The Long-Term, Prospective, Therapeutic Impact of Cannabis on Post-Traumatic Stress Disorder

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Abstract

Introduction: Given the increasing availability and use of cannabis among individuals with post-traumatic stress disorder (PTSD) and the addition of PTSD as an eligible diagnosis in several U.S. medical cannabis programs, the efficacy of dispensary-obtained cannabis needs to be thoroughly examined.

Materials and Methods: This prospective study assessed PTSD symptoms and functioning every 3 months over the course of a year in two samples of participants diagnosed with PTSD: (1) those with PTSD using dispensary-obtained cannabis (cannabis users) and (2) those with PTSD, who do not use cannabis (controls). Linear mixed-effects models and generalized estimating equations tested whether trajectories of symptoms differed between the two subsamples.

Results: A total of 150 participants (mean [standard deviation] age, 50.67 [15.26] years; 73% male) were enrolled in the study. Over the course of 1 year, the cannabis users reported a greater decrease in PTSD symptom severity over time compared to controls [group × time interaction = −0.32 (95% confidence interval [CI] = −0.59 to −0.05, $R^2 = 0.13$; $t = -2.35$, $p = 0.02$). Participants who used cannabis were 2.57 times more likely to no longer meet DSM-5 criteria for PTSD at the end of the study observation period compared to participants who did not use cannabis (95% CI = 1.12–6.07; $p = 0.03$).

Conclusions: This study provides evidence that the types of cannabis available in recreational and medical cannabis dispensaries might hold promise as an alternative treatment for PTSD. Randomized placebo-controlled trials are needed to assess safety and determine how different preparations of cannabis impact PTSD and functioning.

Keywords: cannabis; control; longitudinal; post-traumatic stress disorder; PTSD

Introduction

As of 2020, 24 U.S. states have legalized medical cannabis as a treatment for post-traumatic stress disorder (PTSD), a condition that affects an estimated 13.8–30.9% of U.S. military veterans.[1,2] However, the majority of physicians do not currently recommend cannabis to their patients with PTSD,[3] despite the availability of cannabis products for PTSD through state-regulated dispensaries. This reluctance is likely due to the general lack of rigorous prospective epidemiological studies and well-controlled clinical trials demonstrating effectiveness of cannabis as a treatment for PTSD. Accordingly, in order for policy makers, providers, and consumers to make evidence-based decisions, studies are needed to determine whether (1) cannabis can help alleviate PTSD symptoms, (2) any medical benefit from cannabis is sustained over time, (3) PTSD patients who use cannabis through these programs lead

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more productive lives, and (4) cannabis is safe and well tolerated in this patient population.

A growing body of research suggests that the endo-cannabinoid (eCB) system, which includes the primary receptors activated by cannabis' phytocannabinoids, CB1 and CB2, might be directly involved in development and maintenance of PTSD (see Hill et al. for review),[4] suggesting that augmentation of the eCB system might hold therapeutic potential. PTSD's primary neurological hallmarks include hyperactivity of the amygdala and hypoactivity of the medial prefrontal cortex (mPFC),[5] features that can also be produced by deficiencies in eCB signaling.[6] Hyperactivity of the amygdala and hypoactivity of the mPFC account for many of PTSD's symptoms, including overall heightened anxiety and startle,[7] attentional bias to fear and trauma cues,[8] as well as impairments in extinguishing traumatic memories.[9]

While primarily at the pre-clinical stage, this work suggests that at least two of the cannabinoids found in the cannabis plant, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), either individually or in combination, could modulate fear-based learning and fear extinction, either directly or indirectly through activation of the eCB.[10] Specifically, administering THC or CBD before extinction learning trials in rats and mice reduces cue-elicited fear,[11,12] blocks reconsolidation of fear memory,[13,14] and facilitates faster extinction of fear memory in animal models of PTSD.[15,16] These findings provide preliminary evidence of cannabis' therapeutic potential for PTSD, as impaired extinction learning is one of the primary mechanisms of PTSD pathophysiology.[17]

Early-stage, open-label clinical studies generally uphold pre-clinical findings and offer support for developing cannabinoid medications for PTSD.[18–22] While the results of these small-scale clinical studies appear promising (e.g., reduced PTSD symptoms, improvements in sleep, nightmares, and hyperarousal), these studies have only tested single-molecule preparations of cannabinoids (i.e., CBD, THC, and synthetic THC). There are no published randomized clinical trials or matched observational studies that specifically test the short- and long-term impact of the types of cannabis being used by medical cannabis users (i.e., dispensary-obtained cannabis) on PTSD symptoms.

