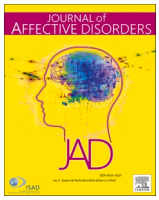
Journal of Affective Disorders 390 (2025) 119829

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad



Research paper

Acute and chronic effects of medicinal cannabis use on anxiety and depression in a prospective cohort of patients new to cannabis

David Wolinsky [a], Rhiannon E. Mayhugh [a], Renuka Surujnarain [a], Johannes Thrul [b,c,d], Ryan Vandrey [a], Justin C. Strickland [a,*]

[a] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA
[b] Department of Mental Health, Johns Hopkins University School of Public Health, 1812 Ashland Ave., Baltimore, MD 21205, USA
[c] Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA
[d] Centre for Alcohol Policy Research, La Trobe University, Melbourne, Australia

ARTICLE INFO

Keywords:
Cannabis
EMA
Marijuana
THC

ABSTRACT

Introduction: Medicinal cannabis has mixed evidence for treating anxiety and depression, yet patients frequently use it as a treatment. This observational study evaluated the effects of medicinal cannabis initiation in adults with clinically significant anxiety and/or depression over a 6-month period.

Methods: Adults with clinically significant anxiety and/or depression initiating medicinal cannabis use in Maryland, USA completed ecological momentary assessment (EMA) and longitudinal follow-up evaluations. Hospital Anxiety and Depression Scale (HADS) assessments were completed at baseline and 1, 3, and 6 months after medicinal cannabis initiation. EMA measures were completed at baseline and daily for 8 weeks after cannabis initiation with measures collected before each cannabis use and at time of expected peak effect. Changes in anxiety and depression were evaluated using linear mixed effect models.

Results: Significant decreases from baseline in anxiety and depression were observed, with mean scores dropping below clinically significant levels within three months of initiation. EMA data indicated that most participants selected THC-dominant cannabis and acute reductions in anxiety, depression, and perceived driving ability along with increased ratings of feeling "high". Acute effects were dose-dependent: 10–15 mg of oral THC and at least 3 puffs of vaporized cannabis yielded the most robust reductions in anxiety and depression.

Conclusions: Initiation of THC-dominant medicinal cannabis was associated with acute reductions in anxiety and depression, and sustained reductions in overall symptom severity over a 6-month period. Controlled clinical trials are needed to further investigate the efficacy and safety of medicinal cannabis for acute anxiety and depression symptom management.

1. Introduction

Depression and anxiety disorders represent enduring public health concerns. With nearly a third of American adults experiencing symptoms of anxiety and/or depression as of 2023 (Panchal et al., 2023), these illnesses are extremely prevalent and carry with them significant health consequences. Depression serves as one of the strongest risk factors for suicide (McIntyre et al., 2023), largely contributing to the nearly 50,000 deaths by suicide that occurred in 2022—a 2.1% increase from the year prior (CDC, 2025). Independent of suicide, depression and anxiety disorders can lead to premature death and other health problems (Wahlbeck et al., 2011; Voshaar et al., 2021; Wanjau et al., 2023). These outcomes underlie enormous annual health care costs: as an example, over 330 billion dollars were devoted to the management of costs related to Major Depressive Disorder (MDD) in 2019 (Greenberg et al., 2023). Serotonergic antidepressants (e.g., fluoxetine, sertraline) are first-line pharmacotherapies for anxiety and depressive disorders, yet can be limited by numerous side effects such as decreased libido, weight change, and gastrointestinal distress (Goethe et al., 2007). Moreover, these medications typically require weeks of use before a therapeutic effect is experienced by the patient, and many patients do not benefit (Trivedi et al., 2006; Insel and Wang, 2009; Pigott, 2015). Given these

* Corresponding author at: Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA.
E-mail address: jstric14@jhmi.edu (J.C. Strickland).

https://doi.org/10.1016/j.jad.2025.119829
Received 7 December 2024; Received in revised form 28 June 2025; Accepted 2 July 2025
Available online 5 July 2025

limitations, there has been significant interest in identifying novel treatments for anxiety and depression that are fast-acting, effective, and with a favorable side effect profile.

Regulatory changes in many jurisdictions now allow for the medicinal use of cannabis and there is a growing acceptance by clinicians of the therapeutic potential of cannabis in the treatment of many health conditions (Schauer et al., 2022). In the U.S., 39 states, including the state of Maryland, and the District of Columbia allow medicinal cannabis use (NCSL, 2023) wherein patients are permitted by an authorized provider to use cannabis to treat qualifying conditions. Patients under this system obtain their medicinal cannabis from a state-licensed cannabis dispensary. Among the more than four million individuals registered as medicinal cannabis patients in the U.S. (Boehnke et al., 2024), anxiety and depression are two of the most frequently cited reasons for using cannabis as a medical treatment (Azcarate et al., 2020). Research has shown an association between dysregulation of the endocannabinoid system and symptoms of depression (Rana et al., 2021) and anxiety (Petrie et al., 2021). Moreover, preclinical (Abame et al., 2021; Sales et al., 2019; Rey et al., 2012) and clinical studies (Linares et al., 2019; Crippa et al., 2011) have shown anxiolytic and antidepressant effects of cannabinoids. Collectively, these data highlight the potential of targeting the endocannabinoid system in the development of novel pharmacotherapeutics (Patel et al., 2017; Hill et al., 2009).

However, the evidence for safety and efficacy of medicinal cannabis use in treating anxiety and/or depression has been mixed. In a recent national cohort study of people with a variety of health conditions using cannabis for therapeutic purposes (mostly CBD-dominant products), cannabis use was associated with lower anxiety and depressive symptoms cross-sectionally compared with a non-user control group (Schlienz et al., 2021). Reductions in anxiety and depression were also observed longitudinally among non-cannabis users who subsequently initiated cannabis use. These results were consistent when focused only on the subset of participants who reported anxiety or depression as the primary reason for medicinal cannabis use (Martin et al., 2021). In contrast, there is evidence indicating that acute and chronic cannabis use may not provide psychiatric benefits and, in fact, worsen symptoms (Aspis et al., 2015; Bahorik et al., 2018a). A single-blind study in which participants were randomized to either receive a medical cannabis card immediately or after 12 weeks did not show any benefits in anxiety or depression among individuals with immediate access to medical cannabis compared to those with delayed access. However, there was a significant improvement in mental well-being among the immediate access group (Gilman et al., 2022). Limitations of the above studies include cross-sectional designs or comparisons, retrospective self-report assessments, poor tracking of exact cannabis products being used, and inclusion of individuals already using cannabis at the outset of the period of observation. Studies designed to identify if—and when—medicinal cannabis use can alleviate mental health symptoms are needed to inform subsequent rigorous randomized controlled trials and optimize the conduct of these studies.

Ecological momentary assessments (EMA) can offer comprehensive data on momentary changes in health due to specific events (like medicinal cannabis use). Consisting of repeated, real-time measures of discrete actions, EMA has several advantages as a research tool over traditional forms of assessment. The brief window between behavior and assessment reduces recall bias and the completion of measures in a participant's natural environment optimizes ecological validity (Shiffman et al., 2008). Moreover, EMA allows for repeated behavioral measurements over extended periods of time that would be impractical for laboratory or residential research designs. This feature allows for the evaluation of both short-term and long-term effects of a specific experimental manipulation, context, or other variable of interest in one individual (Wang et al., 2021; Goodell et al., 2021; Joo et al., 2024).

The present study sought to extend prior research by using a multi-methods approach, incorporating EMA with longitudinal survey assessments in a cohort of adults with clinically significant levels of anxiety and/or depression who planned to newly initiate cannabis use specifically for medicinal purposes. This design allowed for within-subjects assessments of anxiety and depression prior to and after initiation of medicinal cannabis as well as longitudinal evaluation of the impact of cannabis under both acute and chronic dosing time frames. Based on previous work reporting that cannabis use resulted in short-term reductions in anxiety and depression but a worsening of anxiety and depression over an extended period of time (Cuttler et al., 2018), we hypothesized that cannabis would reduce anxiety and depression acutely (assessed via EMA), but that long-term assessment of anxiety and depression of 6 months with the HADS would show a worsening of symptoms over time. In addition, the naturalistic design of this study would allow for exploratory evaluation of differences in response based on the type of cannabis product, route of administration, and dose used by individual participants in real-world everyday-life contexts.

