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Research paper

Short and Long-Term Effects of Cannabis on Symptoms of Post-Traumatic Stress Disorder

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ABSTRACT

Background: Many individuals use cannabis to manage symptoms of post-traumatic stress disorder (PTSD), and evidence indicates that the endocannabinoid system represents a viable target for treating these symptoms.
Method: Data from 404 medical cannabis users who self-identified as having PTSD were obtained from Strainprint®, a medical cannabis app that patients use to track changes in symptoms as a function of different strains and doses of cannabis across time. This sample collectively used the app 11,797 times over 31 months to track PTSD-related symptoms (intrusive thoughts, flashbacks, irritability, and/or anxiety) immediately before and after inhaling cannabis. Latent change score models were used to examine changes in symptom severity and predictors of these changes (gender, dose, cannabis constituents, time). Multilevel models were used to explore long-term consequences of repeatedly using cannabis to manage these symptoms.
Results: All symptoms were reduced by more than 50% immediately after cannabis use. Time predicted larger decreases in intrusions and irritability, with later cannabis use sessions predicting greater symptom relief than earlier sessions. Higher doses of cannabis predicted larger reductions in intrusions and anxiety, and dose used to treat anxiety increased over time. Baseline severity of all symptoms remained constant across time.
Limitations: The sample was self-selected, self-identified as having PTSD, and there was no placebo control group.
Conclusions: Cannabis provides temporary relief from PTSD-related symptoms. However, it may not be an effective long-term remedy as baseline symptoms were maintained over time and dose used for anxiety increased over time, which is indicative of development of tolerance.

1. Introduction

Post-traumatic stress disorder (PTSD) is a disorder of recovery following the experience of a traumatic event, characterized by alterations in arousal and reactivity including irritability, sleep disturbances, and hypervigilance; intrusion symptoms including intrusive distressing memories, flashbacks, and nightmares; persistent avoidance of stimuli associated with the traumatic event(s); and disturbances in cognition and mood (APA, 2013). Lifetime prevalence of PTSD has been estimated to be around 6.8% to 8.7% of the U.S. population (APA, 2013; Kessler, Berglund, et al., 2005), with past-year prevalence of approximately 3.5% (APA, 2013; Kessler, Chiu et al., 2005). Epidemiological studies have demonstrated an over two-fold greater lifetime prevalence of PTSD among women (9.7%) compared to men (3.6%) (NCS, 2005). While a number of effective behavioral treatments are available for individuals with PTSD (e.g., cognitive processing therapy, prolonged exposure), pharmacological interventions typically involve the use of selective serotonin reuptake inhibitors (SSRIs) which generally have small effect sizes and have been associated with various undesirable side effects, low rates of symptom remission, and high rates of dropout (Berger et al., 2009; Cipriani et al., 2018). As such, many organizations (e.g., the International Society for Traumatic Stress Studies [ISTSS, nd], 2018 Department of Veteran Affairs/Department of Defense [VA/DOD, 2017] recommend therapy as the first-line treatment for PTSD, rather than SSRIs or other pharmacological interventions.

While documented evidence of therapeutic effects of cannabis on PTSD symptoms remains somewhat sparse, emerging evidence indicates that the endocannabinoid system may represent a viable target for treating PTSD. Specifically, there is evidence that PTSD may be related to deficiencies in the endocannabinoid system (Hill et al., 2018; Neumeister et al., 2013) and these deficiencies have been associated with more severe symptoms of PTSD including anxiety and extinction of

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aversive memories (Bluett et al., 2014; Hill et al., 2013). Indeed there is now solid evidence that cannabinoids reduce responses to conditioned fear cues, impair retrieval of emotionally aversive memories, and promote the extinction of fear memories (Atsak et al., 2012; Bitencourt et al., 2008; Das et al., 2013; Do Monte et al., 2013; Gomes et al., 2012; Lemos et al., 2010; Pamplona et al., 2006) suggesting that targeting the endocannabinoid system may hold promise for reducing PTSD-related intrusions and flashbacks. Indeed, a recent double-blind placebo-controlled trial found that inhibition of fatty acid amide 31 hydrolase (FAAH; which inhibits the breakdown of the endocannabinoid anandamide) increased levels of anandamide in healthy adults which in turn enhanced fear extinction and attenuated autonomic stress reactivity (Mayo et al., 2019).

