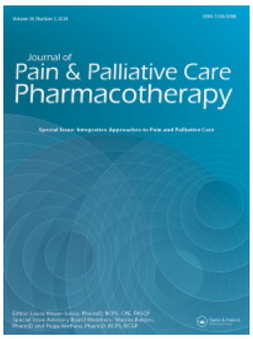

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Changes in Pain and Mental Health Symptoms Associated with Prescribed Medicinal Cannabis Use: A One-Year Longitudinal Study

Andreas Halman, Richard Chenhall and Daniel Perkins

ABSTRACT

Chronic pain and mental health issues like depression and anxiety significantly contribute to disease burden in Western countries. While cannabinoids are suggested to have analgesic, anxiolytic and antidepressant properties, evidence, especially for long-term use, is inconclusive. This 12-month observational study evaluated the effects of prescribed medicinal cannabis for 96 patients suffering from pain, as well as sleep disturbances, depression and anxiety. Treatment outcomes for pain, depression, anxiety and sleep problems were assessed at 3, 6, and 12 months using validated instruments. Significant reductions were observed in pain scores and the interference of pain on daily functions, alongside improvements in mental health and sleep. Many patients reported notable improvements in pain severity and reduced use of pain medications in the first 6 months, with a decline at 12 months. Additionally, sustained improvements in depression, anxiety, stress and sleep were observed, with about half reporting substantial improvement. Adverse effects were common but mostly mild or moderate, most commonly dry mouth and sleepiness. These results show that prescribed medicinal cannabis treatment is associated with improvements in chronic pain and mental health symptoms, such as depression, anxiety and stress. However, findings also suggest reduced effectiveness with longer-term use, emphasizing the need for additional research.

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Cannabis; pain; depression; anxiety; sleep; longitudinal

Introduction

Cannabis is a plant that has been used for thousands of years as a traditional medicine to treat various medical ailments, including pain (1). Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are key components of cannabis that may have therapeutic effects relating to pain as well as mental health (2). THC is the primary psychoactive compound in cannabis, which exerts its effects through partial agonism at cannabinoid receptors type 1 (CB_1) and type 2 (CB_2), with CB_1 being highly expressed in the central nervous systems, including regions involved in stress, anxiety, mood, sleep and pain (2). Activation of CB_2 receptors that are highly expressed in immune cells may relieve pain, such as by decreasing proinflammatory cytokines (3). It is also proposed that THC, being only a partial agonist at $CB_{1/2}$ receptors, might function as a competitive inhibitor of endocannabinoids, potentially reducing $CB_{1/2}$ signaling and may result in anxiogenic effects (4). As for CBD, its ability to reduce stress and anxiety may be attributed to its potent agonism at 5-HT_{1A} receptors and/or partial agonism at dopamine D_2 receptors (2). CBD may also modulate pain by binding to and desensitizing the transient receptor potential vanilloid member 1, a mediator of pain signaling (5) and/or through its activity as an allosteric modulator at Mu and Delta opioid receptors (6).

Despite the long history of cannabis use and the approximately 60 randomized controlled trials conducted over the years, the clinical evidence supporting the efficacy of medicinal cannabis in treating chronic pain remains inconclusive (7). A recent systematic review (8) encompassing randomized controlled trials and observational

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studies assessed the efficacy of various cannabinoids in treating chronic pain. It was concluded that there is evidence of low to moderate strength for small improvements in pain relief during short-term treatment (1–6 months) with products having a high and comparable THC to CBD ratio. Importantly, studies were primarily short-term, with 39% lasting only between 4 and 6 wk and most not exceeding 6 months, which presents a limitation in understanding the treatment of chronic pain, as pain severity can fluctuate in the short term. Therefore, long-term assessments of pain severity are crucial. In a UK Medical Cannabis Registry observational study on patients with a primary diagnosis of depression, medicinal cannabis was associated with reductions in symptoms of depression and anxiety, as well as improvements in sleep quality, for up to 6 months of treatment (9). A retrospective case series on patients with anxiety or poor sleep in the U.S., reported a consistent improvement in anxiety over a 3-month treatment period for ~79% of patients, while sleep improved for two thirds of patients in the first month, but then fluctuated over the following months (10). However, current evidence for the efficacy of cannabis in treating anxiety is inconclusive and limited, with mixed results from surveys, animal studies and clinical trials (11). Regarding insomnia, the limited number of studies on cannabis and sleep disorders revealed little to no concrete evidence of significant improvements (12).

This longitudinal observational study in Australia aims to provide more evidence on the long-term effects of cannabis use for pain, depression, anxiety and sleep problems. The primary outcome is change in pain, with secondary outcomes being changes in mental health (stress, depression and anxiety) and sleep problems over a 12-month period. Additionally, the study identifies adverse effects and changes in the use of prescribed and over-the-counter medications.

