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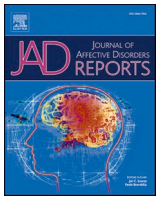

Research Paper

Anxiety severity and prescription medication utilization in first-time medical marijuana users

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ABSTRACT

Background: Anxiety and post-traumatic stress disorder (PTSD) are qualifying psychiatric conditions for medical marijuana (MM) treatment in Pennsylvania. This study examined baseline prevalence and changes in prescription anxiety medication use three months following MM treatment initiation among individuals with these qualifying conditions.

Methods: The study sample was comprised of 108 adults with anxiety or PTSD as a referring condition; they were enrolled in a longitudinal study evaluating biopsychosocial outcomes in new MM patients. Consenting participants completed an assessment battery at baseline and Month 3 (n = 94, 87 % follow-up rate) that included a measure of anxiety severity and questions about current anxiety medication prescription and desired (baseline) and actual (Month 3) reductions in medication use.

Results: Findings indicated that 59 % of participants reported prescription medications for anxiety, with 70 % reporting at least a moderate desire to reduce medication use. Overall and within the medication sub-sample, participants displayed significant reductions in anxiety severity from baseline to Month 3 (p's <0.0001). Furthermore, 32 % reported actual reductions in medication use at Month 3, and reductions were more likely among patients prescribed benzodiazepines than other drug classes.

Conclusions: Results suggest that a significant number of MM patients with anxiety and/or PTSD diagnoses are currently being prescribed antianxiety medications and that MM may help to reduce their use of these medications.

Limitations: Limitations include the observational study design and the lack of a PTSD-specific measure. More controlled longitudinal studies are necessary to better understand the role of MM in the treatment of anxiety and PTSD.

1. Introduction

According to data from the National Comorbidity Study Replication study (Kessler et al., 2005a, 2005b), anxiety disorders (e.g., generalized anxiety disorder, panic disorder, social anxiety disorder) are the most prevalent psychiatric disorders in the United States with almost one-third of adults experiencing an anxiety disorder in their lifetime and one-fifth with a current diagnosis. Furthermore, approximately 7 % of adults have had post-traumatic stress disorder (PTSD) in their lifetime and 4 % have a current diagnosis according to findings from that same study. The overlap between anxiety and PTSD is well documented (e.g., (Daviu et al., 2019; Holman et al., 2000)); in fact, PTSD was characterized as an anxiety disorder until the Diagnostic and Statistical Manual of Mental Disorders-5 (see (Pai et al., 2017) for a review).

Treatments for both conditions include psychotherapy (e.g., cognitive-behavioral therapy), medications [e.g., selective serotonin reuptake inhibitors (SSRIs)], or some combination of both; however, these standard treatments are ineffective in remitting in anxiety in about 40 % of patients (see (Cuijpers et al., 2016) for a meta-analytic review). Furthermore, despite their high addiction potential (Schmitz, 2016), many patients who have anxiety disorders or PTSD are prescribed benzodiazepines to control their anxiety symptoms. In more recent years, medical marijuana (MM) has gained traction as treatment for these conditions despite the lack of high-quality evidence supporting its

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effectiveness (Berger et al., 2022; Boehnke et al., 2022).

It is hypothesized that MM may influence anxiety levels via several pathways; however, the specific mechanism(s) of action is currently unknown (Berger et al., 2022; Sharpe et al., 2020; Stack et al., 2022). Cannabinoid receptors exist throughout the central nervous system including the prefrontal cortex and the limbic system. These receptors are implicated in fear conditioning and can involve serotonin and GABA, among other neurotransmitters (Berger et al., 2022). MM is also hypothesized to have anti-inflammatory properties (Lima et al., 2021), and preliminary studies suggest that there may be a link between anxiety levels and biomarkers of inflammation (Peirce & Alviña, 2019: Vogelzangs et al., 2013).