Consistent with this largely preclinical evidence, an open label clinical trial provided evidence that nabilone (a synthetic analogue of delta-9-tetrahydrocannabinol; THC) reduced nightmares, improved sleep, and reduced flashbacks in patients diagnosed with PTSD (Fraser et al., 2009). Similarly, a retrospective study indicated that nabilone is effective in reducing insomnia, nightmares, and other PTSD symptoms (Cameron et al., 2014). Moreover, the results of a double-blind placebo-controlled cross-over study indicated that nabilone significantly reduced nightmares, improved PTSD symptom severity, and enhanced general wellbeing in 10 men with PTSD (Jetly et al., 2015). However, the sample sizes used in these studies are modest and most of the aforementioned studies relied on synthetic THC or other cannabinoids rather than examining the potential therapeutic effects of whole plant cannabis or phytocannabinoids (i.e., cannabinoids obtained from the cannabis plant).

Nevertheless, a growing number of individuals with PTSD are using cannabis (Bonn-Miller et al., 2012; Bonn-Miller & Rousseau, 2014), with both trauma exposure and PTSD diagnosis having been associated with increased odds of cannabis use in nationally representative samples (Cougle et al., 2011; Kevorkian et al., 2015). Studies have suggested that those with PTSD turn to cannabis when existing psychological or pharmacological interventions fail (Bonn-Miller et al., 2011). Indeed, cannabis appears to be used by this population, specifically, to cope with negative affect and sleep difficulties (Betthauser et al., 2015; Bonn-Miller et al., 2007; 2014). A recent study that utilized ecological momentary assessment (EMA) to determine the antecedents and consequences of cannabis use among trauma-exposed young adults exhibiting PTSD symptoms demonstrated that PTSD hyperarousal symptoms were predictive of subsequent cannabis use, which in turn was associated with reductions in state anxiety (Buckner et al., 2018). However, the cannabinoid content of the cannabis used by participants was not assessed and ratings were not taken immediately prior to and following use of cannabis, preventing the analysis of acute, within-moment effects (Buckner et al., 2018).

Another major limitation of the body of research on PTSD and cannabis/cannabinoids has been the paucity of longitudinal data which has obscured understanding of whether cannabinoids need to be administered chronically, or if acute doses are sufficient to reduce PTSD symptoms (Loflin et al., 2017). Failures to consider long-term effects of cannabis use on PTSD is particularly concerning given that the chronic cannabis use is associated with a broad range of negative outcomes (Karila et al., 2014). Therefore, two recent studies have extended prior work by examining the short- (3 week) and long-term (12 month) effects of cannabis with different ratios of THC and cannabidiol (CBD) on PTSD symptomatology (Bonn-Miller, Brunstetter et al., submitted; Bonn-Miller, Sisley et al., submitted). Findings suggest that THC-dominant, CBD-dominant, and balanced THC:CBD cannabis preparations were associated with short-term reductions in PTSD symptoms, though none separated from placebo ((Bonn-Miller, Sisley et al., submitted). However, long-term use of primarily THC-dominant cannabis was associated with lower PTSD symptomatology (primarily driven by reductions in hyperarousal symptoms) as well as a greater than two-fold reduction in the likelihood of PTSD diagnosis at 12 months, relative to non-users (Bonn-Miller, Brunstetter et al., submitted).

The present study was designed to address the limitations of the extant literature by using a very large dataset to examine changes in PTSD symptomatology (intrusions, flashbacks, irritability, anxiety) from immediately before, to shortly after, cannabis use as well as potential predictors of these symptom changes including gender, dose, THC concentrations, CBD concentrations, and THC x CBD interactions. We further sought to explore potential long-term consequences of repeatedly using cannabis to manage symptoms of PTSD by investigating changes in the efficacy of cannabis, changes in dose, and changes in baseline PTSD symptoms (i.e., symptom severity ratings before each cannabis use session) across cannabis use sessions over a 31-month time period.

2. Methods

2.1. Procedure

Archival data were obtained from Strainprint®, a medical cannabis technology platform with a journaling app that allows users to track changes in symptom severity as a function of their cannabis use. Immediately prior to engaging in medical cannabis use, Strainprint® users can select the specific condition/symptom(s) they are using cannabis to manage and rate their severity from 0 (none) to 10 (extreme). For instance, users preparing to self-medicate for anxiety would be asked to respond to the question “How bad is your anxiety?” by rating the severity of this symptom on a 0 to 10 scale. Users are then prompted to indicate their method of administration (smoke, vape, dab bubbler, dab portable, oil, edible, pill, spray, transdermal, tincture). Next, they indicate the strain of cannabis that they are about to use as well as the producer/distributor of that strain by choosing from a selection of over 3,000 cannabis products sold in Canada. Lab verified cannabinoid content (% THC and CBD) is pre-populated within the app using data from the websites of cannabis distributors in Canada. Alternatively, if a particular product is not pre-populated within the app, Strainprint® users can manually enter the strain name and cannabinoid content of the product they are about to use. After rating their initial symptom severity and identifying their cannabis product and method of administration, app users then indicate the dose (number of puffs) taken during their medical cannabis use session. After an onset period determined by the method of administration chosen (e.g., 20 minutes after inhalation), the app provides a push notification reminder to prompt users to re-rate the severity of their symptom(s).