Two types of studies are needed to determine whether the types of cannabis currently used by medical cannabis users are an effective treatment for PTSD: (1) experimental and (2) observational. Both methods have a number of advantages and disadvantages, and together would provide the knowledge missing from this literature. A controlled observational study of the impact of dispensary-obtained cannabis on PTSD symptoms was chosen for the current investigation because such a study could provide important information regarding "real-world" and long-term patient use behaviors and the impact of such use on patient symptoms. Moreover, a clinical trial that tests administration of the cannabis products currently commercially available to cannabis users in states with medical and recreational cannabis laws would not be legally permitted in the United States and most other countries, as these products remain illegal under the U.S. controlled substance act and international drug control treaties. The aim of this study was to assess PTSD symptoms and functioning using structured assessments in a sample of 150 Colorado residents (military veterans and non-veterans) with PTSD (half non-cannabis users and half medical or recreational users) over the course of a year.

Materials and Methods

Study design

The study was a 1-year, longitudinal, prospective assessment of PTSD symptoms among Colorado residents with PTSD, which compared PTSD symptoms and functioning among cannabis-using participants and nonusing controls. Structured assessments were conducted at the Denver Veterans Affairs (VA) Medical Center and the de-identified data were analyzed at the San Diego VA Medical Center. The study was approved by the Denver VA, University of Colorado, and San Diego VA Institutional Review Boards. All participants gave written informed consent before enrollment. Participants completed clinician-administered standardized outcome assessments at baseline and then again at 3-month intervals for the subsequent calendar year (i.e., 3, 6, 9, and 12 months). Wrist actigraphs (Philips Respironics Actiwatch) were worn for 1 week after each in-person structured assessment was completed. Actigraphy data were scored based on behavioral sleep medicine guidelines.[23] Participants were compensated up to $300 for completing all assessments and actigraphy.

Participants

Participants were included in the study if they were 18 years of age or older, met DSM-5 criteria for PTSD, and either (1) reported using cannabis at least once per

week from a licensed medical or recreational dispensary in Colorado (cannabis group), or (2) reported no cannabis use in the prior 6 months. Cannabis use was assessed using a timeline follow-back diary, which collected information on past 3-month (1) frequency of cannabis use in days, (2) preparation of cannabis (i.e., flower, concentrate, edible, and tincture), (3) quantity of use per day (in grams for flower and concentrates and milligrams for edibles and tinctures), and (4) THC concentration of cannabis products used. Cannabis use was also verified by urine toxicology. Potential participants reporting symptoms of psychosis and those who were pregnant or breastfeeding were excluded.

After enrollment, all participants were tracked for 1 year to determine whether cannabis users would reduce their use over time or controls would initiate use. Only participants who continued to use (cannabis users) or did not initiate regular use (controls) were included in the final analysis of symptom outcomes.

Outcome assessments

The primary outcome measure was change in total severity score on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[24] across all time points. Secondary outcome measures included the following:

1. Rate of change in PTSD diagnosis based on diagnosis of PTSD on the CAPS-5. PTSD diagnostic status was based on whether the participant met DSM-5 criteria at the time of assessment. Individual symptom severity scores were dichotomized into present or absent based on whether the severity score was rated ≥ 2 (moderate/threshold). To meet DSM-5 criteria for PTSD, participants had to report the presence of at least one criterion B symptom (intrusions), one criterion C symptom (avoidance), two criterion D symptoms (mood/cognitions), and two criterion E symptoms (hyperarousal) over the past 30 days.
2. Change in overall psychosocial functioning based on Inventory of Psychosocial Functioning (IPF)[25] total score
3. Change in patient reports of sleep, as measured by total insomnia symptoms on the Insomnia Severity Index (ISI),[26] and overall sleep quality on the Pittsburgh Sleep Quality Index (PSQI)[27]
4. Change in objective indicators of sleep quality, as measured by wrist actigraph.[28] Actigraphy parameters included the following: change in sleep-onset latency (SOL), sleep efficiency (SE),

wake after sleep onset (WASO), number of awakenings (NWAK), and total sleep time (TST).
5. Change in physical activity level on the International Physical Activity Questionnaire (IPAQ).[29]

Study power

Total enrollment was 150 participants ($n = 75$ per group) to allow for the detection of a small to medium ($d > 0.40$) between-group effect in change in total CAPS-5 scores with 80% power.

