

Using Smartphone Technology to Track Real-Time Changes in Anxiety/Depression Symptomatology Among Florida Cannabis Users

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ABSTRACT

Objective: Recent scientific attention has focused on the therapeutic effectiveness of cannabis use on a variety of physical and mental ailments. The present study uses smartphone technology to assess self-reported experiences of Florida cannabis users to understand how cannabis may impact anxiety and depression symptomatology. **Method:** Several hundred Releaf App™ users from the state of Florida provided anonymous, real-time reports of their symptoms of anxiety and/or depression immediately before and after cannabis use sessions. Linear mixed-effects modeling was used to analyze the data at the symptom and user level. **Results:** Results showed that for the majority of users, cannabis use was associated with a significant decrease in depression and anxiety symptomatology. While symptom type, doses per session, consumption method, and CBD levels were significant predictors of relief change, their effect sizes were small and should be interpreted with caution. At the user level, those who had positive relief outcomes in anxiety reported more doses and sessions, and those in the depression group reported more sessions. **Conclusions:** Our results generally support the therapeutic effectiveness of cannabis against depression/anxiety symptomatology. Future work should include standardized statistics and effect size estimates for a better understanding of each variable's practical contribution to this area of study.

Key words: = CBD; cannabinoids; medical cannabis; mobile application; mood disorders; THC

A recent poll found that 91% of U.S. adults believe that marijuana should be legal in some form – either for medical and recreational use (60%) or medical use only (31%; Green, 2021). This shift in public opinion is buoyed by rapid scientific advancement. A PubMed keyword search shows that between 1990-1999, researchers published fewer than 4,000 papers on cannabis/marijuana; since 2010, they've authored over 30,000. As public and scientific interest grows, the present paper turns its focus to an intersection with one of the most pressing issues of our time: mental health.

Over 31% of Americans will suffer from an anxiety disorder at some point in their lives; close to 17% will suffer from major depressive disorder (Kessler et al., 2012). Yet, while antidepressants remain one of the three most frequently prescribed therapeutic drug classes in the country – currently used by over 40 million adults (CDC, 2018; Brody & Quiping, 2020) – multiple meta-analyses have demonstrated only modest benefits over placebo (Kirsch et al., 2002; 2008), with a recent analysis co-authored by the Food & Drug Administration suggesting only 15% of participants experience a substantial

antidepressant effect beyond a placebo effect in clinical trials (Stone et al., 2022). Pharmaceutical options, particularly anxiolytic medications (such as benzodiazepines), are also weighted by troubling side effects, including an addictive potential that can lead to severe psychological and physical dependence (Edinoff et al., 2021). In the past few years, researchers have increasingly warned that benzodiazepine abuse is reaching “epidemic levels” (Schmitz, 2016; Sarangi, 2021).

Conversely, cannabis – now legal in some form in over 70% of U.S. states and territories – has attracted interest due to its ability to alleviate symptoms of both conditions with minimal, non-serious side effects such as drowsiness, dry mouth, tachycardia, and short-term impairment of memory, concentration, and motor performance (Prashad & Filbey, 2017; Stith et al., 2018; Wang et al., 2008). Surveys of medical cannabis users across the country have shown that relief from symptoms of anxiety and depression are among the most commonly cited reasons for using medical cannabis (Rosenthal & Pipitone, 2021; Reinerman et al., 2011). Likewise, Corroon et al. (2017) found that the odds of reporting substituting cannabis for prescription drugs were more than one and a half times greater among those reporting the use of cannabis to manage anxiety and depression. And yet, while cannabinoids have been shown to dose-dependently induce antidepressant-like effects (Sales et al., 2019) and significantly reduce ratings of anxiety and stress (Cuttler et al., 2018), far less is known about the specific cannabinoid profiles that are most effective for patient use.

Cannabinoids may have both a direct and indirect role in depression and anxiety, and their effects are dose-dependent. The endocannabinoid system helps to ensure an appropriate response to stressful events and plays a role in extinction of aversive memories (Jurkus et al., 2016; Marsicano et al., 2002; Stern et al., 2015). When antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs) are effective, recent data suggest that their antidepressant actions may not be directly related to increasing allegedly low serotonin levels, but rather by encouraging neurogenesis in the hippocampus (Santarelli et al., 2003). Preliminary studies suggest that cannabinoids may play a role in regulating hippocampal neurogenesis (Jiang et al., 2005; Zhang et al., 2014), which may be one

mechanism by which they regulate depression. Additionally, THC is a partial agonist of CB1 receptors, which are involved in the regulation of mood (Ashton & Moore, 2011; Valverde & Torrens, 2012). Anxiety may be associated with decreased levels of endocannabinoids and an upregulation of CB1 receptors, especially in the amygdala, hippocampus, and anterior cingulate gyrus (Ligresti et al., 2016). A double-blind study of patients with social anxiety disorder found that those who received a dose of CBD before a public speaking task had significantly reduced anxiety, cognitive impairment, discomfort during speech, and lower blood pressure and heart rate compared to controls (Beramaschi et al., 2011).

Cuttler et al. (2018) also examined the relationship between cannabinoid ratios and symptom relief, finding that low THC/high CBD cannabis was best for reducing perceived symptoms of depression, while high THC/high CBD cannabis was best for reducing perceived symptoms of stress.

While cannabis is widely recognized for its ability to reduce acute symptoms of anxiety and depression (Sexton et al., 2016), variations in cannabinoid profiles can produce significantly different effects. For instance, unlike CBD, human clinical studies demonstrate a common anxiogenic response to THC (LaFrance et al., 2020b), especially at higher doses (Sharpe et al., 2020). As CBD may attenuate the acute effects of THC (Freeman et al., 2019), identifying ratio recommendations for these two particular cannabinoids in the treatment of anxiety and depression is important.