1.1. Status of medical marijuana

In the United States, MM is currently legal in 38 states, 3 territories, and the District of Columbia (National Conference of State Legislatures, 2023) for the treatment of a host of medical conditions including cancer, chronic pain, epilepsy, HIV/AIDs, and multiple sclerosis, and psychiatric conditions such as anxiety disorders and PTSD. The determination of which qualifying conditions are eligible for MM treatment is established at the state-level, and MM laws and policies vary from state to state (Kimless et al., 2022). Despite MM's wide-spread adoption in the United States, marijuana remains classified as a Schedule 1 drug at the federal level (i.e., no currently accepted medical use and a high potential for abuse). This Schedule 1 status continues to present significant barriers to conducting randomized controlled trials (RCTs) to examine MM's safety and efficacy as a treatment for these various medical conditions. As such, the adoption of MM has grown at a much faster rate than our understanding of its safety and efficacy.

1.2. Efficacy of medical marijuana

Several reviews have been conducted on the strength of evidence supporting the use of MM as a treatment for conditions for which they have been approved. To date, the strongest evidence supporting the use of MM as an effective treatment has been for neuropathic pain and quality of life issues experienced by patients with multiple sclerosis and non-cancer chronic pain diagnoses (Hall et al., 2019). Despite the absence of strong empirical evidence supporting its efficacy, MM is perceived to be an effective treatment for anxiety and related conditions (e.g., Ashare et al., 2022; Leung et al., 2022), including PTSD, which is often characterized by severe anxiety. In fact, studies have shown anxiety and PTSD to be among the most common reasons for MM treatment initiation (e.g., Boehnke et al., 2022; Kimless et al., 2022; Leung et al., 2022).

However, systematic reviews on the efficacy of MM as a treatment for psychiatric conditions like anxiety and PTSD have concluded that the quality of evidence is inconsistent, low quality, and has a high risk of bias (Berger et al., 2022; Hall et al., 2019; Hindocha et al., 2020; Solmi et al., 2023; Stanciu et al., 2021; Wilkinson et al., 2016) as the large majority of studies published to date do not employ rigorous empirical experimental designs, have limited sample sizes, and examine only short-term outcomes. For example, Ergisi et al. (2022) conducted a case-series evaluation of from 67 patients in the UK Medical Cannabis Registry who were undergoing MM treatment and had a generalized anxiety disorder (GAD) diagnosis. They found significant improvements from baseline to six months in anxiety severity and sleep quality in the sample. However, the internal and external validity of the study was limited for a number of reasons (e.g., individuals for whom GAD was not a primary diagnosis were included, there were high rates of missing data, all participants having privately paid for their treatment). In contrast, Lee et al. (2022) examined changes in anxiety severity as measured by the clinical encounter data from over 5000 MM patients in Canada. Findings from this population-based study indicated no improvements in anxiety severity as measured by the GAD-7 in the six months following MM treatment initiation, even among those whose baseline score was in the moderate to severe range. More generally, the limited literature on anxiety and MM suggests that CBD and low to moderate levels of THC may have anxiolytic properties, while higher THC content may have the potential to be anxiogenic (e.g., Berger et al., 2022; Sharpe et al., 2020; Stack et al., 2022).

The high prevalence of anxiety disorders and PTSD in the general population, coupled with the fact that these patient populations represent a large proportion of individuals using MM, point to the need for additional research, especially controlled experimental research, on how MM treatment affects anxiety-related symptoms. Furthermore, research is needed to improve our understanding of how MM impacts patients' use of prescribed anxiety medications, including benzodiazepines which have a high addiction potential.

1.3. Study overview

Anxiety and PTSD are among the 24 approved conditions for MM treatment in PA (Pennsylvania Department of Health, 2023). Similar to national trends, studies (Ashare et al., 2022; Buonomano et al., 2022; Leung et al., 2022) have shown anxiety and PTSD to be among the three most common certifying conditions in the commonwealth of PA, along with chronic pain. The current study used data from an ongoing longitudinal observational trial examining biopsychosocial functioning over time among patients initiating MM treatment for any approved condition in PA. This sub-study investigated the extent to which anxiety symptom severity had changed in the three months following MM treatment initiation among individuals who had diagnoses of anxiety or PTSD as a qualifying condition. In addition, changes in use of anxiety medications over this three-month period were examined. This study is observational in design given the clinical trial-related restrictions associated with Schedule 1 substances.