2. Methods

2.1. Study design overview

This prospective, observational, cohort study involved an assessment of the short and long-term effects of medicinal cannabis among individuals with clinically significant anxiety and/or depression newly starting medicinal cannabis use in Maryland. At the time of this study, medicinal cannabis use was legal in Maryland, but recreational cannabis use was not yet legalized. Baseline levels of mood, anxiety, sleep, pain, and overall functioning were assessed via a battery of online questionnaires (described in the Baseline and Longitudinal Assessments section below) for up to eight weeks prior to starting medicinal cannabis. Following initiation of medicinal cannabis, participants completed EMA surveys four times daily for 8 weeks: once on waking, once prior to sleep, and twice at random prompts during the day. The EMA surveys consisted of visual analog scales (VAS) assessing self-reported ratings of depression, anxiety, subjective "high" feeling, and perceived driving ability. In addition to these four surveys per day, participants were prompted to complete an EMA survey immediately prior to any use of a cannabis product and then again after each acute dose of cannabis at the expected time of peak therapeutic effect, which differed based on route of administration. Longitudinal effects of medicinal cannabis were measured via repeated completion of the baseline questionnaire battery 1, 3, and 6 months following the initiation of medicinal cannabis use. All procedures were approved by the Johns Hopkins University School of Medicine Institutional Review Board (IRB), who provided ethical review of the study before it was initiated (IRB00201190).

2.2. Participants

Eligible participants were adults aged 18 years or older with clinically significant anxiety and/or depression who reported intending to newly initiate medicinal cannabis use. Clinically significant anxiety and depression was determined through completion of the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), a well-validated tool that assesses anxiety and depression via two 7-item subscales: one for anxiety and one for depression. Items are scored on a 4-point Likert scale (0–3 range) with a maximum score of 21 on each sub scale. The presence of clinically significant depression was defined as a HADS score ≥ 8 for either the composite anxiety or depression subscales. Volunteers were required to report no more than five instances of cannabis use over the six months prior to starting the study. Additionally, participants had to have been approved for access to medicinal cannabis in the state of Maryland (USA) by an independent clinician with the intention of only purchasing cannabis from state-regulated cannabis dispensaries before beginning the study. We did not control for the type of cannabis used, no reimbursement was provided for cannabis purchased, and each participant was able to use the cannabis

type of their choice. Individuals were excluded if they (a) lacked ability to fluently read, write, and speak in English, (b) did not own a smartphone device that could operate the EMA application, (c) worked in a field with non-traditional sleep schedules (i.e. shift work) and/or (d) had obligations that would prevent them from completing tasks necessary for data collection. Recruitment materials with information on enrolling in the study were distributed at locations that individuals from the target demographic would likely visit, including medicinal cannabis provider locations. Study recruitment materials were also distributed by a health consultant company that specialized in medicinal cannabis use (Veriheal, Denver, CO, USA) to clients who resided in Maryland at the time of study recruitment. Study volunteers provided oral consent for participation; this mode of consent, which was approved by the Johns Hopkins IRB, is commonly used in low-risk observational studies when obtaining written consent is impractical. Additionally, each participant completed an eligibility assessment over the phone or via video call with a study team member.

2.3. Baseline and longitudinal assessments

A baseline questionnaire assessed participant demographics and general health, including current health conditions, medications (including antidepressants), and use of licit and illicit substances with addictive potential. A battery of questionnaires was completed at baseline (before cannabis use initiation) and again 1, 3 and 6 months after the initiation of medicinal cannabis use. The battery included the HADS, the World Health Organization Quality of Life (WHOQOL)-BREF, Brief Inventory of Psychosocial Functioning (B-IPF), General Health/Well-Being (SF-36), Brief Pain Inventory-Short Form (BPI), Insomnia Severity Index (ISI), Comprehensive Marijuana Motives Questionnaire (CMMQ), Marijuana Problem Scale (MPS) and the Marijuana Effect Expectancy Questionnaire (MEEQ). At each designated time point, a link to the questionnaire battery was e-mailed to study participants for completion on a secure web-based platform (Qualtrics, Provo, UT, USA).

2.4. EMA surveys

EMA surveys were used to evaluate acute changes in anxiety, depression, subjective "high" feeling, and perceived driving ability. LifeData (Marion, IN, USA) served as the EMA service provider. The surveys consisted of items taken from the Edmonton Symptom Assessment System Graph (ESAS) (Chang et al., 2000) and were collected via an 11-point Visual Analog Scale (VAS; range = 0–10). Assessments were completed four times daily for up to eight weeks before cannabis initiation and for 8 weeks after cannabis initiation. Each day, two assessments were completed via user-initiated surveys including upon waking (Wake Up assessment) and prior to bed (End of Day assessment). Two assessments (Midday 1 and Midday 2) were triggered by the LifeData App at random times between 6–8 and 8–10 h after waking respectively. Participants completed a brief sleep evaluation during their Wake-Up assessment in which they rated their sleep quality overnight and how well rested they felt in the morning.

In addition to the 4 standard daily assessments, participants were also asked to report each instance of cannabis use. When they indicated on the EMA App that they were about to take a dose of cannabis, the EMA App triggered a pre-dose VAS questionnaire and prompted participants to take a picture of the cannabis product used (with the Maryland state-regulated label information) and to report the dose taken and route of administration. The EMA App then prompted participants to complete a post-dose VAS questionnaire 20–30 min later if the route of administration reported was smoked or vaped or 90–120 min later if the route of administration reported was oral or topical. These times were selected to capture the expected timing of peak efficacy and allow for the onset of acute adverse effects based on prior laboratory studies (Spindle et al., 2018; Vandrey et al., 2017; Schlienz et al., 2020; Spindle et al., 2021).

2.5. Data analysis

Descriptive statistics were used to summarize the overall sample, cannabis use patterns, and adherence rates. Web-based self-report assessments were analyzed using a linear mixed effect model with a main effect of timepoint (Baseline, 1-, 3-, and 6-months) to account for the within-subject measurement and missing data. Sensitivity analyses using a last observation carried forward to account for missing data showed similar results (Supplemental Materials; Supplemental Fig. 5). Linear mixed effect models were then used to evaluate the association between cannabis use on a given day and subjective reporting on the End of Day assessment. Time, defined as the numerical week of participation in the study, was used as both a fixed and random effect. These models also included demographic (age and gender) and health predictors (baseline antidepressant use) as fixed effect covariates. Acute effects of cannabis use measured by EMA were evaluated using linear mixed effect models with the dependent outcome of changes in anxiety, depression, subjective high, and perceived driving ability. These models included route of administration (topical was removed for inferential tests due to its low prevalence), age, gender, concomitant antidepressant medication use, and number of prior medicinal cannabis uses (5+ versus 5 or less) as fixed effects. Finally, the impact of dose was tested in linear mixed effect models for the two most common routes (oral and vaporized). Oral dosing was calculated based on standard THC doses (5 mg doses). Vaporized doses were calculated as estimated number of puffs taken. All models used type one error rates of 0.05 and two-tailed tests. Plotting and tests were conducted using *R* Statistical Analysis and Prism.

3. Results

3.1. Sample characteristics (see Table 1)

Participants ($N = 33$) had an average age of 40 years (range 20–66). 36 % of participants identified as male and 64 % of participants identified as female. Most participants identified as White (85 %). Most reported some prior experience with cannabis (75 %), but fewer reported any past year cannabis use (37 %).