Statistical analyses

Initial analyses compared patient characteristics across control and cannabis groups with t-tests and analysis of variances for continuous measures and chi-square tests for categorical measures. The analysis of group differences was conducted to identify any demographic characteristics that might be potential nuisance variables in the primary and secondary analyses.

Subsequent longitudinal analyses evaluated changes in primary and secondary outcomes across groups over time. Continuous outcomes (CAPS-5, PSQI, ISI, IPF, SOL, SE, WASO, NWAK, and TST) were analyzed using linear mixed-effects models and ordinal outcomes (IPAQ) were analyzed using generalized linear mixed-effects models with a cumulative log link. Mixed-effects models included random intercepts and slopes, and fixed effects of group, time, and their interaction. The models were fit using restricted maximum likelihood estimation. A survival analysis was conducted to evaluate group differences in time to PTSD remission. Owing to the small number of measurement occasions, the survival analysis used a discrete-time hazard model with a complementary log-log link.

Mixed-effects and hazard models were conducted in R version 3.6.1[30] using the lme4,[31] ordinal,[32] and survival[33] packages. Primary and secondary outcomes were analyzed using more conservative two-tailed tests for significance. *A priori* alpha for all primary and secondary outcome analyses was set at $p < 0.05$.

Post-hoc analysis

Post-hoc analysis was conducted to describe the observed result of the primary outcome. Linear mixed-effects models tested whether cannabis users showed a rate of symptom decline compared to controls for each PTSD subscale score on the CAPS-5 (e.g., Intrusive memories [CAPS-5 Subscale B], Avoidance [CAPS-5

Table 1. Demographic Characteristics of Sample by Group (N = 150)

Baseline characteristics	Controls (n = 75)	Cannabis users (n = 75)	Total (N = 150)	p-Value
Age, mean (SD)	57.49 (15.32)	44.36 (12.64)	50.67 (15.26)	<0.01
Sex, no. (%)				0.27
Male	58 (77%)	52 (69%)	110 (73%)	
Female	17 (23%)	23 (31%)	40 (27%)	
Veteran status, no. (%)				<0.01
Veteran	71 (95%)	51 (68%)	122 (81%)	
Non-veteran	4 (5%)	24 (32%)	28 (19%)	
Marital status, no. (%)				0.03
Married	40 (53%)	24 (32%)	64 (43%)	
Single	14 (19%)	25 (33%)	39 (26%)	
Cohabitating	1 (1%)	6 (8%)	7 (5%)	
Widowed	5 (7%)	4 (5%)	9 (6%)	
Divorced/separated	15 (20%)	16 (21%)	31 (21%)	
Ethnicity, no. (%)				0.49
Non-Hispanic	62 (84%)	64 (85%)	126 (85%)	
Hispanic	12 (16%)	11 (15%)	23 (15%)	
Race, no. (%)				0.32
Caucasian/white	52 (69%)	51 (68%)	103 (69%)	
Black or African American	10 (13%)	13 (17%)	23 (15%)	
Native American/Alaskan Native	2 (3%)	6 (8%)	8 (5%)	
Multiracial	2 (3%)	1 (1%)	3 (2%)	
Other	9 (12%)	4 (5%)	13 (9%)	
Trauma exposure, no. (%)				
Transportation accident	64 (85%)	67 (89%)	131 (87%)	0.46
Fire or explosion	59 (79%)	55 (73%)	114 (76%)	0.44
Natural disaster	65 (87%)	60 (80%)	125 (83%)	0.27
Serious accident at work, home, or recreational activity	45 (60%)	48 (64%)	93 (62%)	0.61
Exposure to toxic substance	55 (73%)	39 (52%)	94 (63%)	<0.01
Physical assault	66 (88%)	67 (89%)	133 (89%)	0.80
Sexual assault	61 (81%)	64 (85%)	125 (83%)	0.51
Other unwanted sexual experience	39 (52%)	40 (53%)	79 (53%)	0.87
Combat exposure	37 (49%)	39 (52%)	76 (51%)	0.75
Captivity	61 (81%)	49 (65%)	110 (73%)	0.03
Life-threatening illness or injury	60 (80%)	54 (72%)	114 (76%)	0.25
Severe human suffering	54 (72%)	53 (71%)	107 (71%)	0.86
Sudden violent death	54 (72%)	48 (64%)	102 (68%)	0.29
Sudden accidental death	60 (80%)	58 (77%)	118 (79%)	0.69
Perpetrated serious injury/harm/death	57 (76%)	55 (73%)	112 (75%)	0.71
Other	37 (49%)	39 (52%)	76 (51%)	0.74
Screened trauma type, no. (%)				<0.01
Combat trauma	44 (59%)	30 (40%)	74 (49%)	
Sexual trauma	15 (20%)	9 (12%)	24 (16%)	
Other	16 (21%)	36 (48%)	52 (35%)	
Concurrent medications, mean (SD), no.	5.64 (3.04)	3.61 (2.70)	4.63 (3.04)	<0.01
PTSD medications, no. (%)	7 (9%)	4 (5%)	11 (7%)	0.35
Comorbid psychiatric conditions, mean (SD), no.	1.58 (1.66)	1.58 (1.24)	1.58 (1.46)	0.99
PTSD severity, CAPS-5 total score, mean (SD)	36.33 (8.46)	36.88 (8.52)	36.61 (8.46)	0.69
Interpersonal functioning, IPF total score, mean (SD)	3.44 (0.83)	3.16 (1.04)	3.30 (0.95)	0.08
Sleep quality, PSQI total score, mean (SD)	11.65 (4.11)	10.25 (3.77)	10.95 (3.99)	0.03
Insomnia, ISI total score, mean (SD)	14.30 (6.03)	14.60 (6.67)	14.45 (6.39)	0.77
Physical activity, IPAQ, no. (%)				
Low	28 (38%)	13 (18%)	41 (28%)	
Moderate	25 (34%)	26 (35%)	51 (35%)	
High	21 (28%)	35 (47%)	56 (38%)	

