabis withdrawal symptoms during the first weeks of cannabis abstinence. We observed a protracted course of resolution of withdrawal symptoms during cannabis abstinence by one week in those with a current or lifetime psychiatric diagnosis. A protracted withdrawal syndrome by one week may be one factor accounting for differences in cannabis use prevalence, severity, and difficulty quitting among those with a lifetime psychiatric diagnosis.

Findings from this study replicate prior work suggesting that psychiatric diagnosis is associated with several indicators of greater severity of cannabis use[4,6,8]. In our sample, psychiatric history was associated with more frequent and heavier cannabis use in the prior 90 days, but unlike other studies[27,43,44], not with earlier onset of use or more symptoms of a cannabis use disorder.

Consistent with our hypothesis, we found a shift in time to resolution of cannabis withdrawal symptoms, such that those with a psychiatric history required an additional week of abstinence before withdrawal symptoms significantly abated. Importantly, this effect remained after controlling for several potential confounds. Although frequency of cannabis use and anhedonic depression predicted level of withdrawal, their impact was constant over time. Therefore it is unlikely that these factors accounted for the differential rate of resolution of withdrawal symptoms by diagnostic group. Interestingly, severity of cannabis withdrawal after one week of abstinence was associated with more cannabis dependence symptoms, more frequent cannabis use, and earlier age of cannabis use initiation.

There are several potential explanations for the finding of more persistent cannabis withdrawal among young adult cannabis users with psychiatric illness. Young adults with psychiatric illness may be more likely to experience, or are more sensitive to, the symptoms of cannabis withdrawal, which overlap with symptoms of many psychiatric illnesses. This may be due to shared influences on the endocannabinoid system[45–47], and may be particularly apparent in adolescence and young adulthood when the endocannabinoid system is maturing[48]. Despite the fact that only 16% of those in the PD+ group met criteria for a *current* Axis I diagnosis, it is also possible that those young adults with a lifetime psychiatric illness endorse greater withdrawal symptoms due to sub-syndromal current illness. This is supported by the finding that baseline anxiety independently predicted withdrawal in the first two weeks of abstinence. However, purely non-specific symptoms would not be expected to resolve after two weeks of cannabis abstinence.

The present results underscore the need to take into account co-morbidities when assessing cannabis withdrawal and calls for further work investigating the extent of symptomatic overlap between cannabis withdrawal and various psychiatric diagnoses. Yet these study results should be interpreted in light of the study limitations. The sample size was modest, hampering our ability to detect small effects, to detect the impact of specific withdrawal symptoms on the time course of resolution of total withdrawal scores (e.g., negative affect and sleep disruption[49]), and to evaluate potential moderators such as differential effects on withdrawal by sex[50]. The study also involved young adults, and generalizability to older or younger cannabis using populations is not known. Additionally, many prior studies on cannabis withdrawal investigated treatment-seeking cannabis users with more frequent, heavier and earlier initiation of use than the average participant enrolled in the current trial. It is therefore possible that patterns of withdrawal by psychiatric history may differ for more severe patient populations[23, 50–51]. Another noteworthy limitation is that, although the time since last cannabis use was within one week of the baseline visit, it was not standardized beyond that parameter. However, there was not a group difference in duration of abstinence at baseline, and therefore it is unlikely that time since last cannabis use accounted for the differential time-course of cannabis withdrawal observed. Finally, the average score on the

CWS after four weeks of abstinence was not zero, and therefore it is not known whether these remaining low-level symptoms represent a full return-to-baseline. The scale items are non-specific and may reflect normal variability in daily functioning, sub-threshold symptoms common among people with a lifetime psychiatric diagnosis, or persistent withdrawal. This would be clarified by future studies that prospectively examine psychiatric history and cannabis withdrawal during regular use, acute deprivation, short-term sustained abstinence, and longer-term abstinence.