3.2. Global trajectories of clinical outcomes

Retention across health survey assessments was good with 88 %, 76 %, and 73 % of participants completing the 1-, 3-, and 6-month assessments. Participants with and without missing data did not differ in baseline anxiety ($p = .92$; $d = 0.04$), depression ($p = .71$; $d = 0.14$), quality of life ($p = .63$; $d = -0.18$), or health satisfaction ($p = .58$; $d = 0.21$) scores. Fig. 1 includes participant-reported anxiety (left panel) and depression (right panel) scores on the HADS at each follow-up. A significant effect of time was observed for anxiety ($p < .001$) and depression ($p < .001$) that was reflected in significant decreases in participant-reported anxiety and depression from baseline at each follow-up assessment (results for individual items are in Supplemental Table 1). The percentage of individuals who reported clinically significant levels of anxiety or depression (HADS score ≥ 8) fell from 81 % and 76 % at baseline to below 50 % by 3 months and 1 month after medicinal cannabis initiation, respectively (Fig. 1 bottom panels). The HADS scores for both anxiety and depression qualitatively increased between the 3-month and 6-month time points, but aggregate scores were still below the clinically significant score of HADS >8 and significantly lower than baseline scores.

Improvements in quality of life and health satisfaction, as measured by the WHOQOL-BREF, were observed during the 6-month follow-up period (Fig. 2). Quality of life improved significantly at the 1-month follow-up ($p < .01$) but was no longer significantly different from baseline at the 6-month follow-up. Health satisfaction, however, continued to improve throughout the 6-month observation period and was significantly different from baseline at all follow-up time points (p

Table 1
Demographics and health history variables ($N = 33$).

Variable	Mean (SD) / % (n)
Age[a]	40 (12)
Gender	
Male	36 % (12)
Female	64 % (21)
BMI	28 (6)
Race	
White	85 % (28)
Black or African American	9 % (3)
Asian	3 % (1)
Prefer to Self-Identify	3 % (1)
Hispanic	6 % (2)
Income	
<$15,000	6 % (2)
$15,000–$50,000	12 % (4)
$50,001–$100,000	33 % (11)
$100,001–$150,000	24 % (8)
$150,001+	24 % (8)
Education	
High School Degree	33 % (11)
Trade Degree	6 % (2)
Bachelor's Degree	36 % (12)
Master's Degree	15 % (5)
Professional Degree	9 % (3)
Veteran	9 % (3)
Antidepressant Use	42 % (14)
Cannabis use history	
Lifetime[a]	75 % (24)
Past Year[a]	37 % (11)

Note. Lifetime and past year cannabis use history was missing for 1 and 3 participants respectively (missing data not included).
[a] Age range is 20–66 years old.

< .001).

Medicinal cannabis use was not associated with the development of physical or psychological problems, as the scores on the MPS scale remained low and did not differ from baseline across the 6 months of follow-up (Supplemental Fig. 1). Improvements on other measures of psychological, psychosocial, and physical health were observed on the B-IPF, ISI, and SF-36 (p values < .05; see Supplemental Figs. 2–4 for point comparisons).

3.3. Adherence to EMA surveys

Fig. 3 (bottom panel) includes response rates for daily user-initiated events (i.e., Wake Up and End of Day assessments) and triggered events (i.e., Midday 1 and 2 assessments) as well as event-contingent reports (i.e., post-cannabis use follow-up assessments). An overall median response rate of 66 % (range = 4 %–99 %) was observed for daily assessments. Response rates were highest for morning assessments with a median response rate of 80 % (range = 5 %–100 %). Responses generally decreased across weeks with the lowest response rates observed in the final two weeks (Fig. 3 top panel). A total of 846 cannabis use events were reported (median = 16; range = 1–129) indicating the number of times participants used cannabis over the 8-week EMA period. Follow-up responses after cannabis use were recorded for 778 events (92.0 % adherence). At the individual level, participants responded to a median of 100 % post-dose reporting events (range = 3.7 %–100 %). Of note, one participant consistently used cannabis products prior to bed and therefore had a very low post-dose response rate due to being asleep at the time the post-dose assessment was triggered.

3.4. Day level variation in anxiety, depression, and adverse effects

Cannabis use was reported on 44 % of days in which an End of Day assessment was also available (462 of 1056 assessments). Use of medicinal cannabis on a given day was associated with lower ratings of Anxiety ($p < .001$) and Depression ($p < .001$) on the End of Day assessment (see Table 2 for coefficients). Similarly, medicinal cannabis use was associated with higher ratings of feeling "High" and lower ratings of Driving Ability on End of Day assessments ($p < .001$). "High" feeling decreased as a function of weeks of use ($p < .05$) suggestive of tolerance, but no significant effects were observed for anxiety, depressed mood, or perceived driving ability.

3.5. Cannabis use behavior and acute effects

Of the 846 cannabis use events reported, the majority involved a THC-dominant product ($n = 623$; 74 %). Vaporization was the most common route of administration ($n = 414$; 49 %) followed by oral ($n = 304$; 36 %), smoked ($n = 109$; 13 %), and topical ($n = 19$; 2 %) routes of administration. The median number of puffs taken during a vaping event was 4 (IQR = 2–6). The median THC dose when using oral products was 7 mg (IQR = 3–10 mg).

On the 11-point VAS scales, participants reported an average 2.0-point reduction in anxiety ($p < .001$), a 1.3-point reduction in depression ($p < .001$), and a 2.2-point reduction in perceived driving ability ($p < .001$) after cannabis use. An average increase of 4.1 points for ratings of "High" was observed following acute cannabis use episodes ($p < .001$). Table 3 contains coefficients from linear mixed effect models evaluating the impact of person-level factors including age and gender as well as route of administration on reported changes. Effects generally did not differ by route of administration, although a modestly greater increase in ratings of "High" was noted for vaporized products (~0.7 points; $p < .05$). Initial use events (i.e., first five uses) were associated with significantly larger reductions in perceived driving ability (~1.1-point reduction relative to later use events, $p < .001$). No significant associations between initial use events and outcomes were observed for anxiety, depression, or ratings of high.

Figs. 4 and 5 display changes in subjective rating by oral dose (Fig. 4) and vaporized puff number (Fig. 5) based on EMA surveys completed pre- and post-cannabis administration. Linear mixed effect models indicated that oral THC doses of 10 mg to 15 mg produced the qualitatively greatest magnitude reductions in Anxiety ($b = -0.79$, $p < .05$) and Depression ($b = -0.74$, $p < .05$) ratings compared to oral doses that were less 5 mg THC (the reference group). These doses also tended to produce the greatest ratings of High and reductions in perceived Driving Ability (Fig. 5; bottom panel). "Dose"-related increases in ratings of High were also observed with the number of vaporized puffs administered (Fig. 5) and anxiety was reduced to a greater degree as more puffs were administered (Fig. 5).

4. Discussion

In this prospective, observational study, medicinal cannabis use was associated with significant decreases in self-reported anxiety and depression compared with pre-cannabis use initiation baseline assessments among individuals with clinically significant anxiety and/or depression. Reductions in anxiety and depression were observed acutely following individual episodes of cannabis use and overall symptom reductions were sustained over the six-month period of observation based on retrospective self-report assessments. This study extends prior research in several important ways. First, the cohort of individuals in this study was not using cannabis at baseline and was newly initiating use through a state-regulated medicinal cannabis access program. Prior