Concurrent PTSD medications represent those medications reported by participants as being prescribed specifically for PTSD. Medications included Latuda, Valium, Prazosin, Prozac, Bupropion, Fluoxetine, Sertraline, Trazodone, Citalopram, Wellbutrin, and Duloxetine

CAPS-5, Clinician-Administered PTSD Scale for DSM-5; IPAQ, International Physical Activity Questionnaire; ISI, Insomnia Severity Index; PTSD, post-traumatic stress disorder; SD, standard deviation.

Subscale C], Negative alterations in mood/cognitions [CAPS-5 Subscale D], and Hyperarousal [CAPS-5 Subscale E]).

Results

Sample characteristics

One hundred fifty-nine individuals were screened and consented for a final sample of 150 eligible participants. The overall attrition rate was 33%. One hundred fifty participants (100%) completed the baseline assessment, 117 (78%) completed the 3-month assessment, 103 (69%) completed the 6-month assessment, 97 (65%) completed the 9-month assessment, and 101 (67%) completed the final 12-month assessment. Attrition did not significantly differ by group [χ^2 (1) = 0.16, $p = 0.68$].

Sample demographics appear in Table 1. At baseline, groups significantly differed by number of prescription medications ($\Delta = 2.03$, $t = 4.32$, $p < 0.01$), age ($\Delta = 12.55$, $t = 5.51$, $p < 0.01$), marital status [χ^2 (1) = 11.04, $p = 0.03$], ratio of veterans to civilians [χ^2 (1) = 17.56, $p < 0.01$], and primary trauma type identified at screening [χ^2 (2) = 11.84, $p < 0.01$]. Given the strong correlations between ratio of primary trauma type and veteran status, and age and marital status, only veteran status and age were included in the adjusted models to limit overfitting.

Cannabis use frequency, quantity, and concentration (THC %) are summarized by assessment and appear in Table 2. At baseline, participants in the cannabis group reported that they primarily smoked flower cannabis and that they primarily used THC-dominant cannabis ($n = 63/69$ reporting; 91%); three participants reported pri-marily using CBD-dominant cannabis (4%), and three participants reported primarily using a balanced composition of THC:CBD (4%). This ratio of primary type of cannabis used over the past 90 days did not significantly change across assessment time points [χ^2 (8) = 1.57, $p = 0.99$]. Over the course of the study period, one participant stopped using cannabis and two initiated cannabis use. The two participants in the control condition who initiated and maintained cannabis use during the course of the observation year were excluded from analyses. Patterns of significance were not dependent on whether participants were excluded or included in the models.

Primary outcome

Results of the mixed-effects model for CAPS-5 total scores are displayed in Table 3 and Figure 1 (see Supplementary Figure 1 for estimated marginal means). After controlling for age and veteran status, total PTSD symptom severity decreased in both groups over time, with cannabis users reporting a significantly greater rate of decline over time compared to controls (group × time interaction = -0.32 [95% confidence interval, CI = -0.59 to -0.05], $R^2 = 0.13$; $t = -2.35$ $p = 0.02$).