Recently, smartphone technology has facilitated the collection of large amounts of data from cannabis users. One popular smartphone app – Releaf App™ – has been used worldwide by researchers, healthcare professionals, and cannabis product manufacturers to collect real-world data on the effects of consuming legal cannabis and hemp-derived CBD products. Data collected in the patented Releaf App have been published in more than 12 peer-reviewed articles in journals such as *Yale Journal of Biology & Medicine*, *Scientific Reports*, and *Frontiers in Pharmacology*. Tracking patient-reported symptoms through smartphone technology, the present paper seeks to add to existing literature by assessing self-reported experiences of cannabis users in the state of Florida, with a focus on how

cannabis alters symptoms of anxiety and depression along with its relationship to doses per session, consumption method, cannabinoid profile (THC/CBD), gender, and age. This approach builds on earlier research that has used smartphone technology to explore the role of cannabis in treating fatigue, insomnia, migraine- and headache-related pain, obsessive-compulsive disorder, and post-traumatic stress disorder (Kuhathasan et al., 2022; LaFrance et al., 2020a; Li et al., 2020; 2022; Stith et al., 2020; Mauzay et al., 2021). This approach also provides researchers with a more natural and authentic perspective on an individual's use and perceived outcomes with cannabinoid products. Using a smartphone application such as the Releaf App allows individuals to anonymously track their real-time use of cannabinoid products from the comfort of their home while collecting their perspective before, during, and after cannabis consumption. Using a mobile application in this way thus provides a more ecologically valid setting than what most clinical settings offer. This change in environment could result in participants experiencing different levels of anxiety than what their baseline is while in their regular daily routine.

METHODS

Procedure

This dataset was observational and was provided to us by Releaf App after the data had been collected, making it archival in nature. All data came from the state of Florida between March 30, 2018 and December 19, 2021. All data provided were stripped of any identifying characteristics and made anonymous. The Releaf App was designed to help patients monitor the variable effects of cannabinoid-based products and records the types, routes of administration, and labeled cannabis phenotypes and cannabinoid contents of the products consumed. Users indicate the medical conditions for which they are consuming cannabis, real-time symptom intensity levels prior to and following consumption, and any possible side effects experienced, under otherwise naturalistic conditions. Prior to consuming cannabis, users are directed by the app to enter information about the product they intend to consume based on information provided on product labels. Upon

starting a treatment session, the user specifies the symptoms to be treated, reports a starting symptom intensity level (on a visual analog scale from 0 to 10), consumes the cannabis product, updates the symptom level, records side effects, and ends the session. The user can update the symptom intensity level as frequently as they want and can select multiple side effects (side effects were not included in this dataset). Our dataset consisted of participants only reporting using cannabis for anxiety and/or depression. In total, we obtained data on 418 users, who recorded 9,966 sessions, in which 13,063 symptoms were treated (patients could report treating both anxiety and depression in a single session). Users recorded different number of sessions that had a range of 1 – 2,844. Mean value of number of sessions is 31.25 ($SD = 172.7$), and median number of sessions is 6 ($Q0.25 = 3$, $Q0.75 = 12$). Anxiety was treated 7,752 (59.3%) times and depression was treated 5,311 (40.7%) times.

Participants

Out of 418 users, 240 (57.4%) were female, 164 (39.2%) were male, and 14 (3.4%) reported non-binary gender. The average age of users was 36.53 years ($SD = 11.39$).

Symptom Level Analysis

All symptom level analyses were conducted in R v.4.0.3. (R Core Team, 2021), using packages lme4 (Bates et al., 2014) and lmerTest (Kuznetsova et al., 2017) for calculating p-values. Furthermore, data were collected for one or more sessions per user. To reflect this hierarchical order of these data (ratings nested within sessions, which were further nested within user), we analyzed data using linear mixed-effects modeling and specified a three-level random intercept model, which estimates random effects of sessions and users and also estimates fixed effects of each predictor variable used in the study. Significance of predictors was obtained using lmerTest package via Satterthwaite's degrees of freedom method. Analyzing these data using linear mixed-effects approach allowed us to model specifics of the dataset: there were potentially multiple recordings for the same user representing repeated measurements, and each user could have one or more recordings of their sessions, meaning that the design of this study was

imbalanced. Compared to more traditional approaches such as linear regression or repeated measures ANOVA, linear mixed-effects models do not have these conditions as an assumption and can handle this data structure well (Snijders & Bosker, 2012).

First, we entered symptom relief changes, which refers to the amount of relief reported before versus after using cannabis (which is represented by the model intercept). Since symptom severity start levels correlated with symptom relief, multilevel $r(13061) = 0.36, p < .001$, following other work (Li et al., 2020; Stith et al., 2018), we include symptom start level in the model where appropriate as a control. We then estimated fixed effects of symptom type (depression or anxiety), doses per session (the number of inhalations taken in a session), and consumption method (vaping versus smokable flower – joint or pipe). Gender and age variables were then entered to assess their impact, followed by the two most reported cannabinoids in the user's product, THC and CBD levels. It should be noted that values of THC and CBD were self-entered by Releaf App users; thus many failed to provide these data. Among joint and pipe users, 611 cases had missing values, and 267 cases included values that seemed improbable for flower cannabinoid profiles (e.g., >50% of THC and/or CBD). Furthermore, among vape users, 3,608 cases had missing values, and 46 cases had improbable values for THC and/or CBD (e.g., >100% THC/CBD). After these cases were removed, the final sample size for the models that included fixed effects of THC and CBD levels were 180 users who recorded a total of 4295 sessions.