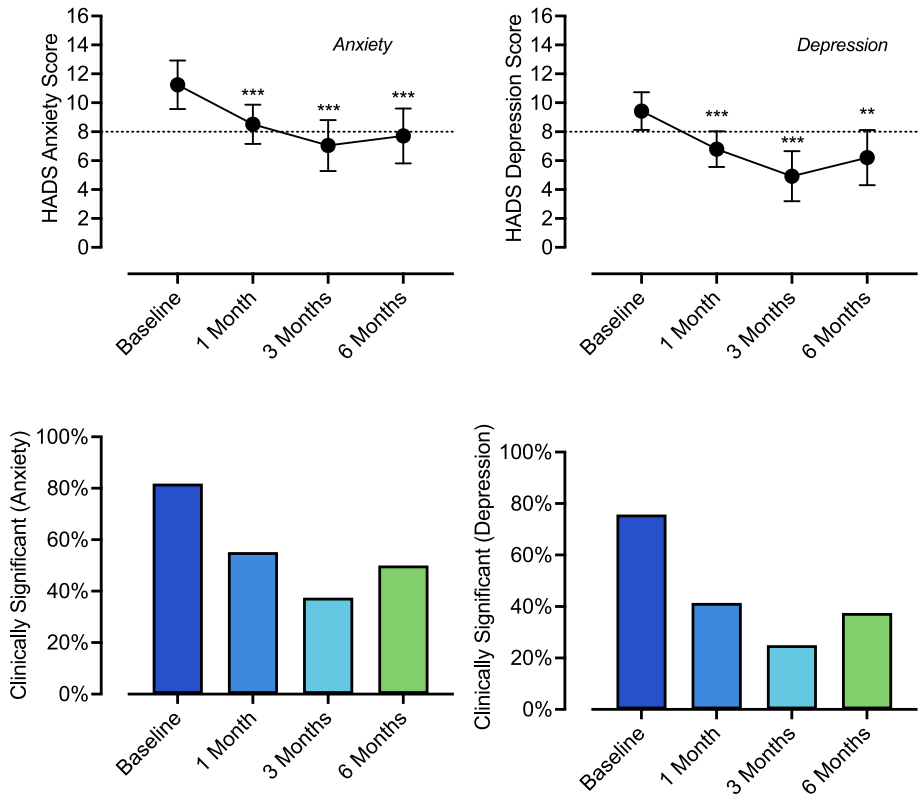


Fig. 1. Overall changes in anxiety and depression following medicinal cannabis initiation. Values are for observed sample for anxiety (left panels) and depression (right panels) scores on the HADS. A cutoff of 8 was used to note clinically relevant symptoms. Values in top panels are mean and 95 % confidence intervals.
** $p < .01$.
*** $p < .001$.

longitudinal studies evaluating the effects of medicinal cannabis use on anxiety and depression included participants who were using cannabis at the start of study participation (Martin et al., 2021; Gilman et al., 2022; Cuttler et al., 2018). These results are consistent with prior work that separately analyzed a cohort of individuals who newly initiated cannabis (Martin et al., 2021) and are also consistent with a retrospective cohort study of medicinal cannabis users in Canada (Sachedina et al., 2022). The lack of long-term change in anxiety and depression in the other studies may be due to the high rate of baseline cannabis use among participants in those cohorts (Gilman et al., 2022; Cuttler et al., 2018).

Another advancement of this study was the use of both validated retrospective clinical assessment instruments and ecological momentary assessment (EMA). Consistent with other research (Vandrey et al., 2017; Li et al., 2020), acute use of medicinal cannabis was associated with post-dose reductions in anxiety and depression. Moreover, ratings of anxiety and depression at the end of the day were lower on days in which cannabis was used versus not used in this study. In addition, the use of EMA allowed for the capture of detailed product use and dosing characteristics. Participants in the present study predominantly used THC-dominant cannabis products whereas participants from the study by Martin et al. (Martin et al., 2021) predominantly used CBD-dominant cannabis products. This difference is likely driven by our recruitment efforts targeting a population explicitly seeking access to cannabis products via a state-regulated cannabis program, which is comprised mostly of THC-dominant products. Because THC-dominant cannabis use was associated with more adverse effects compared to CBD-dominant cannabis in the Martin et al. (Martin et al., 2021) study, the risk-benefit ratio of CBD-dominant cannabis appears more favorable than that of THC-dominant cannabis in the context of use to manage anxiety or depression. However, controlled clinical trials evaluating the comparative safety and efficacy of THC-dominant versus CBD-dominant cannabis are needed to properly guide clinical decision making.

Participants in the present study also endorsed a broad range of THC doses and variation in route of administration. Acute dose effects largely followed an inverted U-shaped dose-response in which median doses (e.g., 10–15 mg THC for oral doses) yielded qualitatively greater reductions in anxiety and depression from pre-dose scores compared with lower or higher doses. This inverted u-shaped pattern has been observed in controlled laboratory studies examining the effect of CBD on anxiety (Linares et al., 2019; Zuardi et al., 2017), but is somewhat different from prior research that has primarily seen an increase in acute anxiety with THC use (Sharpe et al., 2020), though there has also been at least one other study illustrating the ability of lower dose THC to ameliorate anxiety (Childs et al., 2017). Results from this current study did not illustrate any increases in anxiety with higher THC doses. The absence of an anxiogenic effect may stem from the presence of pre-existing anxiety in participants in this study, who are living with a higher degree of stress compared to individuals without anxiety disorders, who may be more sensitive to changes in stress. Additional research on THC dose-response among individuals with clinically significant anxiety and/or mood disorders compared to those without such disorders could help address these discrepancies.

Another surprising outcome of the present study was that most participants did not report use of medicinal cannabis every day as evidenced by the number of user-initiated cannabis use events recorded. Less than daily use may have mitigated tolerance to the beneficial effects of cannabis on mood and prevented the worsening of depression or anxiety that has been seen in other studies of long-term cannabis use (Bahorik et al., 2018b; Schoeler et al., 2018). That said, a qualitative increase in HADS scores for both anxiety and depression from the 3- to 6-month time points hint that the sustainability of reduced anxiety and depression may be limited and needs to be followed-up in longer periods of evaluation. The notable lack of problems related to cannabis use and

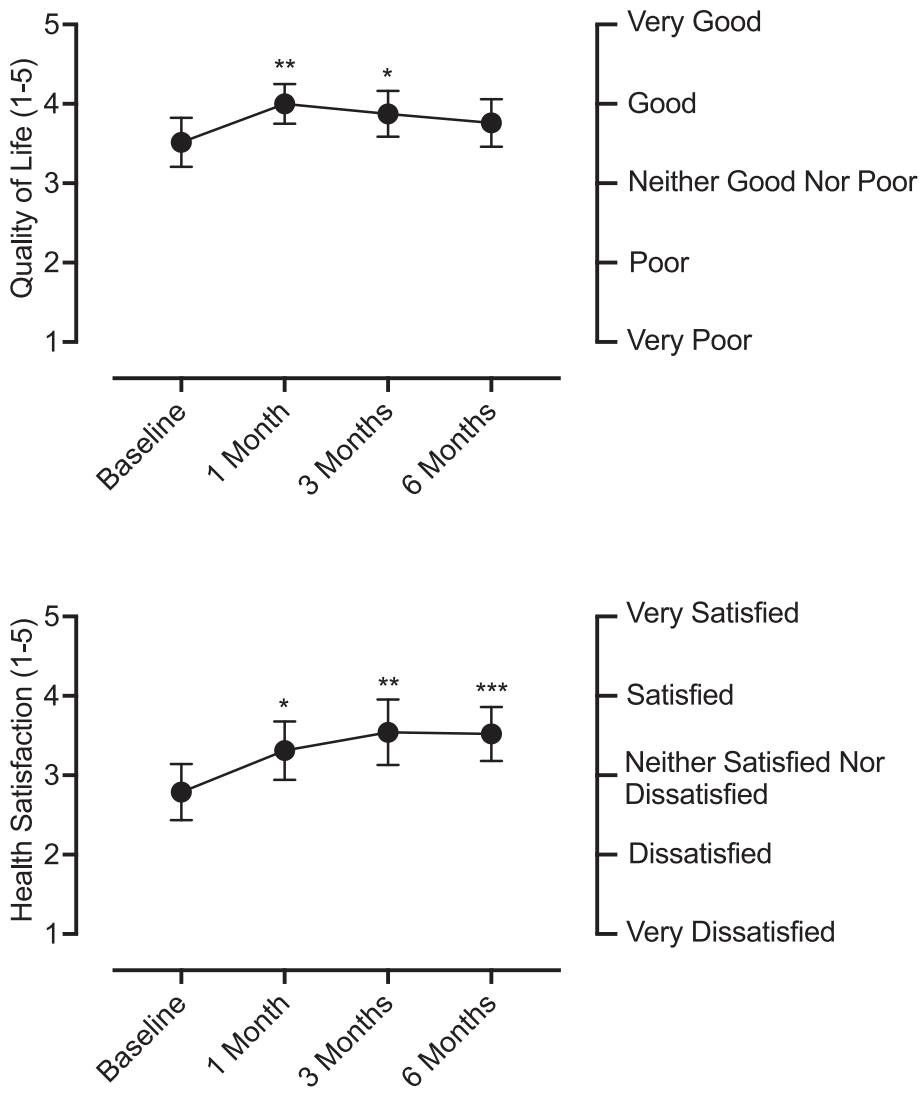


Fig. 2. Overall changes in quality of life and health satisfaction following medicinal cannabis initiation. Values are for observed sample for quality of life (top panel) and health satisfaction (bottom panel) scores. Corresponding labels for Likert scale values are presented on the right y-axis. Values are mean and 95 % confidence intervals.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

worsening of mood in this study may be related to our selection of individuals who were not currently using cannabis at the time of enrollment in this study, the fact that cannabis use was explicitly reported to be for medicinal purposes, and/or the lack of daily use behavior among many study participants. Further studies should evaluate cannabis use frequency, demographic, and symptom specific predictors that would help determine patient-centered dosing regimens to optimize long-term clinical outcomes in this population.