Secondary outcomes

Twenty-six participants reported PTSD symptom severity patterns that fluctuated between meeting and not meeting current DSM-5 criteria for PTSD at each assessment time point, with remission followed by recurrence and possible subsequent remission. We classified these participants according to the first instance of their final

Table 2. Frequency, Quantity, and Concentration of Cannabis Use by Assessment

	Timeline follow-back assessment (past 3 months)				
	Baseline	3 Months	6 Months	9 Months	12 Months
Frequency (days of use), mean (SD)					
Flower	75.55 (25.97)	75.49 (27.39)	67.96 (32.82)	75.10 (26.32)	67.60 (30.82)
Concentrates	65.50 (33.20)	58.17 (36.35)	53.71 (36.27)	73.22 (27.10)	65.27 (34.15)
Edibles	29.00 (29.32)	33.85 (36.84)	33.42 (34.63)	48.41 (38.85)	90.00 (31.84)
Tincture	29.00 (38.97)	49.00 (—)	0	0	2.00 (—)
Quantity, mean (SD)					
Flower (g)	1.75 (1.86)	1.84 (2.15)	1.95 (2.81)	1.66 (1.44)	1.41 (1.31)
Concentrates (g)	.29 (.37)	1.56 (6.20)	0.22 (0.14)	0.28 (0.23)	1.67 (5.08)
Edibles (mg)	72.19 (75.12)	59.58 (68.23)	52.94 (80.85)	47.93 (50.59)	84.88 (157.49)
Tincture (mg)	47.35 (32.30)	(—)	(—)	(—)	(—)
Concentration of THC, mean (SD)					
Flower	23.71 (4.83)	23.21 (4.76)	23.60 (3.95)	23.64 (3.37)	23.11 (3.99)
Concentrates	72.29 (20.11)	70.72 (22.70)	78.00 (5.37)	77.00 (20.95)	82.17 (3.49)
Edibles	(—)	(—)	(—)	30.00 (33.08)	(—)
Tincture	(—)	(—)	(—)	(—)	(—)

Frequency, quantity, and concentration of past 3-month cannabis use assessed using the TLFB Diary Assessment.
(—) = value not available due to too few cases reporting.
THC, tetrahydrocannabinol; TLFB, timeline follow-back.

Table 3. Mixed-Effects Models for Primary and Secondary Outcomes

	Model estimates adjusting for age and veteran status (95% CI)			
Outcome variable	Intercept	Group	Time	Group×time
PTSD severity (CAPS-5 total score)	35.32 (31.39–39.26)	−2.16 (−5.18 to 0.86)	−0.48* (−0.66 to −0.29)	−0.32 (−0.59 to −0.05)
Sleep quality (PSQI total)	11.11 (9.42–12.80)	−1.59* (−2.94 to −0.23)	−0.11* (−0.18 to −0.03)	−0.01 (−0.12 to 0.10)
Insomnia (ISI total)	15.62 (12.91–18.33)	−0.55 (−2.68 to 1.57)	−0.14* (−0.25 to −0.04)	−0.12 (−0.27 to 0.03)
Psychosocial functioning (IPF total)	3.50 (3.09–3.91)	−0.34* (−0.67 to −0.02)	−0.01 (−0.03 to 0)	0 (−0.02 to 0.02)
SOL, min	27.94 (15.92–39.95)	4.73 (−5.16 to 14.61)	−0.25 (−0.95 to 0.44)	0.30 (−0.68 to 1.28)
SE, %	79.50 (75.28–83.73)	−3.19 (−6.68 to 0.29)	0.07 (−0.12 to 0.26)	0 (−0.26 to 0.27)
WASO, min	51.17 (41.72–60.62)	7.84 (−0.12 to 15.81)	0.31 (−0.18 to 0.80)	−0.38 (−1.07 to 0.31)
NWAK, n	49.51 (40.86–58.16)	−1.96 (−9.38 to 5.46)	−0.73* (−1.15 to −0.30)	0.73* (0.13–1.33)
TST, min	401.48 (364.15–438.82)	−30.94* (−60.48 to −1.39)	0.78 (−0.88 to 2.44)	−0.10 (−2.45 to 2.24)
IPAQ (low, moderate, and high)	—	−1.29 (0.38–1.22)	0.88* (0.79–0.99)	1.05 (0.92–1.31)

*$p < 0.05$.
Intercept = estimated baseline mean for control group.
Group = group difference in estimated baseline mean, control as reference.
Time = slope of control group.
Group×time = difference in slope by group, control as reference.
PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; IPF, Inventory of Psychosocial Functioning; SE, sleep efficiency; WASO, wake after sleep onset; NWAK, number of awakenings; CI, confidence interval.