Methods

Study

This research utilizes data from a prospective, observational study of Australian patients who had been legally prescribed medicinal cannabis products by a doctor. The study was conducted between 25.01.2019 and 25.09.2021, and was approved by the Monash Health Human Research Ethics Committee (RES-18-0000524A). Participants recruitment was tied to the regulatory framework governing medicinal cannabis prescription in Australia. At the time of recruitment, doctors seeking to prescribe these products were required in most cases to obtain approval from their state's health authority and/or the Commonwealth Therapeutic Goods Administration. When issuing an approval to prescribe, health authorities in the Australian state of Victoria also provided doctors with a survey invitation alongside the approval letter, which doctors were asked to share with their patients. This invitation included information for patients describing the study and participation details. Patients could enroll in the study via a survey web link. The first question of the survey contained information about the study and required written consent prior to proceeding to the survey questions. The inclusion criteria for participation were being at least 18 years of age and using a medicinal cannabis product prescribed by a doctor. The voluntary online surveys covered areas such as cannabis tolerability, adverse effects, effectiveness and patient experience. Data were collected at baseline and 3-, 6- and 12-month follow-ups.

Instruments

Patients were asked to provide details of the primary condition for which medicinal cannabis had been prescribed, the primary symptom it was being used to treat and any secondary symptoms they were experiencing, regardless of whether medicinal cannabis was intended to treat these (pre-defined conditions and symptoms are listed in Supplementary Table S1). The product that patients had been prescribed was surveyed via a pre-filled list containing all medicinal cannabis products available in Australia at that time (plus an "other" option for any newly approved products). Patients reported the prescribed products at each time point and those who were prescribed two products were required to identify both. The research team determined the THC: CBD ratios by reviewing the information for each product.

Patients were asked about any change in the use of other medications for the treatment of their symptoms (including change in dose, frequency and strength), and had to indicate whether their usage since commencing medicinal cannabis had decreased, increased or remained the same.

For patients identifying pain as a symptom the Brief Pain Inventory (BPI) was used to gauge the intensity of pain and its impact on daily functions (13). Pain intensity was assessed using a 0 to 10 numerical rating scale, with higher values indicating more intense pain. A decrease of 10–20% can be considered as minimally important, 30% or more as moderate improvement and at least 50% as substantial improvement (14). The Depression Anxiety Stress Scale-21 (DASS-21) was used to assess the current mental health status of all patients across the depression, anxiety and stress subscales, with higher scores indicating greater severity (15). For depression, anxiety and stress, normal ranges were 0–9, 0–7 and 0–14, respectively, with increasing scores indicating severity from mild to extremely severe. Symptom Assessment Scale (SAS) (16) was used to assess levels of distress caused by pain, anxiety, depression and sleep problems via an 11-point scale from 0 (no distress) to 10 (worst possible distress). Patients' perceived change from baseline in the overall severity of their condition was assessed via a Patient Global Impression of Change Instrument (PGIC) (17).

Finally, patients were asked about adverse effects, where they had the opportunity to choose one or more options from a predefined list of 47 adverse effects related to mental health/emotional, neurological, gastrointestinal and other/uncategorised categories (or specify an unlisted adverse effect as "other"; all options listed in Supplementary Table S2), along with the severity of each (mild, moderate or severe).

Statistical analysis

Data was collected and managed using the REDCap data collection system based at the University of Melbourne. All records were analyzed with R statistical software v4.1.2. Patients were categorized into three groups based on the THC to CBD ratio of the medication they were taking. A "THC dominant" group comprised patients who were administered medications with a THC:CBD ratio of ≥2:1 (including 0% CBD). In contrast, "CBD dominant" group consisted of individuals using medications for which the CBD to THC ratio was at least 2:1 (including 0% THC). The "Balanced" group included patients whose medications had both THC: CBD and CBD:THC ratios of less than 2:1. The "Mixed" group included patients who took medications from different categories simultaneously. Since some patients' medication was changed once during the treatment period, their categorization by product group was adjusted accordingly to reflect the medication they were taking at each subsequent assessment point.

Linear Mixed Models (LMM) were applied using the lmerTest R package (18) to assess differences between groups and temporal variations within groups. In all models, individual patients were treated as random effects to account for within-subject variations, while time point and medication group were designated as fixed effects. The dependent variable was either the test score or the response value from a Likert scale question. The impact of each predictor was examined by deriving an ANOVA output from the LMM utilizing the Satterthwaite's method for approximating degrees of freedom. Effect sizes were determined using the effect size R package (19), with partial eta-squared (η_p^2) accompanied by 95% confidence intervals (CI) presented. Effect size values of ≥0.01 were set to indicate a small effect, ≥0.06 a medium effect and ≥0.14 a large effect (20). *Post-hoc* examinations, adjusted using the Holm-Bonferroni method, were carried out to examine significant differences. These analyses were conducted employing the emmeans package in R (21) and results are described with estimated marginal means (EMM), their associated standard error (SE), mean difference scores (M_{diff}) and *p*-values. A *p*-value threshold of 0.05 was set for statistical significance.