2. Methods

2.1. Design and procedures

This prospective, observational study was conducted under the ethical oversight of the Philadelphia College of Osteopathic Medicine's Institutional Review Board (#H17–060). Individuals included in the analytic sample were recruited from four MM dispensaries located in Western and Central Pennsylvania as a part of a larger longitudinal study examining the impact of MM on clients' biopsychosocial functioning over of the first year following treatment initiation. To be eligible to participate in the larger trial, individuals had to be at least 18 years of age, have a PA-issued MM card, and be naïve to MM (prior recreational use was permitted). Individuals meeting these inclusion criteria were invited to participate in the study and were informed that the study was designed to examine how MM treatment affected health and functioning in different life areas. Following the informed consent process with a site-based research assistant, participants completed the baseline assessment battery (see measures below) and were scheduled to return to complete a follow-up assessment three months later. Participants received a $25 debit card payment for each study visit and a discount on their MM purchases.

Individuals from the larger study who reported an anxiety or PTSD diagnosis as their MM qualifying condition were selected for inclusion in the analytic sample for the current paper. A total of 108 individuals met this criterion and comprised the analytic sample. Approximately 87% of these participants (n = 94) completed the three-month follow-up assessment.

2.2. Measures

Data used in the present analyses were obtained from a comprehensive assessment battery completed by participants at baseline and

Month 3 post-baseline. Specific measures used in these analyses are described below.

2.2.1. Addiction severity index-5 lite (ASI-Lite; (Cacciola et al., 2007))

The ASI-Lite is a reliable and valid multidimensional assessment of current and lifetime psychosocial functioning across seven domains commonly impacted by substance use (i.e., medical, employment, psychiatric, alcohol use, drug use, legal, and family/social). In addition, the assessment contains a general section containing self-reported demographic items. Demographic variables including gender identity, age, racial identity, ethnicity, educational attainment, and marital status used in the analyses were taken from the ASI-Lite general section.

2.2.2. Generalized anxiety disorder 7-Item (GAD-7; (Spitzer et al., 2006))

The GAD-7 is a well-validated, brief, 7-item assessment of generalized anxiety disorder (GAD) and its severity. Items ask patients how often they have been bothered by each of the seven anxiety-related problems during the past two weeks with the following response options: not at all (0), several days (1), more than half of days (2), and nearly every day (3). Scale scores can range from 0 to 21 with scores from 5 to 9 indicating mild anxiety, 10–14 indicating moderate anxiety, and 15–21 indicating severe anxiety.

2.2.3. Anxiety medication items

Individuals who reported an anxiety-related disorder completed questions about their use of anxiety medications. Specific items from the baseline survey were as follows: (1) *Are you taking any prescribed medications on a regular basis for anxiety relief? If yes, specify medication.* and (2) *To what extent do you hope to reduce your use of prescribed anxiety medications after initiating medical marijuana treatment?* [rated on a 5-point Likert-type scale ranging from 1 (not at all) to 5 (extremely)]. Responses to the medication specification item were recoded into three categories: antidepressant [i.e., norepinephrine and dopamine reuptake inhibitors (NDRIs), selective serotonin reuptake inhibiters (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tetracyclics, serotonin modulators], benzodiazepine, and other (e.g., antipsychotics, anticonvulsants, antihistamines, alpha blockers, beta blockers). At the follow-up assessment, individuals were asked the following question: *To what extent have you decreased the amount (e.g., dosage, frequency) of anxiety medications you use since beginning medical marijuana treatment?* using the same 5-point Likert-type scale.

2.3. Data analysis

Descriptive statistics were used to characterize the sample on demographic and baseline status variables including the anxiety mediation-related items. Changes in GAD-7 anxiety severity scores from baseline to three months were examined using paired samples t-tests for the overall sample ($n = 94$) and for the subsample of participants who reported anxiety medication use at baseline ($n = 54$). Within the medication sample, descriptive statistics and, where appropriate, chi-square analyses were used to examine three-month self-reported reductions in anxiety medication use overall and as a function of treatment goal (i.e., whether participants reported a desire to reduce anxiety medication use after initiating MM treatment) and anxiety medication type (i.e., antidepressant, benzodiazepine, other). Finally, a Spearman rank-order correlation analysis was used to examine the extent to which reported reductions in anxiety medication use (as measured by the 5-point Likert-type item described above) was associated with the observed magnitude of change in GAD-7 scores from baseline to follow-up (i.e., month 3 score minus baseline score). All analyses were performed using SAS version 9.4.