PTSD diagnostic status in the survival analysis. For example, a participant who reported no longer meeting criteria for a PTSD diagnosis at 3 months, PTSD recurrence at 6 months, and again not meeting criteria for PTSD at 9 and 12 months was classified as no longer meeting PTSD criteria at month 9.

Results of the survival analysis for PTSD diagnosis found a significant difference by group in likelihood of meeting DSM-5 criteria for PTSD over time [χ^2 (1) = 2.21 hazard ratio = 2.57 (95% CI = 1.12–6.07), p = 0.03]. Adjusted for age and veteran status, cannabis users were 2.57 times more likely to no longer meet
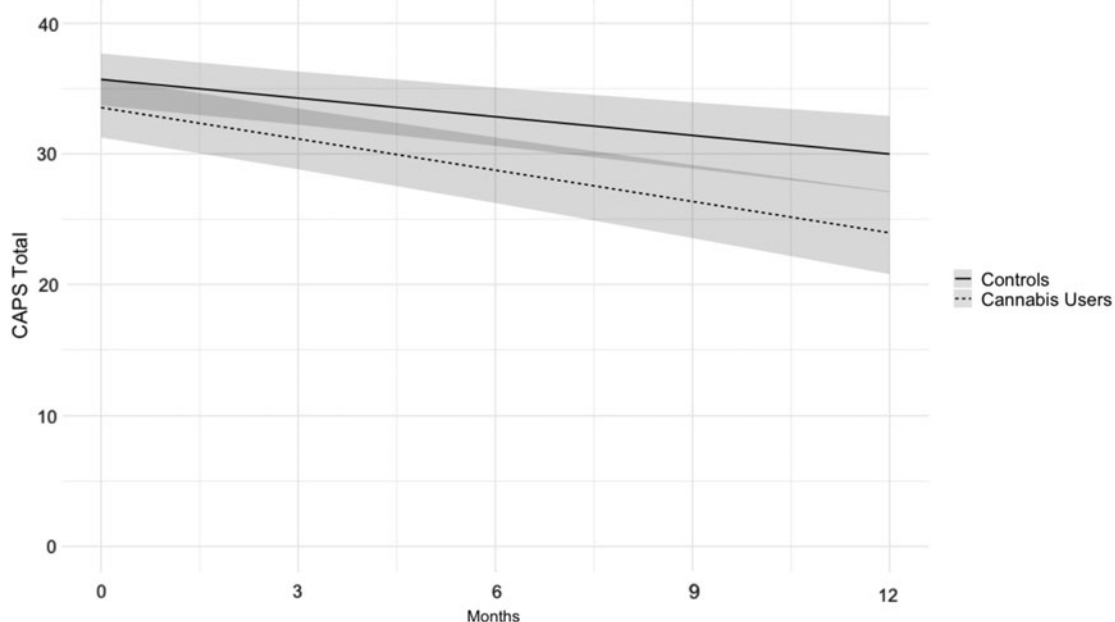
Note. Group x time interaction = -.32 (95%CI = -.59, -.05), t = 2.35, p = .02

FIG. 1. Estimated PTSD symptom severity scores by group, adjusted by age and veteran status. PTSD, post-traumatic stress disorder.

DSM-5 criteria for PTSD at each assessment point after baseline compared to controls (See Fig. 2 for estimated rate of PTSD diagnosis over time).

Analysis of between-group differences over time in rate of change on the patient-reported continuous secondary outcome measures (PSQI, ISI, and IPF) failed to reach significance (Table 3). Analysis of group differences in rate of change between physical activity level (low, moderate, and high on the IPAQ) over time also failed to reach significance ($Z = 1.05$ [95% CI = 0.92–1.31], $p = 0.29$). Mixed-effects models for the objective sleep parameters revealed one significant between-group difference over time for NWAK (Table 3), where cannabis users recorded a lower rate of reduction in number of awakenings after adjusting for age and veteran status (group × time interaction = 0.73 [95% CI = 0.13–1.33], $R^2 = 0.19$; $t = 2.38$, $p = 0.02$).

Post-hoc outcomes

Results of the *post-hoc* analysis of CAPS-5 subscale scores appear in Table 4. Adjusting for age and veteran status, cannabis users showed a significantly greater rate of decline for hyperarousal symptoms compared to controls. While not statistically significant, there was a trend for group differences in avoidance. Rate of change in intrusive thoughts and negative alterations in mood and cognitions failed to reach significance.