Results

Characteristics of patients

A total of 139 participants with pain enrolled, with 105 completing at least one follow-up survey. After removing duplicate enrollments and

excluding one participant who did not provide answers to the majority of questions, 96 participants remained and were included in the final dataset. The study cohort included 44 males, 51 females and one participant of unspecified gender, aged between 22 and 83 years (mean = 51.9, SD = 14.2) at baseline. The most common condition for which medicinal cannabis had been prescribed was pain (63.5%; N = 61), followed by cancer (10.4%; N = 10) and arthritis (6.2%; N = 6), with each of the remaining conditions individually accounting for less than 5%. Pain was reported as the primary symptom medicinal cannabis had been prescribed to treat by 95 patients and as a secondary symptom by 1 (with anxiety and depression as primary). In addition to pain, patients commonly reported other secondary symptoms including sleep problems (69.8%; N = 67), anxiety (56.2%; N = 54) and depression (47.9%; N = 46) (Figure 1(A)). A total of 36.5% (N = 35) specified an additional "other" symptom (all answers are listed in Supplementary Table S3). Almost all patients (95.8%; N = 92) identified more than one symptom and 50.0% (N = 48) reported four or more symptoms (Figure 1(B)).

Based on the product prescribed to patients at baseline, 35.4% (N = 34) were categorized into the "Balanced" group, 31.2% (N = 30) into the "CBD dominant" group and 7.3% (N = 7) into the "THC dominant" group. Additionally, 26% (N = 25) of patients, concurrently prescribed two products from different categories, were classified in the "Mixed" group. A second product was reported as being used by 33.3% (N = 32) of patients. Across all groups, 35.4% (N = 34) of patients reported taking the product twice daily, 15.6% (N = 15) three times daily, 11.5% (N = 11) as required, 10.4% (N = 10) once daily and 1.0% (N = 1) four times daily, while 26.0% (N = 25) did not specify the frequency of use.

Changes in pain measures

Severity, interference and distress

To explore the potential therapeutic effects of medicinal cannabis on pain, changes in pain severity, distress caused by pain and impact of pain on daily functions were evaluated. The severity of pain, as assessed using the BPI (Figure 2(A)), had a significant variation over time ($p < 0.0001$) with a large effect size (η_p^2 = 0.17, 95% CI [0.07, 0.26]). Compared to the baseline (mean = 4.93, SD = 1.87), pain levels decreased significantly by the 3 months (M_{diff} = −1.22, $p < 0.0001$), with this