User Level Analysis

The goal for analyzing responses from participants at the user level was to investigate whether there were any differences among participants who ended up experiencing positive relief (averaged across sessions for each user) after consuming cannabis compared to those who experienced averaged negative or no relief outcomes (since there were only 5% of participants who had negative relief outcomes, no relief and negative relief individuals were grouped together

and pitted against those who experienced positive relief). The data were averaged at the user level and analyzed separately for symptoms of anxiety and depression. Variables of interest between the two relief outcome groups were total number of sessions, symptom start and end levels, doses per session, consumption method, age, and gender.

RESULTS

Zero-order multilevel correlations between the amount of relief and all quantitative independent variables used in the study were analyzed first¹. Amount of relief was significantly correlated with symptom intensity at the start of the session, doses per session, and age, but not with THC and CBD levels, symptom start multilevel $r(13061) = 0.36, p < .001$; doses per session multilevel $r(13061) = 0.08, p < .001$; age multilevel $r(13061) = 0.05, p < .001$; THC multilevel $r(4293) = 0.01, p = ns$; CBD multilevel $r(4293) = -0.03, p = ns$.

Symptom Level Analysis

Findings from the linear mixed-effects models for predicting relief based on user demographics and characteristics of consumed cannabis are presented in Table 1. Results showed that depression/anxiety symptomatology was significantly reduced after cannabis sessions in general (Model 1). Since symptom severity start levels correlated with symptom relief, multilevel $r(13061) = 0.36, p < .001$, following other work (Li et al., 2020; Stith et al., 2018), we included symptom start levels and found it to be a significant predictor of relief (Model 2). After entering symptom type, doses per session, and consumption method into the model, all three predictors were found to be significantly related to relief, although each effect size was relatively small (standardized beta weights smaller than .1; Nieminen, 2022; Model 3). Gender and age variables were entered next, with both variables failing to significantly impact relief (Model 4). Last, THC and CBD levels were entered. THC did not significantly impact relief; however, CBD levels did (Model 5).

¹The R Package correlation (Makowski et al., 2019) used in this study does not provide multilevel correlations for categorical variables (e.g., symptom type), as they are treated as random effects variables, hence no correlation coefficients are provided in those contexts.

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Table 1. Results of the mixed-effects modeling analysis of relief after cannabis consumption, results at the symptom level of analysis.

Predictors	Model 1			Model 2			Model 3			Model 4			Model 5		
	<i>B</i>	β	<i>p</i>												
Intercept	2.17		<0.001	-0.13		0.241	-0.36		0.002	-0.55		0.114	-0.33		0.078
Symptom start				0.44	0.39	<0.001	0.44	0.39	<0.001	0.42	0.45	<0.00	0.48	.48	<0.001
Symptom type							0.04	0.01	0.026	0.03	0.01	0.112	-0.01	-.00	0.657
Doses per session							0.02	0.05	<0.001	0.04	0.08	<0.00	0.02	.05	<0.001
Consumption method							0.16	0.05	0.007	0.20	0.08	0.001	0.09	.03	0.538
Age										0.00	0.02	0.655			
Gender										0.12	0.05	0.572			
THC													0.00	.00	0.864
CBD													-0.01	-.05	0.022
Random effects															
σ^2		0.84			0.66			0.66			0.70			0.52	
$\tau_{00 \text{ sess_id:user}}$		2.18			1.95			1.94			1.80			2.12	
$\tau_{00 \text{ user}}$		4.60			3.34			3.30			3.32			3.49	
ICC		0.89			0.89			0.89			0.88			0.92	
$N_{\text{sess_id}}$		9966			9966			9966			8356			4295	
N_{user}		418			418			418			390			180	
Observations		13063			13063			13063			11085			5705	
Marginal R^2 / Conditional R^2		0.000 / 0.889			0.217 / 0.913			0.224 / 0.913			0.166 / 0.899			0.241 / 0.936	

Note. Symptom type reference category is ‘anxiety’; consumption method reference category is ‘smokable flower (joint or pipe)’; gender reference category is ‘female’; *B* unstandardized regression coefficient; β standardized regression coefficient; σ^2 Residual variance; $\tau_{00 \text{ sess_id:user}}$ intercept variance at session level; $\tau_{00 \text{ user}}$ intercept variance at user level.

User Level Analysis

Anxiety

For continuous IVs, Welch’s independent samples *t*-tests were used to assess differences between users who were in the positive (68%, or 257 users) or negative/no relief group (32%, or 121 users), and a chi square test of independence was used to inspect any differences in gender. Individuals who had positive relief outcomes had significantly more sessions, $t(361.15) = 2.18$, $p = .03$, $d = .21$, and consumed more doses per session, $t(327.5) = 3.35$, $p < .001$, $d = .34$, than those in the negative/no relief group. Age, $t(214.47) = -1.04$, $p = .3$, $d = -.12$, and gender, $\chi^2(1, N = 365) = .01$, $p = .91$, were not significantly different among the two relief groups. In order to investigate consumption method differences between those in the two relief outcome groups, we calculated the proportion of each consumption method used

(smokable flower [joint, pipe] or vape) for each user across all sessions. There were no differences in consumption methods (vape vs. smokable flower) between the positive relief and negative/no relief groups, $t(224.08) = 1.09$, $p = .28$, $d = .12$. See Supplementary Table 1 for all descriptive and inferential statistics for this analysis.