Discussion

This study found significant group differences in PTSD symptom severity (primary outcome) and rate of PTSD diagnosis over time, which were driven by greater observed reductions in PTSD hyperarousal symptoms in cannabis users relative to nonusers.

Despite cannabis users and controls showing significant differentiation on the primary outcome, this study found no group difference in any secondary measure of functioning, including overall psychosocial functioning, subjective and objective measures of sleep, and physical activity. It is surprising that the cannabis group reported significantly greater sustained improvements in PTSD symptoms on the CAPS compared to controls, including greater reductions in hyperarousal symptoms, when they did not show differentiation from controls
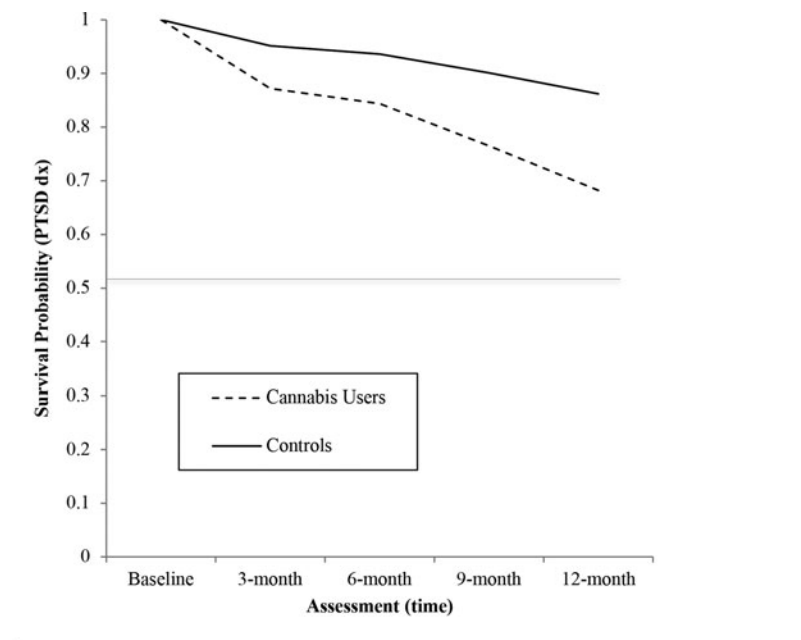
Note. PTSD dx = Participants retaining their PTSD diagnosis based on assessment on the CAPS-5
Estimate of Group Difference = .81 (95%CI = 1.12, 6.07), OR = 2.57

FIG. 2. Fitted survival probability of retaining PTSD diagnosis (dx) by group, adjusted for age and veteran status.

Table 4. Post-Hoc Mixed-Effects Models for CAPS-5 Subscale Scores

Outcome variable	Model estimates adjusting for age and veteran status (95% CI)			
	Intercept	Group	Time	Group × time
Intrusions subscale	9.54 (8.24–10.84)	−0.47 (−1.47 to 0.53)	−0.14* (−0.2 to −0.07)	−0.07 (−0.16 to 0.03)
Avoidance subscale	4.06 (3.47–4.64)	0.42 (−0.06 to 0.90)	−0.05* (−0.09 to −0.02)	−0.04 (−0.04 to 0.01)
Mood/cognitions subscale	11.93 (10.06–13.80)	−1.31 (−2.80 to 0.18)	−0.23* (−0.32 to −0.14)	−0.1 (−0.24 to 0.03)
Hyperarousal subscale	9.80 (8.56–11.03)	−0.7 (−1.69 to 0.29)	−0.07* (−0.13 to −0.01)	−0.11* (−0.21 to −0.02)

*$p < 0.05$.
Intercept = estimated baseline mean for control group.
Group = group difference in estimated baseline mean, control as reference.
Time = slope of control group.
Group × time = difference in slope by group, control as reference.

with respect to sleep and insomnia on sleep-specific measures. This effect might be attributable to cannabis differentially impacting symptoms even within the same subscale (e.g., having a larger effect on difficulty relaxing than insomnia). Moreover, there are many precipitating factors for PTSD-related insomnia and not all are due to hyperarousal. Patients' sleep difficulties might be due to nightmares (which would fall within the intrusive subscale) or depression (mood subscale).