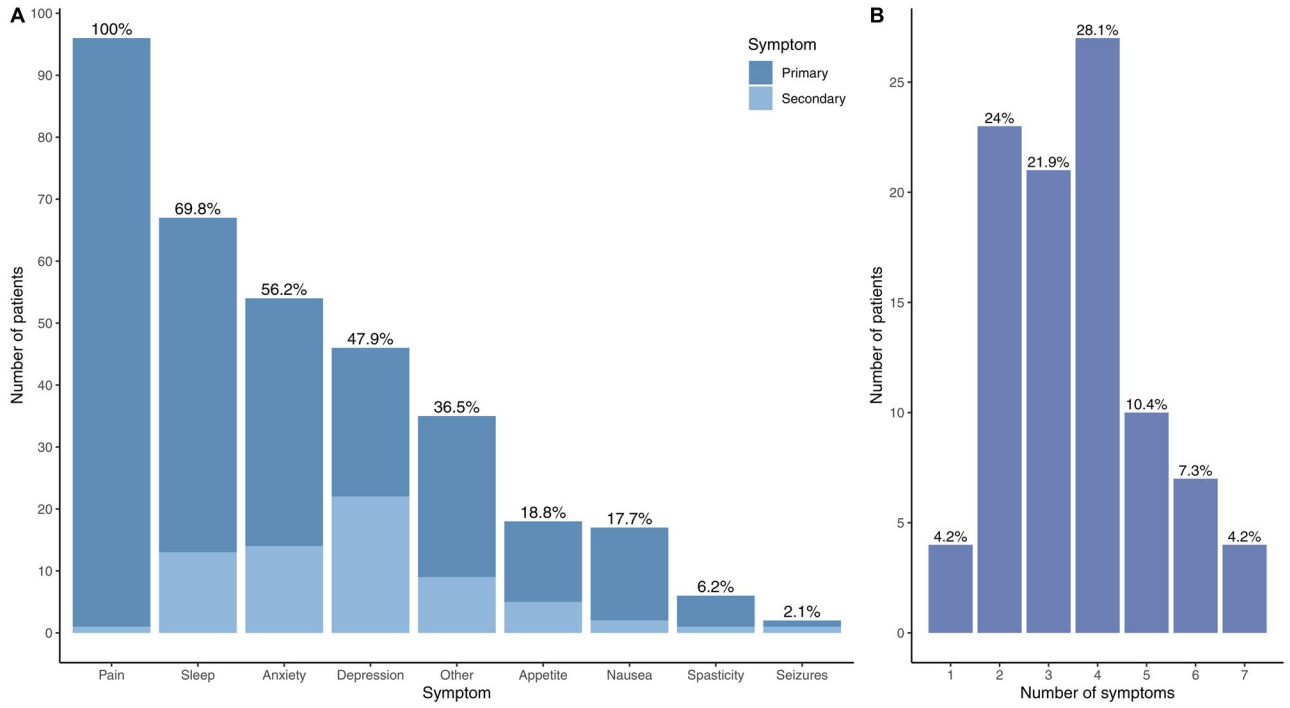

Figure 1. (A) Breakdown of symptoms and (B) total number of symptoms experienced at commencement.

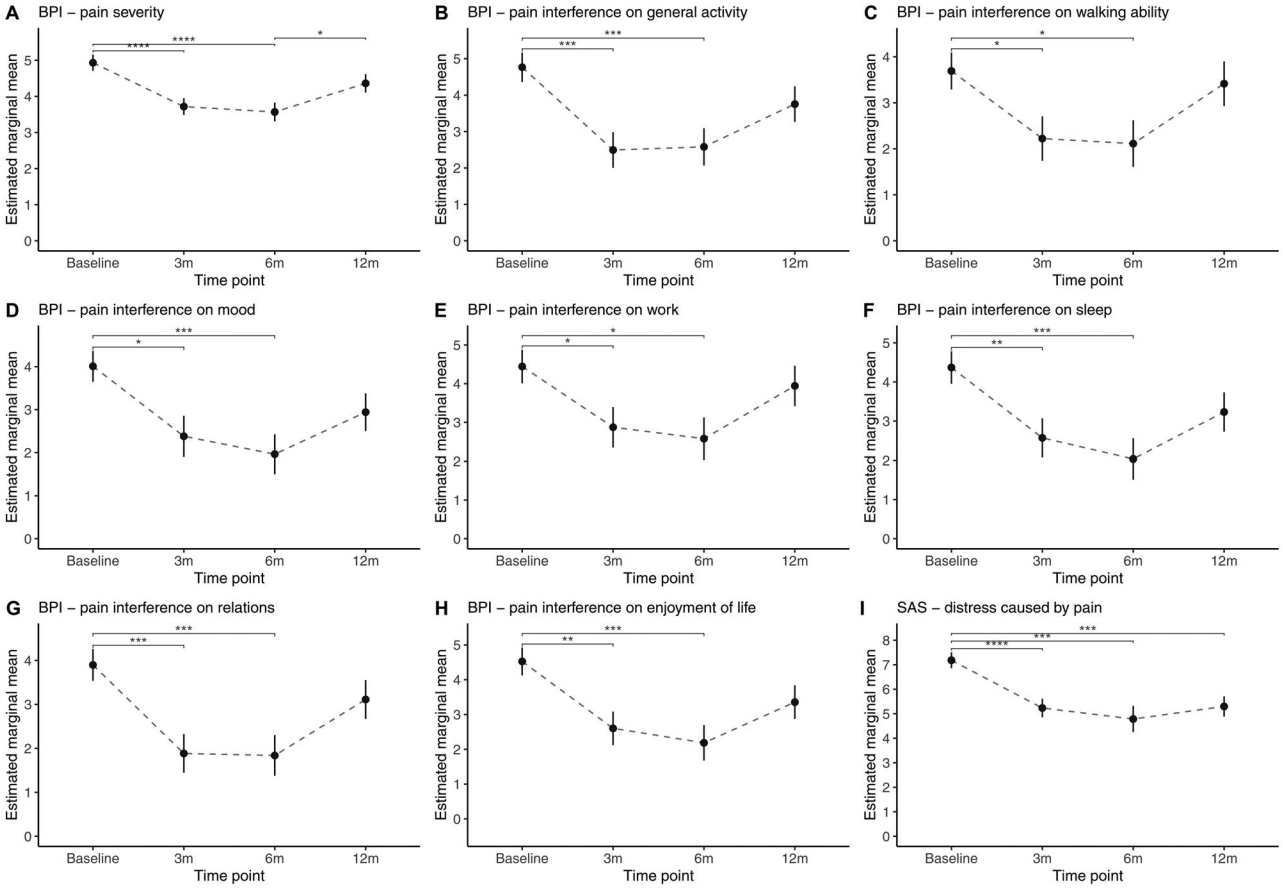

Figure 2. Brief Pain Inventory results for (A) pain severity and (B–H) interference on daily functions, and (I) Symptom assessment scale: distress caused by pain. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$ significance level.