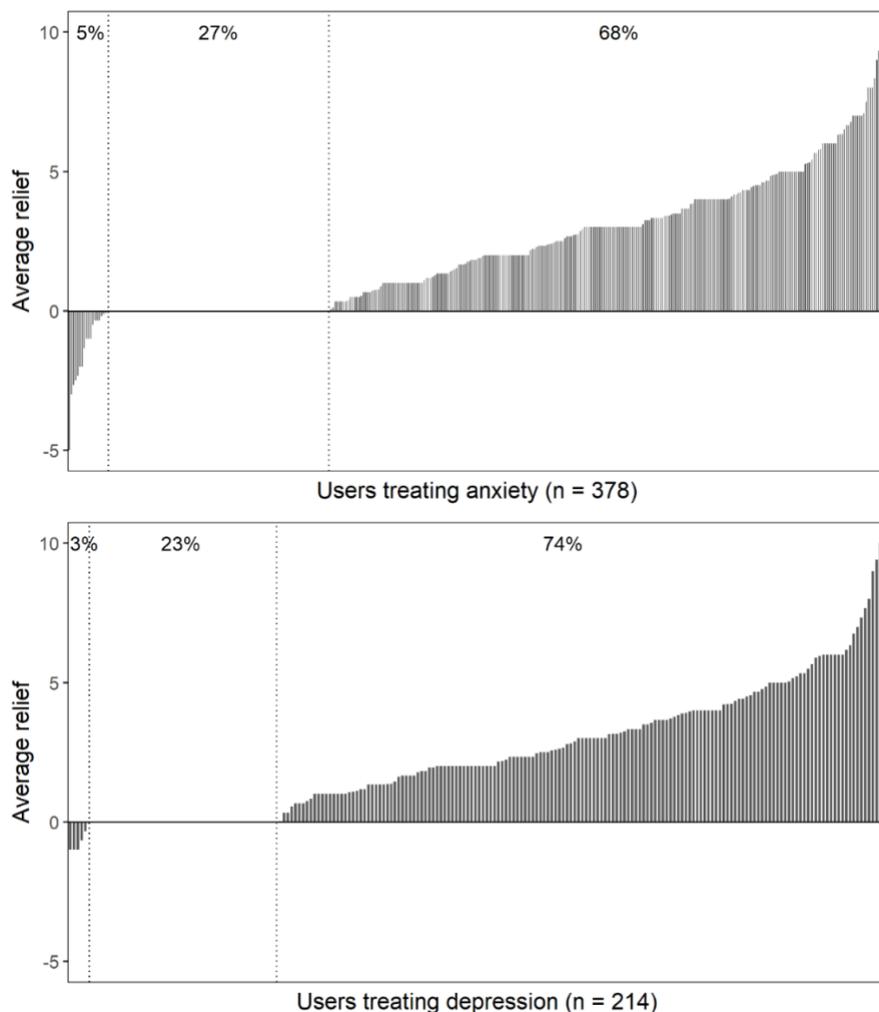
Depression

The same tests described above for anxiety were used to detect differences among the different relief outcome groups for depression. See Figure 1 for a graphical depiction of all users’ depression relief amount. Individuals who had positive relief outcomes (74%, or 159 users) had significantly more sessions, $t(168.58) = 2.03$, $p = .044$, $d = .23$, than those in the negative/no relief group (26%, or 55 users). Doses per session, $t(85.05) = 1.48$, $p = .14$, $d = .24$, age, $t(100.7) = .24$, $p = .81$, $d = .04$, and gender, $\chi^2(1, N = 204) = .05$,

$p = .82$, were not significantly different among the two relief outcome groups. See Supplementary Table 2 for all descriptive and inferential statistics for this analysis. The calculation of each consumption method proportion used within the two relief outcome groups was the same as

described above for anxiety. There were no differences in consumption methods (vape vs. smokable flower) between the positive relief and negative / no relief groups, $t(87.85) = .95$, $p = .34$, $d = .15$.

Figure 1. Average relief for anxiety and depression symptomatology before and after cannabis use sessions for users in the study ($N=418$). Lines shown above 0 on the y-axis indicate positive relief outcomes (68% and 74% of users respectively). No lines present represent no change in relief (27% and 23% respectively). Lines shown below 0 on the y-axis indicate negative relief outcomes (5% and 3%, respectively).



DISCUSSION

The present study explored real-time changes in Florida cannabis users' depression and anxiety symptomatology immediately before and after using cannabis. Analyzing the data using linear mixed-effects modeling allowed us to investigate effects not only between participants, but also

across multiple sessions for the same user. Compared to more traditional approaches such as linear regression or repeated measures ANOVA, these models handle the data structure particularly well (Snijders & Bosker, 2012); other work has used similar analytical techniques (e.g., Stith et al., 2018).

First, multilevel zero-order correlations between the symptom intensity at the start of the

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session, doses per session, and age showed significant correlations with amount of relief. However, aside from symptom intensity at the start of the session, only the variable doses per session approached an effect size considered practically meaningful (Cohen, 1988). THC and CBD levels were not significantly correlated with amount of relief.

Results from the symptom level analysis showed that both depression and anxiety symptoms significantly decreased after cannabis use in general; results at the user level of analysis showed that the majority of users experienced positive relief outcomes. This replicates previous work which has shown decreases in depression (Cutler et al., 2018; Li et al., 2020; Sachedina et al., 2022; Stith et al., 2018) and anxiety (Cutler et al., 2018; Sachedina et al., 2022; Sharpe, 2020; Stith et al., 2018) symptomatology following real-time cannabis consumption. Gender and age also did not play a significant role in affecting symptom relief. Similarly, Cutler and colleagues (2018) found no significant gender differences with regards to alleviation of depression symptoms, although, in their study, women perceived a greater decrease in anxiety symptoms than men. Factoring in symptom type, doses per session, and consumption method revealed significant effects, although interpreting each predictor's standardized beta coefficient showed very small effect sizes and should be interpreted with caution (see below for a discussion). Therefore, the effect of consumption method (or lack thereof), at least for depression, is similar to findings from Li et al (2020). While THC levels did not significantly impact symptom relief, CBD levels did. But, like doses per session and consumption method, CBD's effect size was small; thus, caution is warranted when interpreting any practical significance based on the presented model. What is more, not all users reported THC and/or CBD levels in their product, making the results difficult to generalize to all users in the study. While emerging research suggests that cannabis may significantly reduce ratings of depression (Li et al., 2020) and anxiety (e.g., Cutler et al., 2018), far less is known about the specific cannabinoid profiles that may be most useful to patients. For instance, unlike CBD, human clinical studies demonstrate a common anxiogenic response to THC (LaFrance et al., 2020b), especially at higher doses (Sharpe et al.,