For this study, we obtained anonymous data from Strainprint® for users who self-identified as having PTSD and who used the app to track symptoms of intrusive thoughts, flashbacks, irritability, and anxiety. More specifically, the obtained data included anonymous ID codes, cannabis treatment session numbers, gender, age, symptoms, self-reported symptom severity before and after each tracked session of medical cannabis use, cannabinoid content (% THC, % CBD) for the cannabis used in each session, the method of obtaining the cannabinoid content data (i.e., cannabis producer vs. user-generated), as well as the method of administration and dose for each cannabis use session. The Office of Research Assurances deemed this anonymous archival study exempt from the need for IRB review.

2.2. Inclusion/Exclusion Criteria

Due to potential discrepancies in the efficacy and onset of different routes of administration of cannabis (e.g. oral vs. inhaled), we included only tracked sessions in which individuals indicated that they used an inhaled method of administration (smoking, vaping, concentrate, dab bubbler, or dab portable). Sessions involving other methods of administration (e.g. tincture, edibles) were not included in the present study. Furthermore, only tracked sessions in which individuals re-rated their symptoms within 4 hours of cannabis use were included in the present

Table 1
Demographic Characteristics and Tracked Sessions

		Age		Gender (*n*)		# Tracked Sessions		
Symptom	*N*	*M (SD)*	Range	Men	Women	*N*	*M (SD)*	Range
Intrusions	82	41.74 (8.810)	18 – 58	25	55	1101	142.56 (192.68)	1 – 651
Flashbacks	198	42.29 (10.55)	18 – 65	95	196	2768	126.93 (135.82)	1 – 508
Irritability	213	37.85 (8.83)	18 – 70	82	126	2515	48.38 (62.53)	1 – 290
Anxiety	299	38.92 (10.12)	18 – 65	124	169	5413	85.17 (107.56)	1 – 495
Total Sample	404	39.75 (9.94)	18 – 70	176	220	11797	92.48 (121.99)	1 –651

study, given that the acute effects of inhaled cannabis are known to peak within 10-30 minutes of ingestion, and dissipate after 3-4 hours (Grotenhermen, 2003; Menkes, Howard, Spears & Carins, 1991). Finally, due to concerns with the reliability and validity of self-reported cannabinoid content information, we also opted to only include sessions for which lab-verified cannabinoid content data were obtained directly from the websites of producers by Strainprint® and to exclude session for which users manually inputted information on THC and CBD concentrations.

2.3. Participants

The final sample comprised 404 medical cannabis users who self-identified as having PTSD (220 women, 176 men, 8 "other"). This sample collectively used the Strainprint® app 11,797 times over a span of 31 months (from March 2017 to October 2019), to track PTSD-related symptoms of intrusive thoughts, flashbacks, irritability and/or anxiety. Table 1 displays demographic characteristics and information on the number of cannabis use sessions tracked for the entire sample, and for sub-samples broken down by symptom.

2.4. Data Analysis

To examine change in symptom severity from before to after cannabis use, two-time points latent change score (LCS) models were used. This approach allowed us to examine changes in PTSD symptoms within subjects across time (McArdle, 2009) and as a function of specific predictors of interest (e.g., gender, dose, cannabinoid content). For each symptom of PTSD, three LCS models were estimated. The baseline unconditional LCS models contained no predictors and were used to describe the nature of symptom change following cannabis use. These models provided a mean of the latent change factor, which is an estimate of average change in symptom severity over time. A negative value on this change factor is indicative of improved symptom severity following cannabis use, while a positive value is indicative of a worsening of symptoms following cannabis use. These unconditional models also provided an estimate of the extent to which change in symptom severity covaried with symptom severity scores before cannabis use. A negative covariance value between the latent change factor and symptom severity before cannabis use indicates that, on average, greater symptom severity prior to cannabis use is associated with greater relief following cannabis use. Finally, these baseline models also provided an estimate of the variance of this latent change factor, which describes the extent to which symptom change following cannabis use varied across individuals (i.e., between-subject variability).