improvement persisting at 6 months ($M_{diff} = -1.36$, $p < 0.0001$). However, between 6 and 12 months, pain levels significantly increased ($M_{diff} = 0.79$, $p < 0.05$), and by 12 months, the pain levels were not significantly different from the baseline ($M_{diff} = -0.57$, $p = 0.0657$).

For BPI pain interference, a statistically significant main effect over time was observed for all measures with small to medium effect sizes for reduced interference, including general activity ($p < 0.0001$), walking ability ($p < 0.01$), mood ($p < 0.001$), work ($p < 0.01$), sleep quality ($p < 0.001$), quality of relations ($p < 0.0001$) and enjoyment of life ($p < 0.0001$). Across all interference measures, a consistent pattern emerged. At 3-months, significant improvements from baseline were noted in general activity ($M_{diff} = -2.27$, $p < 0.001$), walking ability ($M_{diff} = -1.47$, $p < 0.05$), mood ($M_{diff} = -1.63$, $p < 0.05$), work ($M_{diff} = -1.57$, $p < 0.05$), sleep quality ($M_{diff} = -1.80$, $p < 0.01$), quality of relations ($M_{diff} = -2.01$, $p < 0.001$) and enjoyment of life ($M_{diff} = -1.92$, $p < 0.01$). At 6-months, significant improvements from baseline persisted and on most of the measures a further decrease in mean scores was observed: general activity ($M_{diff} = -2.19$, $p < 0.001$), walking ability ($M_{diff} = -1.58$, $p < 0.05$), mood ($M_{diff} = -2.05$, $p < 0.001$), work ($M_{diff} = -1.85$, $p < 0.05$), sleep quality ($M_{diff} = -2.34$, $p < 0.001$), quality of relations ($M_{diff} = -2.06$, $p < 0.001$) and enjoyment of life ($M_{diff} = -2.34$, $p < 0.001$). However, at 12-months, scores showed a deterioration across all interference measures and no longer differed significantly from baseline.

In relation to pain-induced distress, there were significant reductions throughout the treatment period ($p < 0.0001$; Figure 2(I)). Compared to the baseline, distress levels were lower at 3-months ($M_{diff} = -1.95$, $p < 0.0001$), 6-months ($M_{diff} = -2.40$, $p < 0.001$) and 12-months ($M_{diff} = -1.88$, $p < 0.001$), indicating sustained improvements throughout the study period. Complete results