3. Results

3.1. Participants

Participant characteristics are presented in Table 1. The majority of the sample identified as female (72 %, $n = 78$) and White (92 %, $n = 99$), and 4 % reported being Hispanic or Latino ($n = 4$). Participants were 47.18 years of age on average ($SD = 15.57$) and approximately half were married or in a domestic partnership (51 %; $n = 55$). Regarding individuals' MM referring conditions, 96 % of sample participants ($n = 104$) reported an anxiety disorder and 20 % ($n = 22$) reported a PTSD diagnosis. Eighteen participants (17 %) reported both anxiety and PTSD diagnoses.

3.2. Medication prescription

Fifty-nine percent of participants ($n = 64$) indicated that they were taking prescribed medications for anxiety relief at entry into the study. Among those who reported taking prescription medications, antidepressants were reported with the most frequency (43 %; $n = 46$; see Table 1 for specific antidepressant types), followed by benzodiazepines (19 %; $n = 12$). A total of 41 % ($n = 26$) of participants taking medication for anxiety reported using a different class of medication (e.g., anticonvulsants, antihistamines, beta blockers).

At the time of the baseline interview, participants who reported taking medication(s) to treat anxiety symptoms rated the extent to which they hoped to reduce their use of prescribed medications after beginning MM treatment. Item responses are provided in Table 1. Overall, the large majority (70 %, $n = 44$) indicated at least a moderate desire to reduce their use of currently prescribed anxiety medications, with almost one third (29 %, $n = 18$) of those on medication reporting an extreme desire to reduce their use.

Table 1
Participant characteristics at study entry ($n = 108$).

Variable		*M/n*	*SD/ %*
Age (years)		47.18	15.57
Gender identity	Female	77	72%
	Male	29	27%
	Non-binary	1	1%
Race	Black	4	4%
	White	99	92%
	Other	5	5%
Ethnicity	Hispanic/Latino/a/x	4	4%
Marital status	Married/domestic partnership		
Referring condition	Anxiety disorder	104	96%
	Post-traumatic stress disorder	22	20%
Prescribed medication		64	59%
Prescribed medication type ($n = 64$)	Benzodiazepine	12	19%
	Antidepressant	46	72%
	NDRI	4	6%
	Serotonin modulator	2	3%
	SNRI	9	14%
	SSRI	30	47%
	Tetracyclic	1	2%
	Other	26	41%
Desire to reduce use of anxiety medication(s) ($n = 63$)	Not at all	11	17%
	Slightly	8	13%
	Moderately	11	17%
	Considerably	15	24%
	Extremely	18	29%
GAD-7 score		10.96	5.62

Note: NDRI = norepinephrine and dopamine reuptake inhibitor, SNRI = serotonin and norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

3.3. Anxiety severity over time

As seen in Table 2, participants in the overall sample displayed significant reductions in GAD-7 scores from the baseline assessment ($M = 11.19$, $SD = 5.61$) to the three-month follow-up assessment, ($M = 7.37$, $SD = 5.04$), $t(93) = 6.67$, $p < .0001$. Similar results were observed among the sub-sample of participants who reported taking anxiety medications with scores decreasing from 11.39 ($SD = 5.16$) to 7.54 ($SD = 5.17$), $t(53) = 5.10$, $p < .0001$.

3.4. Changes in anxiety medication use following mm treatment

Among individuals who reported taking medication for anxiety at baseline and who completed the follow-up assessment ($n = 50$), 32 % ($n = 16$) reported that they had decreased their use of anxiety medication in the three months since beginning MM treatment. In terms of the magnitude of reduction in use, 4 % ($n = 2$) reported extreme reductions, 12 % ($n = 6$) considerable reductions, and 16 % ($n = 8$) moderate reductions. The remaining 68 % of individuals ($n = 34$) reported no reductions in use in the three months following treatment initiation. Importantly, individuals who were taking benzodiazepines ($n = 9$) were more likely to report reductions in use than those who were taking other classes of medications ($n = 41$; 67 % % vs. 24 %, respectively), $X^2(1) = 6.01$, $p < .05$.