The second and third LCS models estimated were conditional models which included predictors of the latent change factor. First, conditional LCS models were used to estimate the influence that time/cannabis use session, gender, dose (# of puffs), THC and CBD concentrations had on the latent change factor. Subsequent conditional LCS models estimated the influence of the same set of predictor variables, as well as the effect of the interaction of THC x CBD on the latent change factor. Estimates for each of these predictors can be interpreted as beta coefficients which describe the average influence of the predictor variable on the change factor. Positive beta coefficients indicate that higher levels of the predictor variable are associated with smaller decreases in symptom severity ratings following cannabis use. In contrast, negative coefficients indicate that higher values of the given predictor are associated with greater decreases in symptom severity from before to after cannabis use. All LCS models were fit using Mplus version 8.3 (Muthén & Muthén, 2017).

Finally, separate repeated measures multilevel models were used to describe changes in (1) baseline PTSD symptom severity (i.e., symptom ratings before each cannabis use session) across time/cannabis use sessions and (2) dose of cannabis used over time/cannabis use sessions. In these unconditional models, which contained no predictors, cannabis use session was centered at Time 1 so that the intercept (Time 0) represented the first session of cannabis use in each model. The fixed and random linear effects of time/cannabis use session on baseline severity and dose were estimated using SAS Proc Mixed, with maximum likelihood estimation and incomplete data treated using missing at random assumptions.

3. Results

3.1. Cannabis Use Characteristics

Cannabis use characteristics for the entire sample, and each symptom appear in Table 2. Specifically, the table displays descriptive statistics pertaining to dose of cannabis (# of puffs), as well as THC and CBD concentrations in the cannabis used to manage each symptom.

3.2. Overall Change in Symptom Severity

Table 3 displays the percentage of tracked sessions in which symptom ratings were reduced after cannabis use, the percentage of sessions in which symptoms were exacerbated after cannabis use, and the percentage of sessions in which symptom ratings were unchanged following cannabis use. Table 3 also shows the mean symptom severity ratings before and after cannabis use, and the difference in these means

Table 2
Cannabis Use Characteristics

	Dose (# of Puffs)		**THC (%)**		**CBD (%)**	
Symptom	***M* (*SD*)**	**Range**	***M* (*SD*)**	**Range**	***M* (*SD*)**	**Range**
Intrusions	10.83 (6.66)	1 – 30	14.77 (7.90)	0.10 – 74.50	2.81 (5.85)	0 – 25.00
Flashbacks	9.57 (5.43)	1 – 30	16.06 (5.90)	0 – 74.50	1.47 (3.93)	0 –25.00
Irritability	8.62 (5.74)	1 – 30	14.62 (6.96)	0 – 74.50	2.46 (5.12)	0 – 25.00
Anxiety	9.10 (5.89)	1 – 30	14.42 (6.81)	0 – 84.40	2.82 (5.42)	0 – 25.00
Total Sample	9.27 (5.86)	1 – 30	14.88 (6.79)	0 – 84.40	2.43 (5.12)	0 – 25.00

Table 3
Changes in Symptom Severity

Symptom	% Sessions Symptom Reduction	% Sessions Symptom Exacerbation	% Sessions No Symptom Change	Rating Before Use *M* (*SD*)	Rating After Use *M* (*SD*)	% Reduction in Rating
Intrusions	97.82%	0.27%	1.91%	6.93 (1.48)	2.60 (1.73)	62.48%
Flashbacks	91.84%	2.93%	5.24%	6.34 (1.74)	3.12 (1.98)	50.79%
Irritability	97.06%	0.68%	2.27%	6.90 (1.85)	2.31 (1.92)	66.52%
Anxiety	93.46%	1.98%	4.56%	6.19 (1.95)	2.65 (1.88)	57.19%

expressed as a percentage.

3.3. Gender Differences.

Intrusive Thoughts. As displayed in Table 3, intrusive thoughts were reduced in almost all tracked sessions (> 97%). Breaking this effect down by gender, there was no gender difference in the percentage of sessions involving improvement in intrusions (Men = 97.82% vs Women = 97.80%), $\chi^2(1) = 0.00$, $p = .98$. However, relative to men, women reported significantly higher symptom severity before cannabis use (Women: $M = 7.13$, $SD = 1.61$, Men: $M = 6.80$, $SD = 1.37$), $t(1094) = 3.73$, $p < .001$, and after cannabis use (Women: $M = 3.15$, $SD = 1.88$, Men: $M = 2.22$, $SD = 1.52$), $t(1094) = 8.99$, $p < .001$.