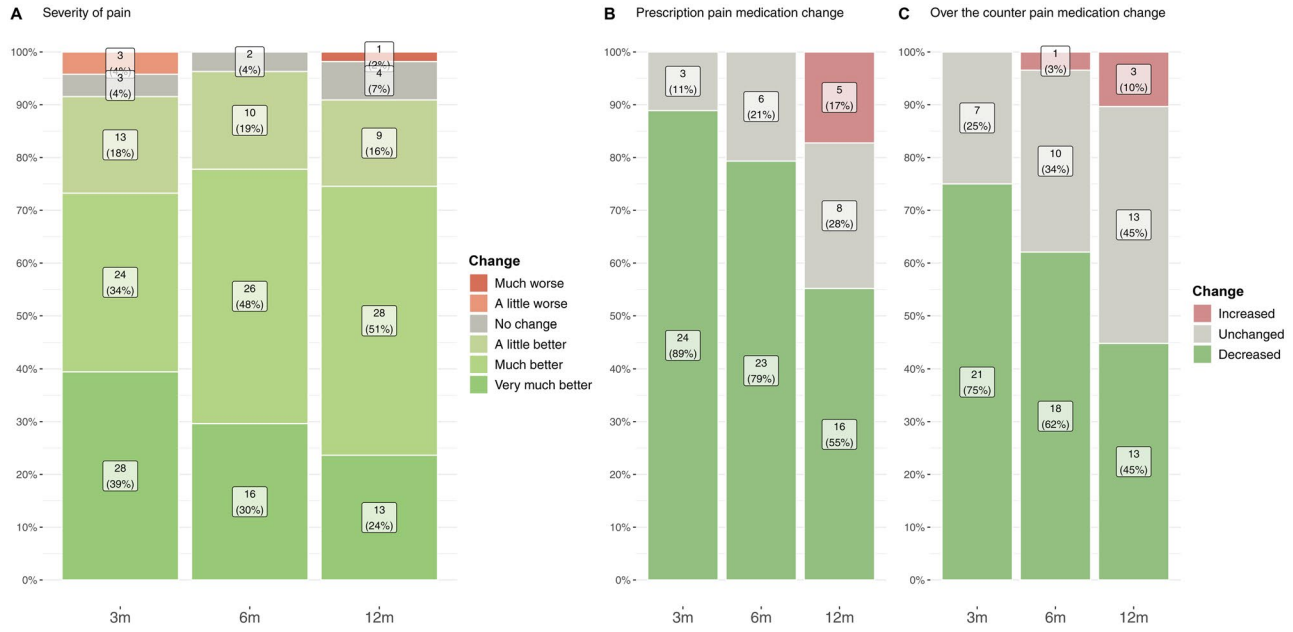

Figure 3. Self-reported change in (A) severity of pain and medication use of (B) prescription and (C) over the counter pain medication.

from the statistical tests on pain are provided in Supplementary Table S4.

Patient self-assessments of pain severity during the treatment period showed promising results (Figure 3(A)). At 3 months, 73% of patients reported their symptoms as "much better" or "very much better" compared to baseline. This proportion increased slightly at 6 months and remained similar (75%) at 12 months. However, over time, more patients reported feeling "much better" rather than "very much better", indicating a possible decline in therapeutic effect.

Change in pain medication use

A large proportion of patients reported decreases in pain medication use since baseline, although this gradually lessened as the study progressed (Figure 3(B,C)). Specifically, a majority at 3 months reported reduced use of both prescription and over-the-counter (OTC) pain medications (89 and 75%, respectively). At 6-months, 79% continued to report reduced use of prescription medications and 62% reduced use of OTC medicines, with one patient reporting an increase. At 12-months more than half of patients (55%) continued to report decreased use of prescription medications, while 45% decreased use of over-the-counter (OTC). However, at the end of the study period, 17 and 10% of patients also reported an increase in prescription and OTC medicines, respectively.

Changes in mental health and sleep

The results relating to anxiety, depression, stress and sleep showed notable and predominantly lasting improvements throughout the study period (Figure 4). Statistically significant main effects of time were observed across all measures, including DASS-21 depression ($p < 0.01$), anxiety ($p < 0.0001$) and stress ($p < 0.0001$), as well as distress related to depression ($p < 0.001$), anxiety ($p < 0.01$) and sleep problems ($p < 0.01$). The observed improvements in mental health outcomes showed medium to large effect sizes, with medium effects noted for DASS-21 depression and anxiety and large effects for DASS-21 stress, distress related to depression and anxiety as well as sleep problems. All statistical results for mental health components are provided in Supplementary Table S5.

Post-hoc tests of the DASS-21 identified a significant improvement in depression at 3-months ($M_{diff} = -4.23$, $p < 0.01$), 6-months ($M_{diff} = -3.59$, $p < 0.05$) and 12-months ($M_{diff} = -3.42$, $p < 0.05$; Figure 4(A)). The SAS for distress caused by depression mirrored these findings, showing significant reductions in distress at 3-months