In addition to the self-reported improvement in anxiety and depression, participants in this study also reported that acute use of THC-dominant cannabis made them feel "high" and reduced confidence in driving ability. Notably, the reported decrease in perceived driving ability was partly reduced in magnitude over time, which suggests that participants developed a tolerance to the acute impairing effects of cannabis, titrated their dose taken to one that resulted in less impairment of functioning, or simply became accustomed to the effect and no longer subjectively perceived that their driving would be impaired. The reduced perceived impairment of driving ability after establishing a routine of medicinal cannabis use is consistent with recent studies in which medicinal cannabis users taking their prescribed doses of cannabis (mostly vaporized THC-dominant or oral balanced THC + CBD products) did not alter performance on a standardized cognitive assessment (Arkell et al., 2023) battery or a sophisticated driving simulator (Manning et al., 2024).

There are a few limitations to this study that need to be acknowledged. The study sample does not effectively represent the Maryland population given it is primarily female and White. Future work with larger sample sizes should account for this overrepresentation by adjusting for differences in gender and race. There was not a no-use control group in this study. Outcomes were primarily described through self-report; as such, results are liable to self-report bias and reporting inaccuracies. These biases are particularly relevant for the data on perceived driving ability given individuals who are intoxicated may not adequately estimate own driving ability. Evaluation of driving ability when using medicinal cannabis by applying psychomotor measurement apps that allow for ambulatory measurement could provide more objective data and should be a goal of future studies. Although we accounted for antidepressant use in our analysis, participant

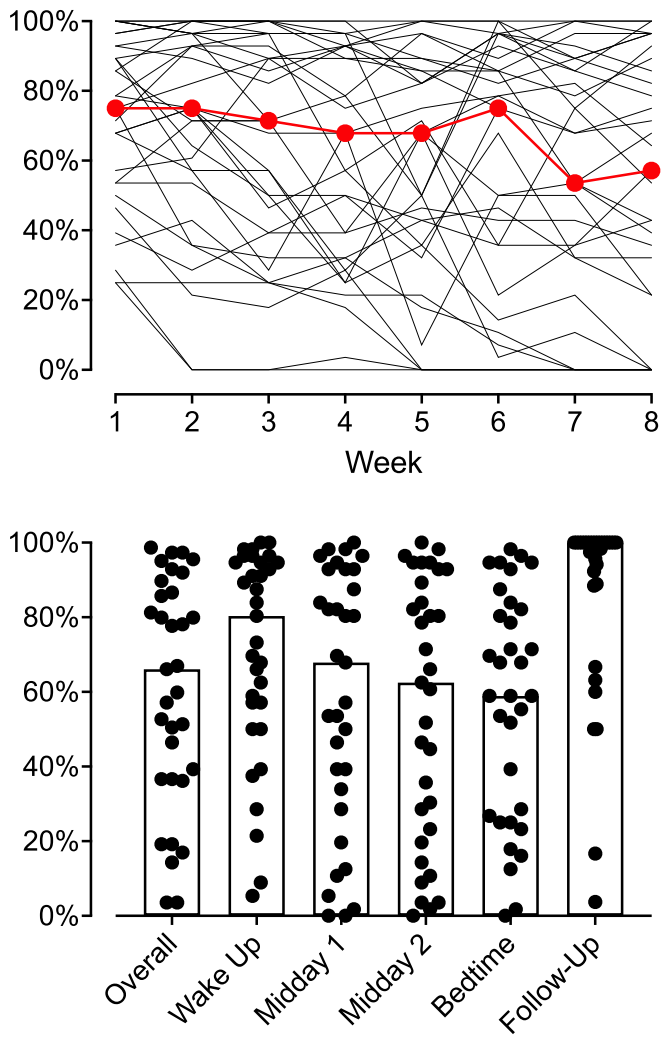


Fig. 3. Response rate and adherence to EMA protocols. Top panel presents individual participant data and median response rate (red line) for EMA adherence during the 8-week protocol. Follow-Up refers to post-cannabis administration timepoint. Bottom panel presents median and individual participant adherence to each response type. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

engagement in psychotherapy or other form of treatment were not tracked and could have impacted study outcomes. Additionally, the HADS scores from the long-term assessments need to be interpreted in the context of an increasing participant drop-out rate, with 27 % of participants having dropped out by 6 months. We do not know how the average HADS anxiety and depression scores at the end of the study might have changed if all participants stayed in the study, though one could hypothesize that these scores would have been higher if participants had remained because one would expect that the individuals stopped taking medicinal cannabis because they did not find it efficacious as the treatment of their psychiatric symptoms. This concern is partly mitigated by the similarities between participants at baseline based on dropout status as well as similar results observed in missing data sensitivity analyses.

The limitations in this study are offset by several strengths. This work represents one of the only studies to apply EMA data collection and analysis to medicinal cannabis users, allowing for an especially accurate capture of medicinal cannabis behavior in participants' natural environment. The design allowed for an investigation of both acute and long-term effects of medicinal cannabis on mood and anxiety using validated measures. The unique study population—cannabis-naïve individuals with clinically significant levels of anxiety and/or depression—lends our work additional value. By excluding participants with ongoing frequent cannabis use at the time of study enrollment, our results are not confounded by cannabis tolerance or the anxiety and depressive symptoms that can be seen in people with Cannabis Use Disorder. Having independent physician approval to use medicinal cannabis in the Maryland state medicinal program as an inclusion criterion optimizes the validity of the study and reduces the risk of including individuals interested in using cannabis for reasons outside of treatment. Additionally, by selecting participants with clinically significant levels of anxiety or depression on an established screening instrument, we gain an understanding of the impact of medicinal cannabis among individuals who are more likely to meet criteria for an anxiety or depressive disorder rather than people who may define their anxiety or depression more colloquially. Finally, this study demonstrates a largely anxiolytic effect of THC distinct from the anxiogenic effect seen in other studies, which may be unique to individuals who are already struggling with intense anxiety. Further investigations of the optimal THC doses for acute management of anxiety symptoms among individuals with anxiety disorders are therefore warranted.

Collectively these data offer insights into the therapeutic effects of medicinal cannabis when it is used by a population with clinically significant anxiety and depression. The positive response, reflected by reductions in anxiety and/or depression by most participants, support the need for continued investigation of medicinal cannabis or related cannabinoid therapeutics as pharmacological treatments for anxiety and depression symptom relief, ideally with randomized, placebo-controlled trials.

CRediT authorship contribution statement

David Wolinsky: Writing – original draft, Investigation, Formal analysis. **Rhiannon E. Mayhugh:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Renuka Surujnarain:** Writing – review & editing, Project administration, Investigation. **Johannes Thrul:** Writing – review & editing,

Table 2
Association of cannabis use and individual variables with end of day reports.