Flashbacks. In over 91% of tracked sessions users reported experiencing symptom reduction (see Table 3). Women reported a greater percentage of sessions during which flashback severity was reduced than did men (Women = 95.14%, Men = 89.33%), $\chi^2(1) = 29.86$, $p < .001$. Women also reported significantly higher flashback severity than did men both before cannabis use (Women: $M = 6.91$, $SD = 1.59$, Men: $M = 5.90$, $SD = 1.70$), $t(2743) = 15.93$, $p < .001$, and after cannabis use (Women: $M = 3.72$, $SD = 1.92$, Men: $M = 2.66$, $SD = 1.88$), $t(2743) = 14.51$, $p < .001$.

Irritability. Table 3 shows that over 97% of cannabis use sessions resulted in reductions in irritability. Comparisons of the genders revealed that men reported significantly more sessions involving reductions in irritability than did women (Women = 96.33%, Men = 97.82%), $\chi^2(1) = 4.86$, $p = .03$. Relative to women, men reported significantly lower irritability at baseline (Women: $M = 7.11$, $SD = 1.90$, Men: $M = 6.72$, $SD = 1.78$), $t(2488) = 5.31$, $p < .001$. However, there was no difference in men and women's post-cannabis use irritability ratings (Women: $M = 2.37$, $SD = 2.01$, Men: $M = 2.24$, $SD = 1.83$), $t(2488) = 1.64$, $p = .10$.

Anxiety. As shown in Table 3, symptoms of anxiety were reduced in 93% of tracked sessions. Breaking down this effect by gender, we found that women reported significantly more sessions in which anxiety was reduced, (Women = 94.85 vs. Men = 92.31), $\chi^2(1) = 14.06$, $p < .001$. Further, men reported significantly lower anxiety at baseline (Women: $M = 6.70$, $SD = 1.88$, Men: $M = 5.76$, $SD = 1.91$), $t(5379) = 17.97$, $p < .001$, and after cannabis use (Women: $M = 3.02$, $SD = 2.11$, Men: $M = 2.33$, $SD = 1.61$), $t(5379) = 13.50$, $p < .001$, than did women.

3.4. Baseline Unconditional LCS Models Predicting Change in Symptom Severity

Results of the four baseline LCS models confirmed that the mean of the latent change factor (μ_Δ) was statistically significant and negative for all four symptoms (Intrusive Thoughts: $\mu_\Delta = -4.33$, $SE = 0.30$, $p < .001$; Flashbacks: $\mu_\Delta = -3.22$, $SE = 0.42$, $p < .001$; Irritability: $\mu_\Delta = -4.60$, $SE = 0.20$, $p < .001$; Anxiety: $\mu_\Delta = -3.55$, $SE = 0.28$, $p < .001$). This confirms that self-reported severity of all four symptoms was significantly reduced from before to after cannabis use. Figure 1 displays average severity ratings for anxiety, irritability, intrusive thoughts, and flashbacks before and after cannabis use.

The covariance between symptom severity before cannabis use and the latent change factor was statistically significant and negative for all four symptoms (Intrusive Thoughts: covariance estimate = -1.38, $SE = 0.42$, $p = .001$; Flashbacks: covariance estimate = -3.22, $SE = 0.42$, $p < .001$; Anxiety: covariance estimate = -2.06, $SE = 0.51$, $p < .001$; Irritability: covariance estimate = -2.43, $SE = 0.31$, $p < .001$). This indicates that more severe symptom severity prior to cannabis use was associated with greater relief, following cannabis use.

The variance of the latent change factor was also statistically significant for all four symptoms (Intrusive Thoughts: variance estimate = 3.57, $SE = 0.70$, $p < .001$; Flashbacks: variance estimate = 5.03, $SE = 0.90$, $p < .001$; Irritability: variance estimate = 5.15, $SE = 0.53$, $p < .001$; Anxiety: variance estimate = 5.04, $SE = 0.60$, $p < .001$). This suggests that there were significant differences across individuals in the rate of change in each symptom following cannabis use.

3.5. Conditional LCS Models with Predictors of Change

As shown in Tables 4 and 5, conditional LCS models predicting symptom rating changes using time/cannabis use session, gender, dose (# of hits), THC, CBD, and THC x CBD interactions suggested that change in ratings of the severity of anxiety and intrusive thoughts from before to after cannabis use were significantly associated with dose of cannabis, with higher doses (i.e., more puffs) predicting greater symptom relief. Finally, time/cannabis use session predicted changes in intrusions and irritability. The negative regression coefficients for the effects of time indicate that later cannabis use sessions were associated with larger reductions in irritability and intrusions than earlier episodes.