2020). As CBD may attenuate the acute effects of THC (Freeman et al., 2019), identifying ratio recommendations for these two particular cannabinoids in the treatment of anxiety and depression is of immediate importance. In addition, the terpenes found in specific chemovars may play a role in relieving symptoms of anxiety and depression (Kamal et al., 2018; Weston-Green et al., 2021).

As with any medication, results vary from person to person. In some, cannabis may increase anxiety. But analyzing the data at the user level revealed that the majority of users experienced positive relief from their cannabis use sessions (68% anxiety, 74% depression) compared to users who experienced no relief (27% anxiety, 23% depression) or negative relief (5% anxiety, 3% depression); see Figure 1.

For those experiencing anxiety, users in the positive relief group reported significantly more cannabis user sessions and more doses than those who experienced no or negative relief outcomes. Although in the current study more user sessions and more doses were associated with an increase in symptom relief, more is not always better. Cannabis has a biphasic dose response curve. Lower doses of THC can decrease subjective reports of anxiety, whereas higher doses may be anxiogenic (Andrade et al., 2019; Sharpe et al., 2020). The challenge, of course, is that due to the individual differences in the endocannabinoid system, there is no universal standard as to what can be considered a "low" or "high" dose. In addition, this study does not include data on the extent of previous use of cannabis and potential tolerance that may have developed among different users. A previous study on Florida medical cannabis users (Rosenthal & Pipitone, 2021) showed that fewer than one-quarter of medical cannabis patients reported needing more cannabis since beginning treatment to get the desired symptomatic effects. Another recent study in Pennsylvania found about 34% of medical cannabis patients reported needing more use over time (Kimless et al., 2022), suggesting that tolerance may not be a primary factor in leading to more cannabis consumption, but may simply be a result of individual differences in how users in the current study consume their cannabis. Last, consumption method, age, and gender did not significantly differ among the different anxiety relief groups.

For those experiencing depression, those in the positive relief group reported significantly more sessions than those in the no relief/negative relief group. Again, it would be shortsighted to conclude that simply using more cannabis will help treat symptoms of depression. These differences are most likely due to how cannabis users in the study have naturally titrated their consumption to meet their desired needs over time. Future work should attempt to collect data on past cannabis use practices to better establish a connection between cannabis use amount and depression symptom relief. Other variables considered in this analysis – doses per session, age, gender, and consumption method – were all found not to be significantly different between the two depression relief groups.

Incorporating smartphone technology to assess real-time user experiences when consuming cannabis gives researchers the ability to see important time-related changes in mental health following cannabis consumption. In addition, it gives researchers more accurate data on not only what products are being used, but the formulation of those products, their chemovar, and exactly how these products are being consumed. This allows researchers to get real-world data insights from an opt-in registry of the actual cannabis products available in state-regulated dispensaries, while keeping everything anonymous, thus protecting patient and consumer privacy. This leads to more accurate studies rather than relying on patient feedback from review-like sites or effects of products not widely available to consumers in state regulated markets.

Our results, similar to earlier work (Stith et al., 2018), speak to the potential of cannabis to combat acute depression and anxiety with a rapid onset of self-reported relief. For instance, Li et al. (2020) found “widely experienced” relief from depression within two hours or less. This potential warrants particular focus, given that currently available antidepressants often take weeks, or even months, to achieve their full effect (Machado-Vieira et al., 2010), and meta-analyses suggest their effectiveness is marginal or even negligible for patients experiencing mild to moderate depression (Kirsch et al., 2002). The side effects and addictive potential of some anxiolytic drugs are disconcerting. Cannabis users in this and other studies report experiencing symptom relief

within a very short time span after drug administration. While caution must be exercised with cannabis use (as it is with all pharmaceutical approaches), cannabis administration to address acute symptoms of anxiety or depression is a treatment option that deserves further investigation.

Some may argue that intoxication due to cannabis use is the cause of what might be only temporary relief in symptoms of anxiety and depression. Although our data cannot speak to the long-term impacts of medical cannabis use, recent research does shed light on this topic. Martin et al. (2021) followed 368 patients with depression and anxiety for four years—some of whom used cannabis for relief, and others who used traditional SSRI medications. They found that medicinal cannabis use was associated with lower self-reported depression, better sleep, less pain, and a higher quality of life. Furthermore, researchers conducted follow-up assessments every three months throughout the study. Those who used cannabis to control symptoms of anxiety and depression at baseline, as well as those who initiated use during the course of the study, showed improvement in symptoms over time, but those who did not use medicinal cannabis did not show improvement over the four-year trial. Future work investigating the long-term impacts of medical cannabis use will undoubtedly help the scientific community better understand this area.