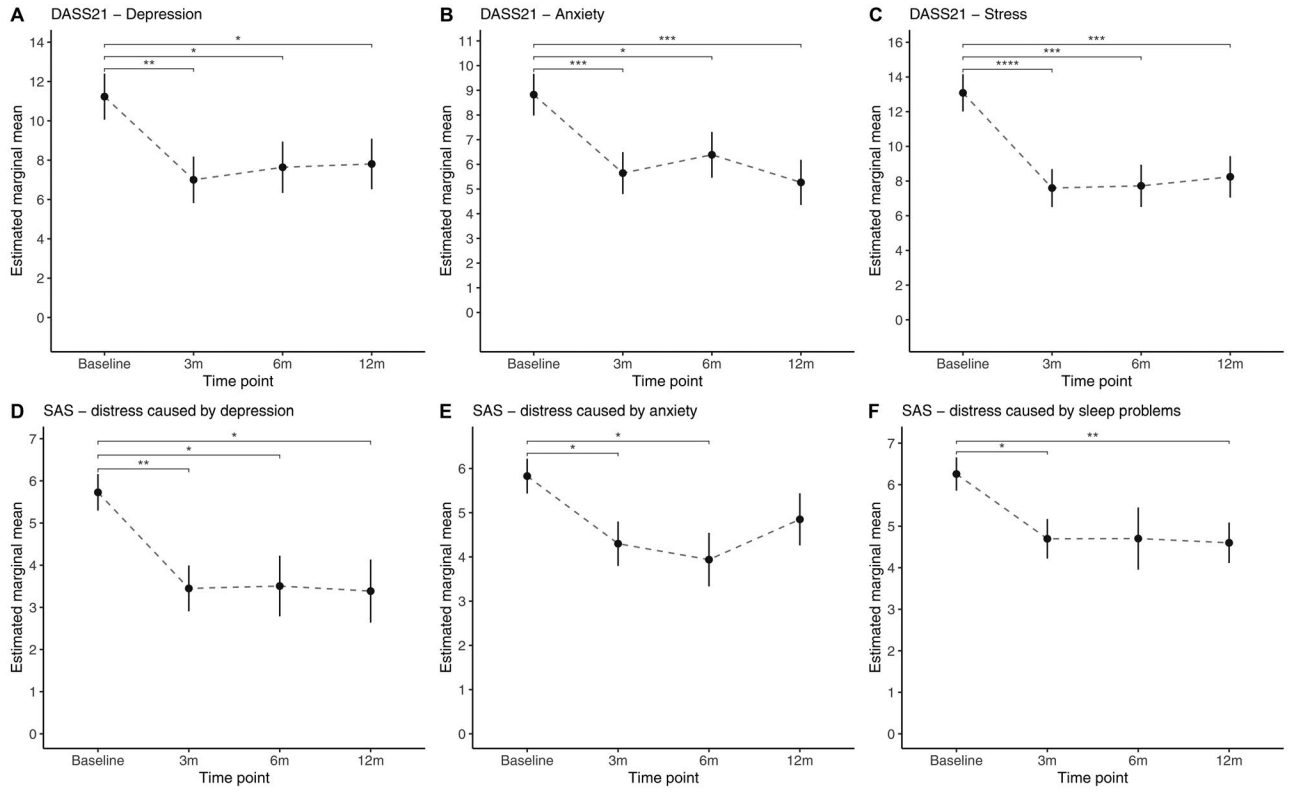

Figure 4. DASS-21 measures levels of (A) depression, (B) anxiety and (C) stress, and symptom Assessment Scale: distress caused by (D) depression, (E) anxiety and (F) sleep problems. *$p<0.05$; **$p<0.01$; ***$p<0.001$; ****$p<0.0001$ significance level.

(M_{diff} = −2.28, $p<0.01$), 6-months (M_{diff} = −2.22, $p<0.05$) and 12-months (M_{diff} = −2.34, $p<0.05$; Figure 4(D)).

Similarly, anxiety levels, as measured by DASS-21, showed sustained improvements, with significant differences from baseline noted at 3-months (M_{diff} = −3.14, $p<0.001$), 6-months (M_{diff} = −2.44, $p<0.05$) and 12-months (M_{diff} = −3.55, $p<0.001$; Figure 4(B)). There were also reductions in distress caused by anxiety (Figure 4(E)) observed at 3-months (M_{diff} = −1.53, $p<0.05$) and 6 months (M_{diff} = −1.89, $p<0.05$). However, by the 12th month, distress scores related to anxiety increased, rendering the difference not statistically significant when compared to the baseline (M_{diff} = −0.98, p = 0.479).

Sustained improvements in stress levels as assessed by the DASS-21, were also observed through the study period, again with significant improvement from baseline seen at 3-months (M_{diff} = −5.49, $p<0.0001$), 6-months (M_{diff} = −5.36, $p<0.001$) and 12-months (M_{diff} = −4.84, $p<0.001$; Figure 4(C)). Finally, the distress caused by sleep problems was assessed, showing a significant improvement at 3-months (M_{diff} = −1.56, $p<0.05$), no significant difference from baseline at 6-months (M_{diff} = −1.55, p = 0.170), but a significant improvement again evident again at 12-months (M_{diff} = −1.66, $p<0.01$; Figure 4(F)).

At each follow-up, patients self-assessed the overall change in the severity of their condition since baseline via the PGIC instrument. For depression (Figure 5(A)), the majority of patients reported substantial improvement at 3-months, which increased slightly at 6-months but decreased at 12-months. Anxiety and sleep disorders (Figure 5(B,C), respectively) followed a similar trend, with improvements peaking at 6-months and slightly declining by 12-months, though the majority still reported feeling improved. However, at 12-months, a few participants reported feeling worse in terms of the severity of anxiety and sleep disorders.