3.6. MLM Predicting Changes Across Cannabis Use Sessions

Changes in Dose Across Time. Four separate multilevel models revealed that dose of cannabis used increased significantly across cannabis use sessions over time for Anxiety ($\beta = .02$, $SE = .01$, $p = .04$). In contrast, no significant changes in dose of cannabis used to manage irritability ($\beta = 0.02$, $SE = 0.02$, $p = .17$), intrusive thoughts ($\beta = .37$, $SE = .54$, $p = .49$)[2], or flashbacks ($\beta = 0.02$, $SE = 0.02$, $p = .26$) were detected across time/cannabis use sessions.

Change in Baseline Symptoms. An additional set of four multilevel models predicting change in baseline symptoms (i.e., symptom ratings immediately before cannabis use) as a function of cannabis use sessions over time revealed that severity of baseline ratings did not change significantly across time/cannabis use sessions (Anxiety: $\beta = .002$, $SE = 0.001$, $p = .14$; Irritability: $\beta = .006$, $SE = .005$, $p = .25$; Intrusive Thoughts: $\beta = .0004$, $SE = .0002$, $p = .13$; Flashbacks: $\beta = 0.006$, $SE = .004$, $p = .19$). This indicates that the repeated use of cannabis to manage these symptoms does not improve or exacerbate their baseline severity over time.

4. Discussion

We sought to investigate the effects of inhaled cannabis on symptoms of PTSD (intrusive thoughts, flashbacks, irritability, anxiety) using data from Strainprint®, a medical cannabis app that provides users with the means to track changes in symptom severity as a function of their use of different strains and doses of cannabis over time. We further sought to determine whether gender, dose, cannabinoid content of

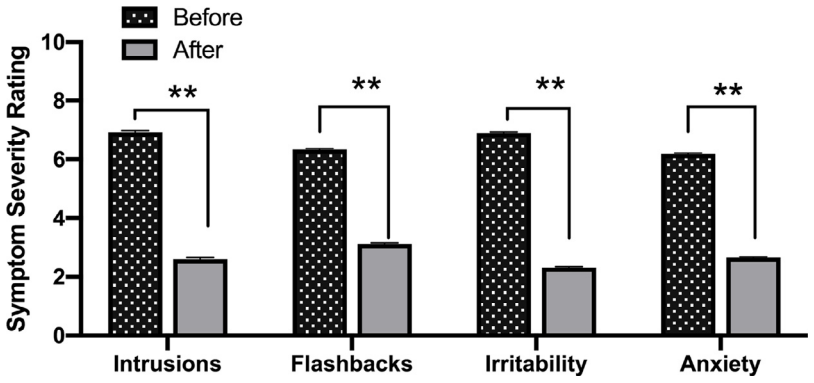


Figure. 1. Change in Severity of Symptoms from Before to After Cannabis Use Note: Error bars represent standard error of the means, * $p < .001$

Table 4
LCS Models with Predictor of Change in Severity of Intrusions and Flashbacks

	Intrusions				Flashbacks			
	Model 1		Model 2		Model 1		Model 2	
Predictor	ß	*SE*	ß	*SE*	ß	*SE*	ß	*SE*
Time/Session	-0.14*	0.07	-0.15*	0.07	-0.04	0.10	-0.05	0.10
Gender	0.01	0.09	0.01	0.09	-0.18	0.13	-0.18	0.13
Dose	-0.23*	0.09	-0.24*	0.09	0.01	0.13	0.01	0.13
THC	-0.10	0.07	-0.14	0.08	-0.02	0.11	-0.04	0.11
CBD	0.10	0.09	-0.06	0.14	-0.07	0.09	-0.25	0.16
THC X CBD			-0.14	0.14			-0.17	0.10

* $p < .05$.***Notes*:** Gender was coded such that women = 0 and men = 1. Model 1 does not include the THC X CBD interaction term. Model 2 includes the interaction term.

Table 5
LCS Models with Predictor of Change in Severity of Irritability and Anxiety

	Irritability				Anxiety			
	Model 1		Model 2		Model 1		Model 2	
Predictor	ß	*SE*	ß	*SE*	ß	*SE*	ß	*SE*
Time/Session	-0.21**	0.06	-0.21**	0.06	0.01	0.07	0.01	0.07
Gender	0.07	0.07	0.07	0.07	-0.05	0.07	-0.05	0.07
Dose	-0.04	0.07	-0.04	0.07	-0.13*	0.07	-0.13*	0.07
THC	-0.04	0.06	-0.01	0.06	-0.09	0.08	-0.11	0.07
CBD	0.03	0.07	0.09	0.14	-0.07	0.10	-0.12	0.12
THC X CBD			0.10	0.12			0.04	0.09

* $p < .05$.
** $p = .001$ ***Notes*:** Gender was coded such that women = 0 and men = 1. Model 1 does not include the THC x CBD interaction term. Model 2 includes the interaction term.

cannabis used and/or cannabis use sessions across time would predict changes in symptom severity. Results revealed that, on average, respondents self-identifying as having PTSD reported a 62% reduction in the severity of intrusive thoughts, a 51% reduction in flashbacks, a 67% reduction in irritability, and a 57% reduction in the severity of anxiety, from before to after inhaling cannabis. Moreover, these symptom reductions were reported in the majority of cannabis use sessions for intrusive thoughts (98%), flashbacks (92%), irritability (97%), and anxiety (93%).