While researchers are utilizing different and better statistical approaches (e.g., linear mixed-effects models) to better understand how cannabis can affect mental health outcomes, more interpretable data needs to be provided, namely estimates of effect size and/or the use of standardized statistics (Nieminen, 2022). For example, it is difficult to interpret unstandardized regression coefficients across different research articles using bivariate or multiple regression, hence we cannot directly compare our work to other work in this area. Specific to our data, since the linear mixed-effects modeling incorporates multiple sessions from each user and also across every participant, degrees of freedom for certain tests were large, leading to statistical significance occurring even though any practical movement of the data (as measured by the standardized regression coefficients) for some of the variables can be considered negligible.

Limitations

This study was based on self-reported archival data with no experimental intervention/manipulation taking place. There was no control group to compare any effects to and, therefore, the study cannot take into account any expectancy effects towards positive affect. The study measured the acute effects on mood immediately before and after cannabis use rather than in-between session effects. Also, individuals who don't find cannabis to be effective for reducing symptoms of anxiety and depression are likely underrepresented in this data, as such individuals are likely to decline participation and/or discontinue study involvement. No drug is "one size fits all," and cannabis may be contraindicated in some users. Those with cardiovascular issues or a genetic predisposition for schizophrenia or bipolar disorder may want to consider other treatment options. Literature regarding long-term adverse events related to cannabinoid use is limited, with a 2015 meta-analysis failing to find any studies evaluating the topic specifically, even when searches were extended to lower levels of evidence (Whiting et al., 2015). Future studies warrant independent variable condition manipulation (random assignment to drug/control groups) and should also incorporate blind, placebo-controlled conditions. The present data was provided under anonymous circumstances, thus we do not have any reason to believe it was inherently biased in any major way. However, to understand the true impact of cannabis on depression/anxiety symptomatology, the above experimental procedures are needed.

As we did not have specific details on patient cannabis consumer demographics, it was not possible to differentiate between individuals who were registered medical cannabis card holders and those who were purchasing cannabis from the unregulated black market. Although users provided the route of administration and consumption method, we were not able to regulate the type or quality of cannabis product they used. The scientific community would benefit from the comparative study of specific medical cannabis products, the impact of THC and CBD ratios, as well as the influence of over 100 other cannabinoids and terpenes found in the cannabis plant.

It was also not possible to clinically diagnose depression or anxiety in any person in the study; only the user's subjective interpretations of their own depression and/or anxiety was available.

Smartphones using application technology allows for convenient collection of otherwise difficult-to-obtain data such as real-time experiences following psychoactive drug use. Future work should take the necessary steps to attempt to control for extraneous variables while utilizing this newer technology for a better understanding of the psychological impact of cannabis on symptoms of depression and anxiety.

REFERENCES

- Andrade, A.K., Renda, B., & Murray, J.E. (2019). Cannabinoids, interoception, and anxiety. *Pharmacology, Biochemistry, and Behavior*, *180*, 60-73. <https://doi.org/10.1016/j.pbb.2019.03.006>
- Ashton, C.H., & Moore, P.B. (2011). Endocannabinoid system dysfunction in mood and related disorders. *Acta Psychiatrica Scandinavica*, *124*(4), 251-261. <https://doi.org/1.1111/j.1600-0447.2011.01687.x>
- Bates, D., Mächler, M., Bolker, B., & Walker, S. (2014). Fitting linear mixed-effects models using lme4. arXiv preprint arXiv:1406.5823. <https://doi.org/.48550/arXiv.1406.5823>
- Brody, D. & Qiuping, G. (2020, September 4). Antidepressant use among adults: United States, 2015-2018. *NCHS Data Brief*, *377*. <https://www.cdc.gov/nchs/products/databriefs/db377.htm>
- Centers for Disease Control and Prevention (CDC). (2018). *National Ambulatory Medical Care Survey: 2018 National Summary Tables. Table 23*. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2018-ed-web-tables-508.pdf
- Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Lawrence Erlbaum Associates. <https://www.taylorfrancis.com/books/mono/10.4324/9780203771587/statistical-power-analysis-behavioral-sciences-jacob-cohen>
- Corroon, J.M. Jr., Mischley, L.K., & Sexton, M. (2017). Cannabis as a substitute for prescription drugs - a cross-sectional study. *Journal of Pain Research*, *10*, 989-998. <https://doi.org/10.2147/JPR.S134330>