This study's discrepancy between primary and secondary results could also be attributable to heterogeneity in participant dosing, as the study was entirely observational. Previous studies on cannabis and sleep report mixed results for improving sleep and insomnia, although the impact of cannabis on sleep appears largely dependent on cannabinoid ratio and dose (for review see Babson et al.[34]). The two primary active cannabinoids within the cannabis plant, THC and CBD, vary widely in content across plant types,[35] and are associated with very different psychoactive profiles.[36,37] While data on cannabis type were collected as a possible *post-hoc* predictor, variability in type of cannabis that the sample reported using was too limited to include as an independent variable. Indeed, the overwhelming majority of the sample reported using primarily THC-dominant cannabis. This is consistent with previous data showing that military veterans who use cannabis to self-treat PTSD overwhelmingly choose THC-dominant cannabis, even when barriers to access a range of cannabis types are reduced.[38]

Nevertheless, the major limitation of this study is that condition was not randomly assigned. While attempts were made to adjust for demographic differences between groups in the models, there might be other unaccounted for variables that could also predict the observed group differences (e.g., concurrent psychotherapy and changes in non-PTSD medication use throughout the observation period). The cannabis using group was also already using cannabis at the time that observation began; the drop in symptoms among the cannabis group might be attributable to an observer effect. Moreover, because all participants knowingly and intentionally were using or not using cannabis when they entered the study, observed group differences include expectations of cannabis' effects.

An experimental study of cannabis for the treatment of PTSD could theoretically include double-blind administration, and provide more control of factors such as cannabis administration and potency. However, given that cannabis is classified as a Schedule I substance at the federal level, such a study would require the administration of cannabis obtained from the National Institute on Drug Abuse (NIDA). The types of cannabis available through the NIDA Drug Supply System are not representative of the variety or potency of the cannabis used by patients in Colorado or other medical cannabis states.[39] Thus, there is substantial value and ecological validity in the results of this prospective, observational study, which was able to assess a wider range of drug type. Moreover, the long-term assessment period of this study allowed for evaluation of whether cannabis use was associated with not only short-term but also sustained remission of PTSD symptoms, which would be difficult to achieve in a standard randomized control trial. Nevertheless, while potentially hampered by access, randomized control trials of the types of cannabis used by this population are certainly warranted to determine how different preparations of cannabis impact PTSD and functioning.

Conclusions

Despite limitations, this study's primary outcome supports the theory that cannabis should be trialed as a potential therapeutic for PTSD. Participants who used primarily THC-dominant cannabis reported a greater reduction in PTSD symptom severity over time

compared to controls. Cannabis users also showed a greater than two-fold rate of remission from their PTSD diagnosis (defined by no longer meeting criteria for a PTSD diagnosis on the CAPS-5) compared to controls by the 1-year follow-up assessment. *Post-hoc* follow-up indicated that group differences in PTSD symptom severity were likely driven by greater improvements in avoidance and hyperarousal symptoms among the cannabis-using participants.

Additional work is needed to determine how differences in cannabis preparations, route of administration, and dosing regimens impact PTSD symptomology, and whether the results of this study are upheld in randomized and blinded clinical trials. Finally, future studies are needed to determine safety, including risk of side effects and potential impact on suicidality, associated with using cannabis as a treatment for PTSD.

Disclaimer

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Author Disclosure Statement

Author M.O.B.-M. is an employee of Canopy Growth Corporation, during which time he has received stock options, serves on the Board of Directors for AusCann Group Holdings Limited, was a prior employee of Zynerba Pharmaceuticals, and has received consulting fees from Tilray, Inc. Author M.B. is an employee of Canopy Growth Corporation who, in the course of her employment, has received stock options. Author M.J.L. is on the scientific advisory board for FSD Pharma and has received consulting fees from Greenwich Biosciences in the past 2 years. Author R.V. is on the scientific advisory board for FSD Pharma and receives consulting fees from Canopy Growth Corporation and Zynerba Pharmaceuticals. Author K.A.B. is an employee of Jazz Pharmaceuticals who, in the course of her employment, has received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc. Authors A.S. and H.W. declare no conflicts to report.

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Supplementary Material

Supplementary Table S1

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Abbreviations Used

CAPS-5 = Clinician-Administered PTSD Scale for DSM-5
CBD = cannabidiol
CI = confidence interval
eCB = endocannabinoid
IPAQ = International Physical Activity Questionnaire
IPF = Inventory of Psychosocial Functioning
ISI = Insomnia Severity Index
mPFC = medial prefrontal cortex
NIDA = National Institute on Drug Abuse
NWAK = number of awakenings
PSQI = Pittsburgh Sleep Quality Index
PTSD = post-traumatic stress disorder
SD = standard deviation
SE = sleep efficiency
SOL = sleep-onset latency
THC = tetrahydrocannabinol
TLFB = timeline follow-back
TST = total sleep time
WASO = wake after sleep onset