While inhaled cannabis resulted in significant and substantial reductions in ratings of all four of the PTSD symptoms that we assessed, it is important to note that we detected significant heterogeneity in these effects across individuals, indicating that cannabis may not uniformly reduce PTSD symptoms for everyone. Concretely, while the four baseline LCS models confirmed that the reported symptom reductions were statistically significant, the variance estimates for all four models revealed significant individual differences in the rates of change among participants for each symptom. Taken together, these results provide strong evidence that cannabis can provide temporary relief from symptoms of PTSD, but that the magnitude of these effects varies across individuals. One source of this heterogeneity may have stemmed from differences in baseline ratings of the symptoms. The LCS models revealed significant covariance estimates between symptom severity before cannabis use and the latent change factor for each symptom, which indicates that those with more severe symptoms reported greater reductions in their symptoms after cannabis use. This may indicate that cannabis is more effective for more severe symptoms. Alternatively, this finding could also simply reflect the fact that there is more room for improvement of more severe symptoms.

While the LCS models indicated that gender did not predict changes in symptom severity from before to after cannabis use (above and beyond the potential gender-related differences in dose, cannabinoid content, and time), comparisons of men and women's mean severity ratings before and after canabis use revealed small but statistically significant gender differences. Specifically, women reported significantly greater symptom severity before cannabis use for all four PTSD symptoms we assessed. Women also reported significantly greater post-cannabis use severity for intrusions, flashbacks, and anxiety. This finding that women reported more severe symptoms of PTSD than did men is consistent with previous research indicating women are more likely to meet criteria for PTSD and to demonstrate worse symptom severity (NCS, 2005; Tolin & Foa, 2006). The results further revealed that women reported significantly more cannabis use sessions during which flashback and anxiety severity were reduced than did men. In contrast, men reported significantly more sessions during which irritability was reduced than women. Nevertheless, while these differences were statistically significant, they were small in size and rather trivial (differences smaller than 6% of sessions). Both genders reported that their symptoms were reduced in the vast majority of cannabis use sessions.

Concentrations of THC, CBD, and interactions between THC and CBD appeared to have no influence on changes in any of the four symptoms assessed. Cannabis can contain up to 120 cannabinoids, over 250 terpenes, around 50 flavonoids, as well as a number of other molecules that may exert biological action (Bonn-Miller et al., 2019; Calvi et al., 2018) and therefore it may be one of these other constituents or an entourage effect that is responsible for the therapeutic effects of cannabis on these PTSD symptoms. Unfortunately, information on these other constituents was too sparse in the obtained data to permit for meaningful analyses. Clinical trials are needed where THC, CBD, minor phytocannabinoids and/or terpenes are directly manipulated by investigators to determine the concentrations of these constituents that provide the greatest relief from PTSD symptoms.

Results pertaining to the time/cannabis use session predictor in the LCS models revealed no changes in the efficacy of cannabis in reducing anxiety or flashback severity across cannabis use sessions over time. In contrast, time was a significant predictor of reductions in intrusions and irritability, with later cannabis use sessions predicting greater symptom relief than earlier cannabis use sessions. These findings may indicate

that cannabis becomes a more effective treatment for intrusions and irritability as it continues to be used to manage these symptoms over time. Alternatively, this finding may represent a statistical artifact, such that individuals who obtain the greatest relief in intrusions and irritability from cannabis may simply be the most likely to use cannabis for longer periods of time. Further longitudinal studies are required to better establish the direction of this effect.

The LCS models revealed that higher doses (i.e., more puffs) of cannabis predicted greater symptom relief for anxiety and intrusive thoughts than did lower doses. Moreover, results of multilevel models further revealed that the dose of cannabis used increased significantly across time/cannabis use sessions for anxiety, which may be an indicator of tolerance. Collectively these two sets of results indicate that people are using consistent doses to achieve larger reductions in intrusions over time and higher doses to achieve larger reductions in anxiety over time. The escalations in dose for anxiety adds credence to concerns of individuals with PTSD developing cannabis dependence (Boden et al., 2013), especially given that excess cannabis use has been associated with more negative long-term outcomes in individuals with PTSD (Steenkamp et al., 2017).