There was a significant correlation between reported desire to reduce anxiety medication use at baseline and reported decrease in anxiety medication use at the 3-month follow-up assessment, $r = 0.33$, $p < .05$. Specifically, 41 % ($n = 14$) of individuals who stated a goal of at least moderately reducing their use of anxiety medications ($n = 34$) indicated reductions in use at the 3-month assessment compared with 12 % ($n = 2$) of those who did not have this goal ($n = 16$; $X^2(1) = 4.11$, $p < .05$. Finally, the magnitude of reported reduction in anxiety medication use was not associated with the magnitude of change in anxiety score over time, $r(50) = -0.05$, $p = .73$.

4. Discussion

Findings from this study indicated that a substantial proportion of MM patients with anxiety and PTSD diagnoses had current prescriptions for medications to treat anxiety, with the majority expressing a desire to reduce their medication usage after beginning MM treatment. At the three-month follow-up, participants displayed significant reductions in their anxiety severity as measured by the GAD-7, with average scores for the sample falling into the moderate severity range at baseline and improving into the mild severity range at the 3-month follow-up. The hypothesized mechanism(s) by which MM may relate to anxiety severity include cannabinoid receptor involvement in the limbic system, reductions in inflammation (Stack et al., 2022) or improvements in sleep, but this relationship is not yet well-understood.

Furthermore, almost one-third of individuals who were prescribed other medications for anxiety symptoms reported reductions in their use, and these reductions were more prominent among individuals who reported this as a goal. Importantly, reductions in use were more likely among individuals who had been prescribed benzodiazepines than those who had been prescribed other classes of drugs. This is an important finding given the significant addiction potential of benzodiazepines. Importantly, reductions in anxiety use were not associated with the magnitude of observed reductions in anxiety severity, suggesting no iatrogenic effect of this reduction in medication.

This study has several limitations. First, the observational nature of the study precludes our ability to draw causal inferences that the identified changes in anxiety severity were a direct result of the MM treatment. Furthermore, the outcome variables, including anxiety medication use, were collected via self-report and we did not include a PTSD measure to evaluate changes in condition-specific symptoms, such as re-experiencing of the traumatic event via flashbacks or nightmares.

Table 2
Changes in anxiety score from baseline to 3-month assessment in the overall sample and the medication sub-sample.

Outcome variable	Baseline *M* (*SD*)	Month 3 *M* (*SD*)	*df*	*t*	*p*
GAD-7 score, overall sample ($n = 94$)	11.19 (5.61)	7.37 (5.04)	93	6.67	<0.0001
GAD-7 score, medication sample ($n = 54$)	11.38 (5.16)	7.54 (5.17)	53	5.10	<0.0001

Future studies could use clinical and pharmacy records and other strategies (e.g., MEMS caps) to obtain data on medication use in a more objective manner and may benefit from following MM patients for longer durations. Finally, the study does not have an adequate sample size to examine how MM dosage, route of administration, strain/types, and other MM-related factors moderate the observed reductions in medication use.

Overall, findings from this observational study are consistent with those observed in the literature (Ashare et al., 2022) and provide additional preliminary evidence to support the use of MM to address anxiety and PTSD. More controlled longitudinal studies that include comprehensive measures of anxiety that assess the cognitive, behavioral, and physiological symptoms of anxiety and PTSD are necessary; they will provide a better understanding to the extent to which MM treatment results in longer-term reductions in anxiety severity and use of prescription medications to reduce symptom severity. Finally, future research is needed to understand how different MM chemotypes, dosages, and formulations impact anxiety severity. Unfortunately, as discussed, the federal classification of marijuana as a Schedule 1 continues to be a significant barrier to conducting more controlled experimental studies on the efficacy and safety of MM treatment.

Author statement

The authors confirm contribution to the paper as follows: Michelle R. Lent and Karen L. Dugosh designed the study. Megan M. Short and Thomas R. McCalmont recruited study participants and conducted data collection. Karen L. Dugosh performed data analysis with the support of Paulina Syracuse. Karen L. Dugosh also took the lead in writing the manuscript, with input from all authors. All authors have viewed the results and approved the final version of the manuscript.

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Declaration of Competing Interest

none

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