Variable	Anxiety		Depression		High		Driving ability	
	b	*p*	*b*	*p*	*b*	*p*	*b*	*p*
Intercept	**4.050**	**<0.001**	**3.402**	**<0.001**	0.262	0.489	**9.252**	**<0.001**
Cannabis use	**−0.839**	**<0.001**	**−0.672**	**<0.001**	**2.314**	**<0.001**	**−1.283**	**<0.001**
Week in study	0.045	0.409	0.010	0.865	**−0.073**	**0.020**	0.059	0.208
Age (50+)	−0.484	0.548	−0.028	0.973	0.838	0.124	−1.111	0.121
Gender	−0.999	0.190	−1.435	0.075	−0.327	0.525	−0.674	0.321
Antidepressant	−0.974	0.194	0.304	0.694	**1.429**	**0.009**	−0.505	0.453

Note. All linear mixed effects models included a random effect of Time (Week in Study). Reference group for gender was female. Reference group for age was under 50 years old.
Bold = $p < .05$.

Table 3
Individual variable and route of administration association with acute changes following cannabis use.

Variable	Anxiety		Depression		High		Driving ability	
	b	*p*	*b*	*p*	*b*	*p*	*b*	*p*
Intercept	**−2.679**	**<0.001**	**−1.172**	**0.001**	**3.520**	**<0.001**	**−1.096**	**0.027**
Route								
Vaporized	0.358	0.076	−0.020	0.917	**0.663**	**0.031**	−0.290	0.365
Oral	0.156	0.483	0.019	0.927	−0.318	0.359	−0.230	0.523
Age	0.615	0.347	0.398	0.390	0.557	0.447	−0.936	0.159
Gender	0.044	0.939	0.015	0.970	−0.115	0.861	0.708	0.229
Antidepressant	0.531	0.349	−0.354	0.370	1.090	0.099	**−1.293**	**0.030**
Initial use	0.114	0.493	−0.242	0.128	−0.296	0.237	**−1.146**	**<0.001**

Note. Reference group for route of administration was smoked products. Reference group for gender was female. Reference group for age was under 50 years old. Reference group for initial use was >5 uses (i.e., 5 or fewer versus >5 uses).
Bold = $p < .05$.

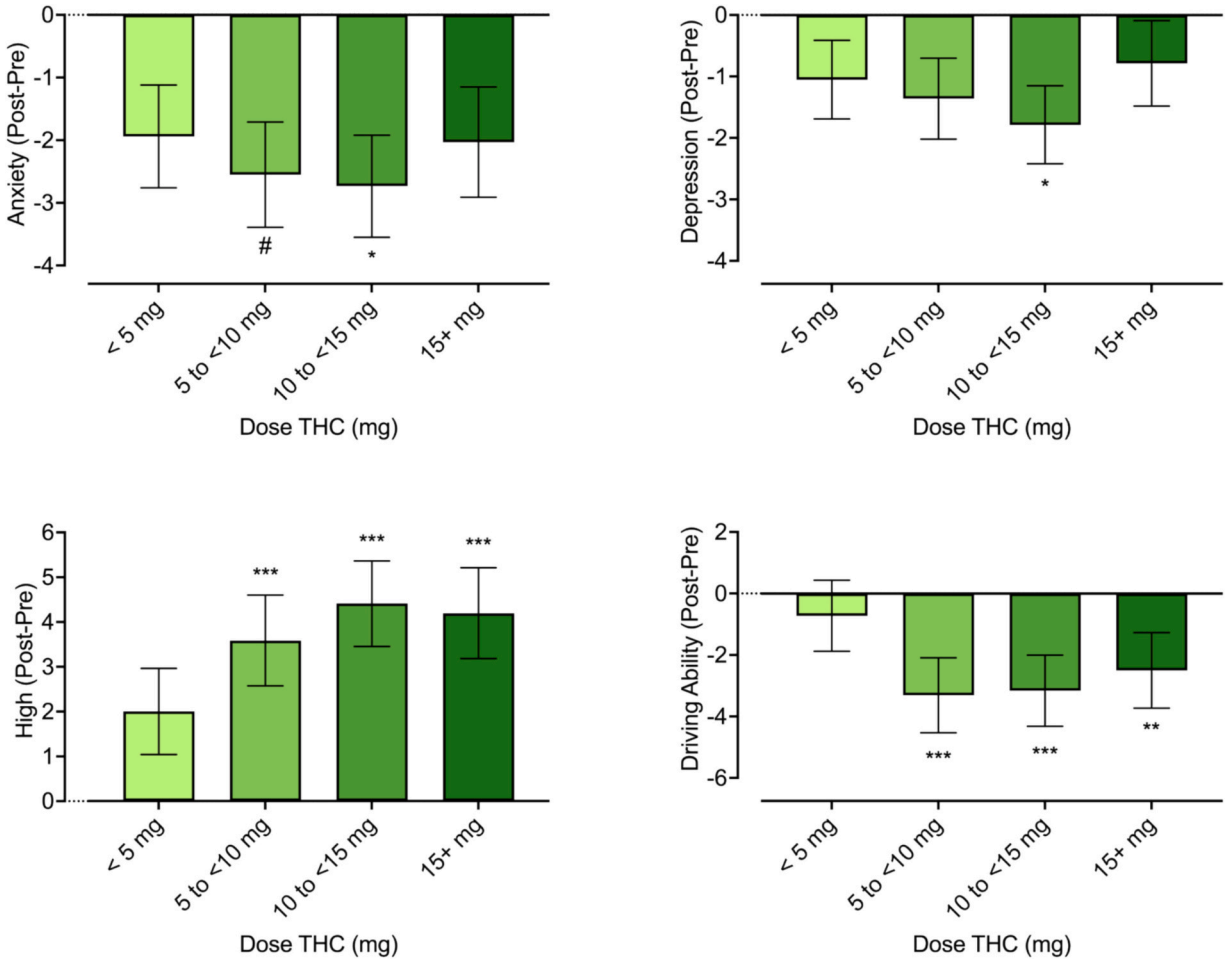


Fig. 4. Association of oral THC dose with anxiety, depression, and adverse effects. Presented are estimated marginal means (with 95 % confidence intervals) from linear mixed effect models predicting changes in subjective ratings pre and post-cannabis administration. Reference group for comparisons is <5 mg.
# $p < .10$.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

Visualization, Formal analysis. **Ryan Vandrey:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Justin C. Strickland:** Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Role of funding source

This study was supported by a pilot grant from the Lambert Center for the Study of Medicinal Cannabis & Hemp at Thomas Jefferson University. Preparation of this manuscript was, in part, supported by the