Interestingly, the severity of baseline symptom ratings did not change significantly across time/cannabis use sessions. This may suggest that while acute use of cannabis leads to perceived reductions in acute symptom severity, these effects may not extend beyond the period of intoxication and regular use of cannabis may simply maintain the disorder over time. In other words, while cannabis intoxication can provide transient relief from PTSD symptoms, long-term cannabis use may not ultimately improve the severity of this disorder. These findings, however, contradict longitudinal data demonstrating long-term benefit of THC on PTSD symptoms and diagnosis over the course of one year (Bonn-Miller et al., submitted) as well as previous research demonstrating that cannabis/cannabinoids impair retrieval of emotionally aversive memories and promote the extinction of fear memories (Atsak et al., 2012; Bitencourt et al., 2008; Das et al., 2013; Do Monte et al., 2013; Gomes et al., 2012; Lemos et al., 2010; Pamplona et al., 2006). Alternatively, it is possible that the present finding of consistent baseline symptoms over time simply reflects a tendency for people to self-medicate with cannabis once their symptoms reach a specific threshold. More controlled longitudinal research is clearly needed to disentangle these complex bi-direction temporal associations.

4.1. Limitations and Strengths

The present study has a number of limitations that should be noted. First, respondents self-identified as having PTSD and it was not possible to verify these diagnoses. As such, some of the individuals in the present sample may have been experiencing sub-clinical PTSD. Further, not all clinically recognized symptoms of PTSD were assessed. While we were able to assess the influence of cannabis on four symptoms of PTSD, several other symptoms for which cannabinoids have shown benefit were not assessed (e.g., nightmares, avoidance, cognitive problems) because they are not available in the Strainprint® app.

Our sample also likely underrepresents individuals who find cannabis to be aversive or ineffective at reducing symptoms of PTSD. This subgroup would be unlikely to continue using cannabis or the Strainprint® app. The evidence for individual differences in the efficacy of cannabis in reducing symptoms further supports this idea that not all individuals will find cannabis equally effective at reducing their symptoms. Finally, it was not possible for us to include a placebo control group. In the absence of this group, it is likely that some of the reported effects were driven by expectations about the therapeutic potential of cannabis for reducing symptoms of PTSD.

Finally, because the app was created for industry, rather than research, purposes only a single item was used to assess each symptom and standard definitions of these symptoms were not provided for users. While single item indicators of constructs such as stress have been demonstrated to possess content, criterion, and construct validity (Elo et al, 2003), it is unclear whether this would generalize to indicators of intrusions, flashbacks, irritability, and anxiety. Further, users may have varied in what they considered an intrusion vs. a flashback. Thus, future research should attempt to replicate these findings with a larger sample of patients with clinician-verified diagnoses of PTSD, using a double-blind placebo controlled clinical trial, and standardized measures of the symptoms being assessed.

These limitations are offset by numerous strengths of the study. First, this study utilized a large sample of over 400 medical cannabis users who tracked over 11,000 cannabis use sessions over a 31-month period of time. These medical users were able to use a large variety of cannabis products in their own natural environment, affording our study very high ecological validity. We also limited analyses to sessions during which lab-verified THC and CBD data were obtained in order to increase confidence in the THC and CBD concentrations. Thus, the present study has excellent ecological validity, and threats to internal validity are more likely to be implicit, in the form of expectancy effects.

5. Conclusions

Results from the present study indicate that acute cannabis intoxication provides temporary relief from intrusions, flashbacks, irritability, and anxiety in individuals self-identifying as having PTSD. However, baseline PTSD symptom ratings did not change over time and we detected evidence that people used higher doses to manage anxiety over time, which may be indicative of the development of tolerance to the drug. Collectively these results indicate that cannabis may reduce PTSD symptoms in the short-term but may not be an effective long-term remedy for the disorder. Future research should examine specific cannabinoid preparations as monotherapy, as well as adjunct to conventional behavioral and pharmacological interventions, within well-powered placebo-controlled trials.

6. Contributors

Carrie Cuttler conceived of the idea and research questions, obtained the data, assisted with analyses, created the figure, interpreted the results, and contributed to the preparation of all components of the manuscript. Emily LaFrance helped to conceive the research questions, conducted the analyses, and assisted in writing the methods and results section. Nicholas C. Glodosky assisted with writing the discussion and assisted with references. Marcel Bonn-Miller helped to conceive of the idea, conducted the literature review, and wrote the introduction. All authors approved the final article.

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Declarations of Competing Interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.132.

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