In summary, notwithstanding the above-mentioned limitations, this study supports the potential clinical significance of the presence of lifetime Axis I illness on the duration of the cannabis withdrawal syndrome among young adults, and has implications for prevention programming.[52] As it is plausible that prolonged cannabis withdrawal may reduce success rates of abstinence attempts and increase relapse, and this may differentially impact those with a lifetime psychiatric illness, tertiary prevention interventions may help individuals identify strategies to cope with withdrawal in order to promote sustained cannabis abstinence. Indicated prevention approaches targeting youth with a psychiatric history prior to cannabis debut may be effective in reducing the prevalence of cannabis use and its associated consequences. Finally, universal prevention including behavioral health programs promoting emotional resiliency in all youth may have a downstream impact on cannabis use outcomes. These programs may preferentially target emotional risk factors such as anxious arousal, which was found to be uniquely associated with cannabis withdrawal in this sample and has been linked with severity of withdrawal from other substances including nicotine[53–55]. Particularly as more states are moving toward legalizing commercial markets for cannabis, it is both critical and timely to delineate potential risk factors for problematic cannabis use among the young adults most likely to use the drug and use the drug heavily, as well as develop interventions for those with or at risk for adverse cannabis use outcomes.

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Highlights

- History of psychiatric illness was associated with more frequent cannabis use.
- Cannabis users with psychiatric illness experienced more protracted withdrawal.
- Early withdrawal intensity was associated with indicators of cannabis use severity.
- Baseline anxiety independently also predicted withdrawal in early abstinence.

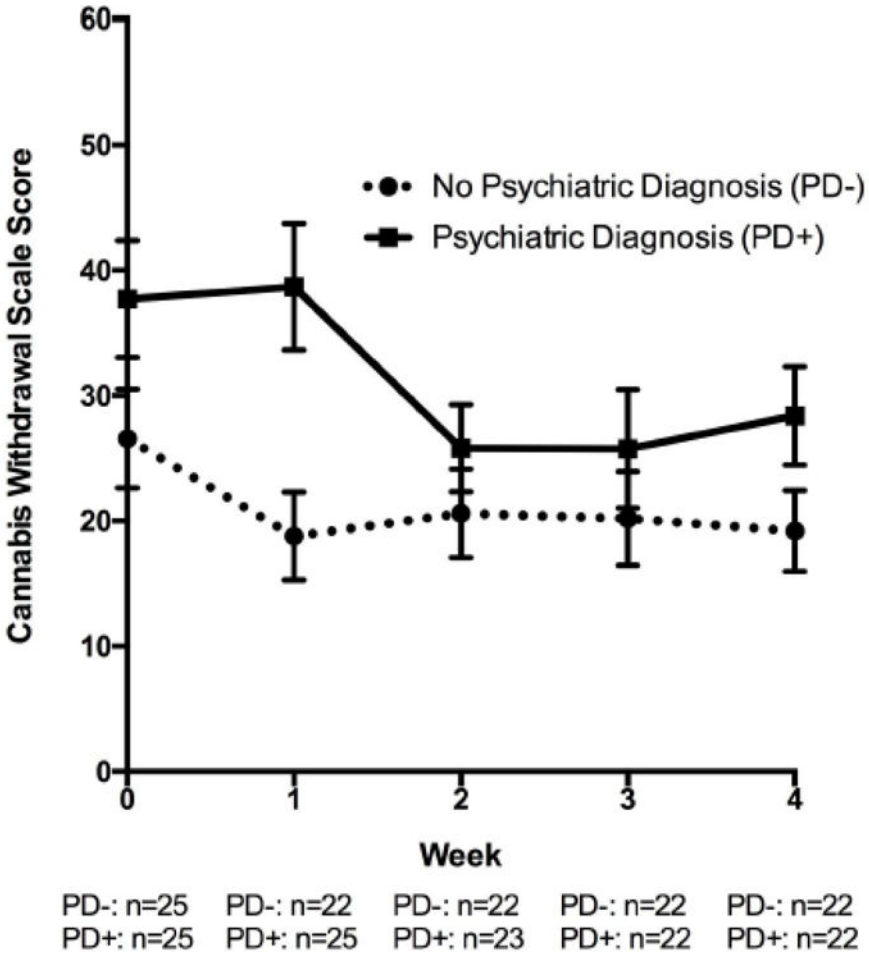

Figure 1.

Weekly Ratings of Cannabis Withdrawal Intensity (Raw Scores) during Four Weeks of Verified Abstinence in Those with and without a Lifetime Psychiatric Illness from the Boston-Area in 2015/16

Note. All values represent raw means and standard errors.