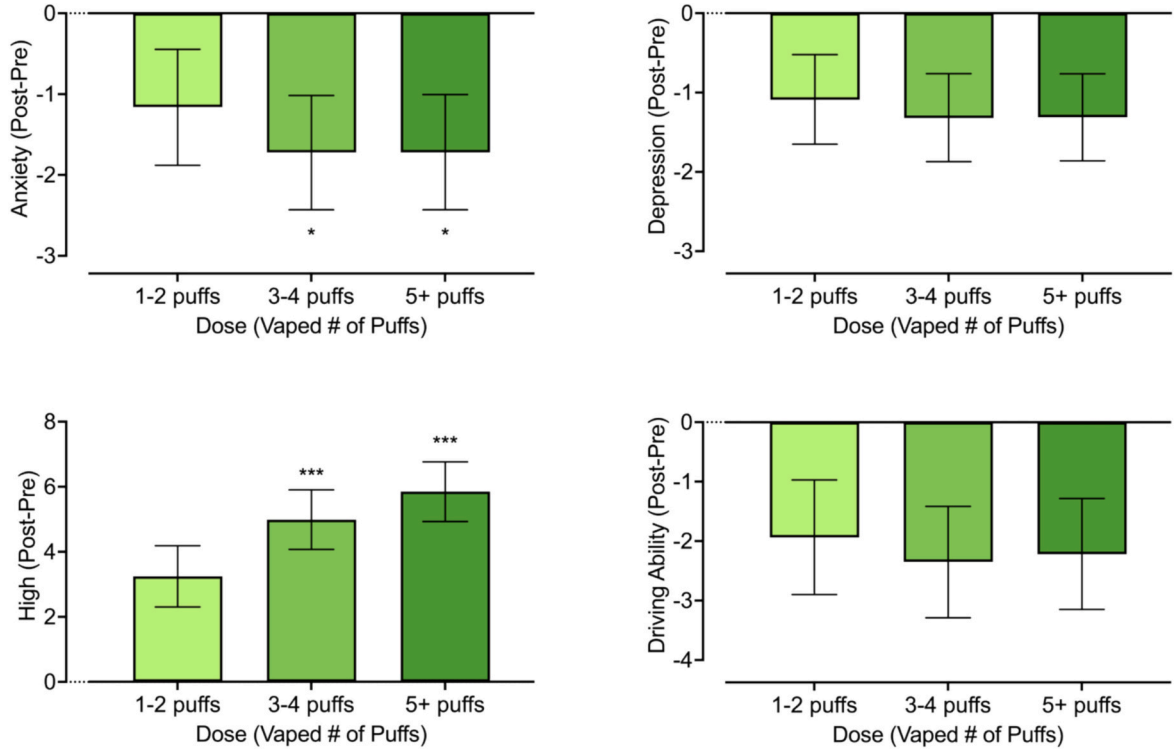


Fig. 5. Association of vaped cannabis puff number with anxiety, depression, and adverse effects. Presented are estimated marginal means (with 95 % confidence intervals) from linear mixed effect models predicting changes in subjective ratings pre- and post-cannabis administration. Reference group for comparisons is 1–2 puffs.
* $p < .05$.
*** $p < .001$.

National Institute on Drug Abuse (NIDA; UM1DA059000). These funding sources had no role in preparation or submission of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Declaration of competing interest

JCS has received research related funding from Canopy Growth Corporation and DynamiCare Health and consulting fees from Merck Corporation in the past three years. RV is a paid consultant or advisory board member for Jazz Pharmaceuticals, Syqe Medical Ltd., WebMD, Charlotte's Web, and Schedule 1 Therapeutics.

Acknowledgements

We acknowledge Veriheal, Fells Point Cannabis Docs, and Skylight-CB2 Insights for support in study recruitment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.119829.

References

Abame, M.A., He, Y., Wu, S., Xie, Z., Zhang, J., Gong, X., Wu, C., Shen, J., 2021. Chronic administration of synthetic cannabidiol induces antidepressant effects involving modulation of serotonin and noradrenaline levels in the hippocampus. Neurosci Lett. 744, 135594. Epub 20201231. https://doi.org/10.1016/j.neulet.2020.135594. PubMed PMID: 33388355.

Arkell, T.R., Manning, B., Downey, L.A., Hayley, A.C., 2023. A semi-naturalistic, open-label trial examining the effect of prescribed medical cannabis on neurocognitive performance. CNS Drugs 37 (11), 981–992.

Aspis, I., Feingold, D., Weiser, M., Rehm, J., Shoval, G., Lev-Ran, S., 2015. Cannabis use and mental health-related quality of life among individuals with depressive disorders. Psychiatry Res. 230 (2), 341–349.

Azcarate, P.M., Zhang, A.J., Keyhani, S., Steigerwald, S., Ishida, J.H., Cohen, B.E., 2020. Medical reasons for marijuana use, forms of use, and patient perception of physician attitudes among the US population. J. Gen. Intern. Med. 35, 1979–1986.

Bahorik, A.L., Sterling, S.A., Campbell, C.I., Weisner, C., Ramo, D., Satre, D.D., 2018a. Medical and non-medical marijuana use in depression: longitudinal associations with suicidal ideation, everyday functioning, and psychiatry service utilization. J. Affect. Disord. 241, 8–14. Epub 20180717. https://doi.org/10.1016/j.jad.2018.05.065. PubMed PMID: 30086434; PMCID: PMC6455811.

Bahorik, A.L., Sterling, S.A., Campbell, C.I., Weisner, C., Ramo, D., Satre, D.D., 2018b. Medical and non-medical marijuana use in depression: longitudinal associations with suicidal ideation, everyday functioning, and psychiatry service utilization. J. Affect. Disord. 241, 8–14.

Boehnke, K.F., Sinclair, R., Gordon, F., Hosanagar, A., Roehler, D.R., Smith, T., Hoots, B., 2024. Trends in US medical Cannabis registrations, authorizing clinicians, and reasons for use from 2020 to 2022. Ann. Intern. Med. 177, 458–466.

Centers for Disease Control and Prevention, 2025, March 26. Suicide data and statistics. https://www.cdc.gov/suicide/facts/data.html.

Chang, V.T., Hwang, S.S., Feuerman, M., 2000. Validation of the Edmonton symptom assessment scale. Cancer: Interdisciplinary International Journal of the American Cancer Society 88 (9), 2164–2171.

Childs, E., Lutz, J.A., de Wit, H., 2017. Dose-related effects of delta-9-THC on emotional responses to acute psychosocial stress. Drug Alcohol Depend. 177, 136–144. Epub 20170530. https://doi.org/10.1016/j.drugalcdep.2017.03.030. PubMed PMID: 28599212; PMCID: PMC6349031.

Crippa, J.A., Derenusson, G.N., Ferrari, T.B., Wichert-Ana, L., Duran, F.L., Martin-Santos, R., Simões, M.V., Bhattacharyya, S., Fusar-Poli, P., Atakan, Z., Santos Filho, A., Freitas-Ferrari, M.C., McGuire, P.K., Zuardi, A.W., Busatto, G.F., Hallak, J. E., 2011. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J. Psychopharmacol. 25 (1), 121–130. Epub 20100909. https://doi.org/10.1177/0269881110379283. PubMed PMID: 20829306.

Cuttler, C., Spradlin, A., McLaughlin, R.J., 2018. A naturalistic examination of the perceived effects of cannabis on negative affect. J. Affect. Disord. 235, 198–205. Epub 20180406. https://doi.org/10.1016/j.jad.2018.04.054. PubMed PMID: 29656267.

Gilman, J.M., Schuster, R.M., Potter, K.W., Schmitt, W., Wheeler, G., Pachas, G.N., Hickey, S., Cooke, M.E., Dechert, A., Plummer, R., 2022. Effect of medical marijuana card ownership on pain, insomnia, and affective disorder symptoms in adults: a randomized clinical trial. JAMA Netw. Open 5(3):e222106-e.

Goethe, J.W., Woolley, S.B., Cardoni, A.A., Woznicki, B.A., Piez, D.A., 2007. Selective serotonin reuptake inhibitor discontinuation: side effects and other factors that influence medication adherence. J. Clin. Psychopharmacol. 27 (5), 451–458.

Goodell, E.M.A., Nordeck, C., Finan, P.H., Vandrey, R., Dunn, K.E., Thrul, J., 2021. Feasibility and acceptability of using smartphone-based EMA to assess patterns of prescription opioid and medical cannabis use among individuals with chronic pain. Internet Interv. 26, 100460.

Greenberg, P., Chitnis, A., Louie, D., Suthoff, E., Chen, S.Y., Maitland, J., Gagnon-Sanschagrin, P., Fournier, A.A., Kessler, R.C., 2023. The economic burden of adults with major depressive disorder in the United States (2019). Adv. Ther. 40 (10), 4460–4479. Epub 20230731. https://doi.org/10.1007/s12325-023-02622-x. PubMed PMID: 37518849; PMCID: PMC10499687.

Hill, M.N., Hillard, C.J., Bambico, F.R., Patel, S., Gorzalka, B.B., Gobbi, G., 2009. The therapeutic potential of the endocannabinoid system for the development of a novel class of antidepressants. Trends Pharmacol. Sci. 30 (9), 484–493.

Insel, T.R., Wang, P.S., 2009. The STAR* D trial: revealing the need for better treatments. Psychiatr. Serv. 60 (11), 1466–1467.

Joo, J., Devkota, J., Stone, B., Dunn, K.E., Zipunnikov, V., Vandrey, R., Finan, P.H., Thrul, J., 2024. Predictors of participant compliance with ecological momentary assessment among individuals with chronic pain who are using cannabis and opioids. Internet Interv. 38, 100784.