- Cuttler, C., Spradlin, A., & McLaughlin, R. J. (2018). A naturalistic examination of the perceived effects of Cannabis on negative affect. *Journal of Affective Disorders, 235*, 198-205. <https://doi.org/10.1016/j.jad.2018.04.054>
- Edinoff, A.N., Nix, C.A., Hollier, J., Sagraera, C.E., Delacroix, B.M., Abubakar, T., Cornett, E.M., Kaye, A.M., & Kaye, A.D. (2021). Benzodiazepines: Uses, dangers, and clinical considerations. *Neurology International, 13*(4), 594-607. <https://doi.org/10.3390/neurolint13040059>
- Freeman, A.M., Petrilli, K., Lees, R., Hindocha, C., Mokrysz, C., Curran, H.V., Saunders, R., & Freeman, T.P. (2019). How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. *Neuroscience Biobehavioral Review, 107*, 696-712. <https://doi.org/10.1016/j.neubiorev.2019.09.036>
- Green, T.V. (2022, November 22). Americans overwhelmingly say marijuana should be legal for recreational or medical use. *Pew Research Center*. <https://www.pewresearch.org/fact-tank/2021/04/16/americans-overwhelmingly-say-marijuana-should-be-legal-for-recreational-or-medical-use/>
- Hill, M. N., & Patel, S. (2013). Translational evidence for the involvement of the endocannabinoid system in stress-related psychiatric illnesses. *Biology of Mood & Anxiety Disorders, 3*(1), 19. <https://doi.org/10.1186/2045-5380-3-19>
- Jiang, W., Zhang, Y., Xiao, L., van Cleemput, J., Ji, S-P, Bia, G., & Zhang, X. (2005). Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic and antidepressant-like effects. *Journal of Clinical Investigations, 115*(11), 3104-16. <https://doi.org/10.1172/JCI25509>
- Jugl, S., Okpeku, A., Costales, B., Morris, E. J., Alipour-Haris, G., Hincapie-Castillo, J. M., Stetten, N. E., Sajdeya, R., Keshwani, S., Joseph, V., Zhang, Y., Shen, Y., Adkins, L., Winterstein, A. G., & Goodin, A. (2021). A mapping literature review of medical cannabis clinical outcomes and quality of evidence in approved conditions in the USA from 2016 to 2019. *Medical Cannabis and Cannabinoids, 4*(1), 21-42. <https://doi.org/10.1159/000515069>
- Jurkus, R., Day, H. L., Guimarães, F. S., Lee, J. L., Bertoglio, L. J., & Stevenson, C. W. (2016). Cannabidiol regulation of learned fear: Implications for treating anxiety-related disorders. *Frontiers in Pharmacology, 7*(454). <https://doi.org/10.3389/fphar.2016.00454>
- Kamal, B.S., Kamal, F., & Lantela, D.E. (2018). Cannabis and the anxiety of fragmentation—A systems approach for finding an anxiolytic cannabis chemotype. *Frontiers in Neuroscience, 12*(730). <https://doi.org/10.3389/fnins.2018.00730>
- Kessler, R.C., Petukhova, M., Sampson, N.A., Zaslavsky, A.M., & Wittchen, H-U. (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International Journal of Methods in Psychiatric Research, 21*(3), 169-184. <https://doi.org/10.1002/mpr.1359>
- Kimless, D., Caloura, M., Markos, V., Ryan, J., Abbonizio, S., Janicki, S. (2022). An observational cross-sectional survey exploring the indications for and responses to medical marijuana use in certified patients in Pennsylvania. *Journal of Primary Care & Community Health, 13*, 1-10. <https://doi.org/10.1177/21501319221129734>
- Kirsch, I., Deacon, B.J., Huedo-Medina, T.B., Scoboria, A., Moore, T.J., & Johnson, B.T. (2008). Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med, 5*(2), e45. <https://doi.org/10.1371/journal.pmed.0050045>
- Kirsch, I., Moore, T. J., Scoboria, A., & Nicholls, S. S. (2002). The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention & Treatment, 5*(1). <https://doi.org/10.1037/1522-3736.5.1.523a>
- Kuhathasan, N., Minuzzi, L., MacKillop, J., & Frey, B. N. (2022). An investigation of Cannabis use for insomnia in depression and anxiety in a naturalistic sample. *BMC Psychiatry, 22*(1), 303. <https://doi.org/10.1186/s12888-022-03948-6>
- Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. (2017). lmerTest package: tests in linear

- mixed effects models. *Journal of Statistical Software*, *82*, 1-26. <https://doi.org/10.18637/jss.v082.i13>
- LaFrance, E. M., Glodosky, N. C., Bonn-Miller, M., & Cuttler, C. (2020a). Short and long-term effects of Cannabis on symptoms of post-traumatic stress disorder. *Journal of Affective Disorders*, *274*, 298-304. <https://doi.org/10.1016/j.jad.2020.05.132>
- LaFrance, E. M., Stueber, A., Glodosky, N. C., Mauzay, D., & Cuttler, C. (2020b). Overbaked: Assessing and predicting acute adverse reactions to Cannabis. *Journal of Cannabis Research*, *2*(1). <https://doi.org/10.1186/s42238-019-0013-x>
- Li, X., Diviant, J. P., Stith, S. S., Brockelman, F., Keeling, K., Hall, B., & Vigil, J. M. (2020). The effectiveness of Cannabis flower for immediate relief from symptoms of depression. *Yale Journal of Biological Medicine*, *93*(2), 251-264. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7309674/>
- Li, X., Diviant, J. P., Stith, S. S., Brockelman, F., Keeling, K., Hall, B., & Vigil, J. M. (2022). The effects of consuming Cannabis flower for treatment of fatigue. *Medical Cannabis and Cannabinoids*, *5*(1), 76-84. <https://doi.org/10.1159/000524057>
- Machado-Vieira, R., Baumann, J., Wheeler-Castillo, C., Latov, D., Henter, I. D., Salvadore, G., & Zarate, C. A. (2010). The timing of antidepressant effects: A comparison of diverse pharmacological and somatic treatments. *Pharmaceuticals* (Basel, Switzerland), *3*(1), 19-41. <https://doi.org/10.3390/ph3010019>
- Makowski, D., Ben-Shachar, M. S., Patil, I., & Lüdtke, D. (2019). Methods and Algorithms for Correlation Analysis in R. *Journal of Open Source Software*, *5*(51), 2306. <https://doi.org/10.21105/joss.02306>
- Marsicano, G., Wotjak, C.T., Azad, S.C., Bisogno, T., & Rammes, G., et al. (2002). The endogenous cannabinoid system controls extinction of aversive memories. *Nature*, *418*, 530-534. <https://doi.org/10.1038/nature00839>
- Martin, E.L., Strickland, J.C., Schlienz, N.J., Munson, J., Jackson, H., Bonn-Miller, M.O., & Vandrey, R. (2021). Antidepressant and anxiolytic effects of medicinal cannabis use in an observational trial. *Frontiers in Psychiatry*, *12*. <https://doi.org/10.3389/fpsy.2021.729800>
- Mauzay, D., LaFrance, E. M., & Cuttler, C. (2021). Acute effects of Cannabis on symptoms of obsessive-compulsive disorder. *Journal of Affective Disorders*, *279*, 158-163. <https://doi.org/10.1016/j.jad.2020.09.124>
- Nieminen, P. (2022). Application of Standardized Regression Coefficient in Meta-Analysis. *BioMedInformatics*, *2*(3), 434-458. <https://doi.org/10.3390/biomedinformatics2030028>
- Prashad, S., & Filbey, F. M. (2017). Cognitive motor deficits in cannabis users. *Current Opinion in Behavioral Sciences*, *13*, 1-7. <https://doi.org/10.1016/j.cobeha.2016.07.001>
- Reinarman, C., Nunberg, H., Lanthier, F., & Heddleston, T. (2011). Who are medical marijuana patients? Population characteristics from nine California assessment clinics. *Journal of Psychoactive Drugs*, *43*(2), 128-35. <https://doi.org/10.1080/02791072.2011.587700>
- Rosenthal, M.S. & Pipitone, R.N. (2021). Demographics, perceptions, and use of medical marijuana among patients in Florida. *Medical Cannabis and Cannabinoids*, *4*, 13-20. <https://doi.org/10.1159/000512342>
- Sachedina, F., Chan, C., Damji, R.S., & de Sanctis, O.J. (2022). Medical cannabis use in Canada and its impact on anxiety and depression: A retrospective study. *Psychiatry Research*, *313*, 114573. <https://doi.org/10.1016/j.psychres.2022.114573>
- Sales, A.J., Fogaça, M.V., Sartim, A.G., Pereira, V.S., Wegener, G., Guimarães, F.S., & Joca, S.R.L. (2019). Cannabidiol induces rapid and sustained antidepressant-like effects through increased BDNF signaling and synaptogenesis in the prefrontal cortex. *Molecular Neurobiology*, *56*(2), 1070-81. <https://doi.org/10.1007/s12035-018-1143-4>
- Sarangi, A., McMahon, T., Gude, J. (2021). Benzodiazepine misuse: An epidemic within a pandemic. *Cureus*, *13*(6), e15816. <https://doi.org/10.7759/cureus.15816>
- Schmitz, A. (2016). Benzodiazepine use, misuse, and abuse: A review. *Mental Health Clinician*, *6*(3), 120-126. <https://doi.org/10.9740/mhc.2016.05.120>
- Sexton, M., Cuttler, C., Finnell, J.S., & Mischley, L.K. (2016). A cross-sectional survey of medical cannabis users: Patterns of use and