Table 1

Characteristics of Young Adult Cannabis Users Recruited in Boston from 2015 to 2016

	No Psychiatric Diagnosis (PD−; n=25)	Psychiatric Diagnosis (PD+; n=25)	p-value
Demographics			
Gender (n, (%) Female)	7 (28)	15 (60)	0.02
Age (years)	20.9 (1.3)	21.0 (1.8)	0.79
Education (years)	14.5 (1.0)	14.5 (1.6)	0.45
Race (%)			
White	68	64	
Black	20	4	0.22
Asian	4	4	
More than One Race	8	24	
Other	0	4	
Ethnicity (n, (%) Hispanic)	2 (8)	3 (12)	0.64
IQ (WTAR)	108.4 (8.4)	107.2 (8.9)	0.60
Psychiatric History			
General Anxiety Symptom Subscale Score (MASQ)	20 (6.1)	21.8 (5.6)	0.28
Anxious Arousal Subscale Score (MASQ)	22.8 (3.9)	25.6 (5.2)	0.03
General Depressive Symptom Subscale Score (MASQ)	22.4 (8.3)	25.9 (7.8)	0.13
Anhedonic Depression Subscale Score (MASQ)	52.3 (12.6)	60.7 (12.8)	0.02
SCID-IV Psychiatric Diagnoses (Current/Lifetime; n)			
Major Depressive Disorder	N/A	1/23	–
Bipolar I	N/A	1/1	–
Panic Disorder	N/A	2/2	–
Agoraphobia	N/A	1/1	–
Social Phobia	N/A	0/0	–
Specific Phobia	N/A	0/1	–
Obsessive Compulsive Disorder	N/A	0/1	–
Post Traumatic Stress Disorder	N/A	1/3	–
Generalized Anxiety Disorder (current only)	N/A	4	–
Anorexia	N/A	0/0	–
Bulimia	N/A	1/2	–
Psychotic Disorders	N/A	0/0	–
Co-Morbidity (n, (%) with 2+ SCID-IV Diagnoses)	N/A	8 (32%)	–
Alcohol Use			
Age of Initiation (years)	15.1 (1.9)	14.9 (2.2)	0.73
Past 90 Day Alcohol Use			
Days Alcohol Consumed	27 (14.1)	21.8 (11.5)	0.15
Drinks Consumed (Mdn, IQR)	87.0 [70, 127]	71.0 [48, 154]	0.21
Dependence Symptoms (AUDIT)	9.2 (6.8)	8.2 (4.7)	0.53
Alcohol Use During Intervention			

	No Psychiatric Diagnosis (PD−; n=25)	Psychiatric Diagnosis (PD+; n=25)	p-value
Drinking Days in 1st Week/Overall	3.0 (1.9)/10.1 (5.5)	3.5 (2.6)/11.0 (5.8)	0.46/0.57
Cannabis Use			
Age of Initiation (First Use)	15.9 (2.1)	15.9 (1.7)	1.00
Past 90 Day Cannabis Use			
Days Cannabis Consumed	44.1 (22.5)	63.5 (22.5)	0.004
Total Times Cannabis Consumed	101.0 (77.9)	159.7 (176.7)	0.14
Grams Consumed (Mdn, IQR)	20.7 [7.8, 55.5]	36.5 [11.6, 81.0]	0.18
Dependence Symptoms (CUDIT)	14.0 (6.3)	14.3 (4.5)	0.82
Days Since Last Use (Mdn, IQR)	1 [1, 2]	1 [1, 1]	0.07
30-Day Abstinence (n, (%) Abstinent)	22 (88%)	22 (88%)	–

Note: All values are means, standard deviations, unless otherwise noted; AUDIT, Alcohol Use Disorders Identification Test; CUDIT, Cannabis Use Disorder Identification Test; CN-THCCOOH, creatinine-adjusted THCCOOH levels; FSIQ, Wechsler Test of Adult Reading Full Scale IQ; IQR, Interquartile range; MASQ, Mood and Anxiety Symptom Questionnaire; Mdn, Median; MJ, cannabis; SCID-IV, Structured Clinical Interview for DSM-IV; TLFB, Timeline Followback (past 30 and 90 days).