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 J. Biol. Med. 93 (2), 251–264 (Epub 20200629. PubMed PMID: 32607086; PMCID: PMC7309674).

Linares, I.M., Zuardi, A.W., Pereira, L.C., Queiroz, R.H., Mechoulam, R., Guimarães, F.S., Crippa, J.A., 2019. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. Braz. J. Psychiatry 41 (1), 9–14. Epub 20181011. https://doi.org/10.1590/1516-4446-2017-0015. PubMed PMID: 30328956; PMCID: PMC6781714.

Manning, B., Arkell, T.R., Hayley, A.C., Downey, L.A., 2024. A semi-naturalistic open-label study examining the effect of prescribed medical cannabis use on simulated driving performance. J. Psychopharmacol. 38 (3), 247–257.

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. Front. Psych. 12, 729800.

McIntyre, R.S., Alsuwaidan, M., Baune, B.T., Berk, M., Demyttenaere, K., Goldberg, J.F., Gorwood, P., Ho, R., Kasper, S., Kennedy, S.H., 2023. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry 22 (3), 394–412.

NCSL, 2023. State Medical Cannabis Laws: National Conference of State Legislatures [updated June 22, 2023; cited 2024 April 12th]. Available from: https://www.ncsl.org/health/state-medical-cannabis-laws.

Panchal, N., Saunders, H., Rudowitz, R., Cox, C., 2023. The implications of COVID-19 for mental health and substance use. KFF. https://www.kff.org/mental-health/issue-brief/the-implications-of-covid-19-for-mental-health-and-substance-use/.

Patel, S., Hill, M.N., Cheer, J.F., Wotjak, C.T., Holmes, A., 2017. The endocannabinoid system as a target for novel anxiolytic drugs. Neurosci. Biobehav. Rev. 76 (Pt A), 56–66. https://doi.org/10.1016/j.neubiorev.2016.12.033. PubMed PMID: 28434588; PMCID: PMC5407316.

Petrie, G.N., Nastase, A.S., Aukema, R.J., Hill, M.N., 2021. Endocannabinoids, cannabinoids and the regulation of anxiety. Neuropharmacology 195, 108626.

Pigott, H.E., 2015. The STAR*D trial: it is time to reexamine the clinical beliefs that guide the treatment of major depression. Can. J. Psychiatry 60 (1), 9–13. https://doi.org/10.1177/070674371506000104. PubMed PMID: 25886544; PMCID: PMC4314062.

Rana, T., Behl, T., Sehgal, A., Mehta, V., Singh, S., Kumar, R., Bungau, S., 2021. Integrating endocannabinoid signalling in depression. J. Mol. Neurosci. 1–13.

Rey, A.A., Purrio, M., Viveros, M.P., Lutz, B., 2012. Biphasic effects of cannabinoids in anxiety responses: CB1 and GABA(B) receptors in the balance of GABAergic and glutamatergic neurotransmission. Neuropsychopharmacology 37 (12), 2624–2634. Epub 20120801. https://doi.org/10.1038/npp.2012.123. PubMed PMID: 22850737; PMCID: PMC3473327.

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 Res. 313, 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. Mol. Neurobiol. 56 (2), 1070–1081. Epub 20180604. https://doi.org/10.1007/s12035-018-1143-4. PubMed PMID: 29869197.

Schauer, G.L., Njai, R., Grant, A.M., 2022. Clinician beliefs and practices related to cannabis. Cannabis Cannabinoid Res. 7 (4), 508–515.

Schlienz, N.J., Spindle, T.R., Cone, E.J., Herrmann, E.S., Bigelow, G.E., Mitchell, J.M., Flegel, R., LoDico, C., Vandrey, R., 2020. Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. Drug Alcohol Depend. 211, 107969. Epub 20200321. https://doi.org/10.1016/j.drugalcdep.2020.107969. PubMed PMID: 32298998; PMCID: PMC8221366.

Schlienz, N.J., Scalsky, R., Martin, E.L., Jackson, H., Munson, J., Strickland, J.C., Bonn-Miller, M.O., Loflin, M., Vandrey, R., 2021. A cross-sectional and prospective comparison of medicinal cannabis users and controls on self-reported health. Cannabis Cannabinoid Res. 6 (6), 548–558.

Schoeler, T., Theobald, D., Pingault, J.-B., Farrington, D.P., Coid, J.W., Bhattacharyya, S., 2018. Developmental sensitivity to cannabis use patterns and risk for major depressive disorder in mid-life: findings from 40 years of follow-up. Psychol. Med. 48 (13), 2169–2176.

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. J. Transl. Med. 18, 1–21.

Shiffman, S., Stone, A.A., Hufford, M.R., 2008. Ecological momentary assessment. Annu. Rev. Clin. Psychol. 4, 1–32. https://doi.org/10.1146/annurev.clinpsy.3.022806.091415 (PubMed PMID: 18509902).

Spindle, T.R., Cone, E.J., Schlienz, N.J., Mitchell, J.M., Bigelow, G.E., Flegel, R., Hayes, E., Vandrey, R., 2018. Acute effects of smoked and vaporized Cannabis in healthy adults who infrequently use Cannabis: a crossover trial. JAMA Netw. Open 1 (7):e184841. Epub 20181102. https://doi.org/10.1001/jamanetworkopen.2018.4841 (PubMed PMID: 30646391; PMCID: PMC6324384).

Spindle, T.R., Martin, E.L., Grabenauer, M., Woodward, T., Milburn, M.A., Vandrey, R., 2021. Assessment of cognitive and psychomotor impairment, subjective effects, and blood THC concentrations following acute administration of oral and vaporized cannabis. J. Psychopharmacol. 35 (7), 786–803. Epub 20210528. https://doi.org/10.1177/02698811211021583. PubMed PMID: 34049452; PMCID: PMC9361180.

Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR* D: implications for clinical practice. Am. J. Psychiatry 163 (1), 28–40.

Vandrey, R., Herrmann, E.S., Mitchell, J.M., Bigelow, G.E., Flegel, R., LoDico, C., Cone, E.J., 2017. Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. J. Anal. Toxicol. 41 (2), 83–99. https://doi.org/10.1093/jat/bkx012. PubMed PMID: 28158482; PMCID: PMC5890870.

Voshaar, R.O., Aprahamian, I., Borges, M., van den Brink, R., Marijnissen, R., Hoogendijk, E., van Munster, B., Jeuring, H., 2021. Excess mortality in depressive and anxiety disorders: the lifelines cohort study. Eur. Psychiatry 64 (1), e54.

Wahlbeck, K., Westman, J., Nordentoft, M., Gissler, M., Laursen, T.M., 2011. Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. Br. J. Psychiatry 199 (6), 453–458. Epub 20110518. https://doi.org/10.1192/bjp.bp.110.085100. PubMed PMID: 21593516.

Wang, Y., Jean Jacques, J., Li, Z., Sibille, K.T., Cook, R.L., 2021. Health outcomes among adults initiating medical Cannabis for chronic pain: a 3-month prospective study incorporating ecological momentary assessment (EMA). Cannabis 4 (2), 69–83 doi: 10.26828/cannabis/2021.02.006. PubMed PMID: 34671723; PMCID: PMC8525881.

Wanjau, M.N., Möller, H., Haigh, F., Milat, A., Hayek, R., Lucas, P., Veerman, J.L., 2023. Physical activity and depression and anxiety disorders: a systematic review of reviews and assessment of causality. AJPM Focus 2, 100074.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67 (6), 361–370.

Zuardi, A.W., Rodrigues, N.P., Silva, A.L., Bernardo, S.A., Hallak, J.E.C., Guimarães, F.S., Crippa, J.A.S., 2017. Inverted U-shaped dose-response curve of the anxiolytic effect of cannabidiol during public speaking in real life. Front. Pharmacol. 8 (259). https://doi.org/10.3389/fphar.2017.00259. Epub 20170511. PubMed PMID: 28553229; PMCID: PMC5425583.