- perceived efficacy. *Cannabis & Cannabinoid Research*, 1(1), 131-138.
<https://doi.org/10.1089/can.2016.0007>
- Sharpe, L., Sinclair, J., Kramer, A., de Manincor, M., & Sarris, J. (2020.) Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. *Journal of Translational Medicine*, 18(1), 374.
<https://doi.org/10.1186/s12967-020-02518-2>
- Snijders, T., & Bosker, R. (2012). *Multilevel Analysis: An Introduction to Basic and Applied Multilevel Analysis* (2nd ed.). Sage Publications.
https://www.researchgate.net/publication/44827177_Multilevel_Analysis_An_Introduction_to_Basic_and_Advanced_Multilevel_Modeling
- Stern, C. A., Gazarini, L., Vanvossen, A. C., Zuardi, A. W., Galve-Roperh, I., Guimaraes, F. S., Takahashi, R. N., & Bertoglio, L. J. (2015). Δ9-Tetrahydrocannabinol alone and combined with cannabidiol mitigate fear memory through reconsolidation disruption. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, 25(6), 958-65.
<https://doi.org/10.1016/j.euroneuro.2015.02.001>
- Stith, S. S., Diviant, J. P., Brockelman, F., Keeling, K., Hall, B., Lucern, S., & Vigil, J. M. (2020). Alleviative effects of Cannabis flower on migraine and headache. *Journal of Integrative Medicine*, 18(5), 416-424.
<https://doi.org/10.1016/j.joim.2020.07.004>
- Stith, S.S., Vigil, J.M., Brockelman, F., Keeling, K., & Hall, B. Patient-reported symptom relief following medical cannabis consumption. (2018). *Frontiers in Pharmacology*, 9, 916.
<https://doi.org/10.3389/fphar.2018.00916>
- Stone, M.B., Yaseen, Z.S., Miller, B.J., Richardville, K., Kalaria, S.N., & Kirsch, I. (2022). Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: individual participant data analysis. *British Medical Journal*, 378, e067606.
<https://doi.org/10.1136/bmj-2021-067606>
- Valverde, O. & Torrens, M. (2012). CB1 receptor-deficient mice as a model for depression. *Neuroscience*, 204, 193-206.
<https://doi.org/10.1016/j.neuroscience.2011.09.031>
- Wang, T., Collet, J.P., Shapiro, S., & Ware, M.A. (2008). Adverse effects of medical cannabinoids: A systematic review. *Canadian Medical Association Journal*, 178(13), 1669-1678. <https://doi.org/10.1503/cmaj.071178>
- Weston-Green, K., Clunas, H., & Naranjo, C.J. (2021). A review of the potential use of pinene and linalool as terpene based medicines for brain health: Discovering novel therapeutics in the flavors and fragrances of cannabis. *Frontiers in Psychiatry*, 12, 583211.
<https://doi.org/10.3389/fpsy.2021.583211>
- Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., Keurentjes, J. C., Lang, S., Misso, K., Ryder, S., Schmidtkofer, S., Westwood, M., & Kleijnen, J. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *Journal of the American Medical Association*, 313(24), 2456-2473.
<https://doi.org/10.1001/jama.2015.6358>

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