Some positive correlations between higher expectations and symptom improvement were observed, such as reduced self-reported pain severity at 12-months (r = 0.426, $p<0.01$), reduced anxiety at 6-months (r = 0.536, $p<0.01$)

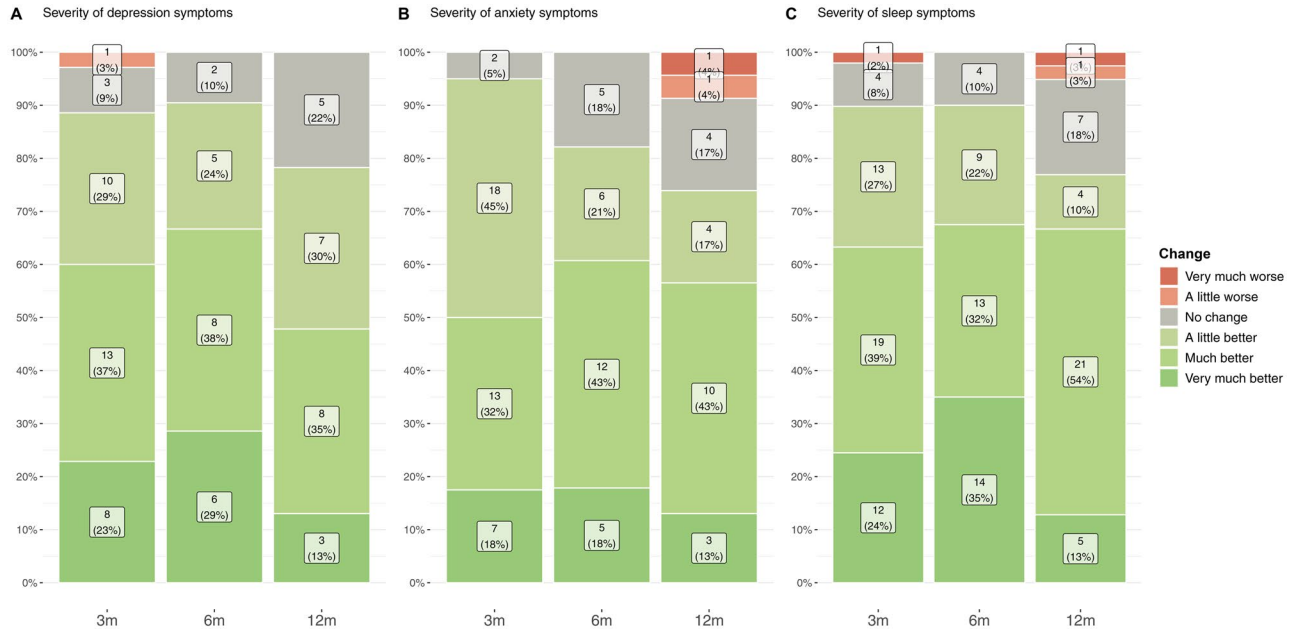

Figure 5. Change in self-assessed severity of (A) depression, (B) anxiety and (C) sleep symptoms.

and improved sleep at 3-months (r = 0.347, $p < 0.05$). However, in contrast, higher expectations were in some instances associated with poorer outcomes, including increased distress caused by pain (r = 0.365, $p < 0.05$) as well as increased distress caused by depression (r = 0.634, $p < 0.01$) and anxiety (r = −0.698, $p < 0.01$) at 12-months. Further, the BPI pain severity and DASS-21 instruments did not show any correlation with expectations. Overall, these mixed results do not show a clear effect of expectation bias on outcomes in this sample.

Finally, patients reported changes in their use of medications for depression, anxiety and sleep compared to the start of the study. Overall, half or fewer patients reported a decrease in medication use, while half or more reported no change. Once again, the greatest improvements were seen during the first 6 months, with the highest reduction in medication use. By 12 months, this figure dropped around 20%, with fewer than 30% of patients reporting a decrease in medication use, while some also noted an increase in use (Supplementary Figure S1).

Cannabinoid group differences

All cannabinoid groups were assessed for all pain measures as well as mental health and sleep. No statistically significant main effect of the treatment group was detected except for SAS distress caused by anxiety ($p < 0.05$), where *post-hoc* tests did not reveal any differences between groups at any time point. After conducting *post-hoc* tests on all measures, significant results were mostly observed only for certain groups and in specific measures (all results are provided in Supplementary Tables S6 and S7), however given the small numbers in each sub-group these results should be interpreted with caution.

Adverse effects

Patients were surveyed for the adverse effects of the treatment at each follow-up. A total of 75% (N = 72) reported experiencing mild side effects, 39.6% (N = 38) moderate side effects and 9.4% (N = 9) severe side effects during the one-year study period. Figure 6 illustrates the most frequent side effects experienced by patients at any time during medicinal cannabis treatment, broken down by the severity (refer to Supplementary Figure S2 for the complete list). The most common side effects for the "CBD dominant" group were dry mouth and sleepiness, affecting 17% and 16% of individuals, respectively, which was followed by increased appetite (8%) and dizziness (5%). For the "Balanced" group, 12% experienced

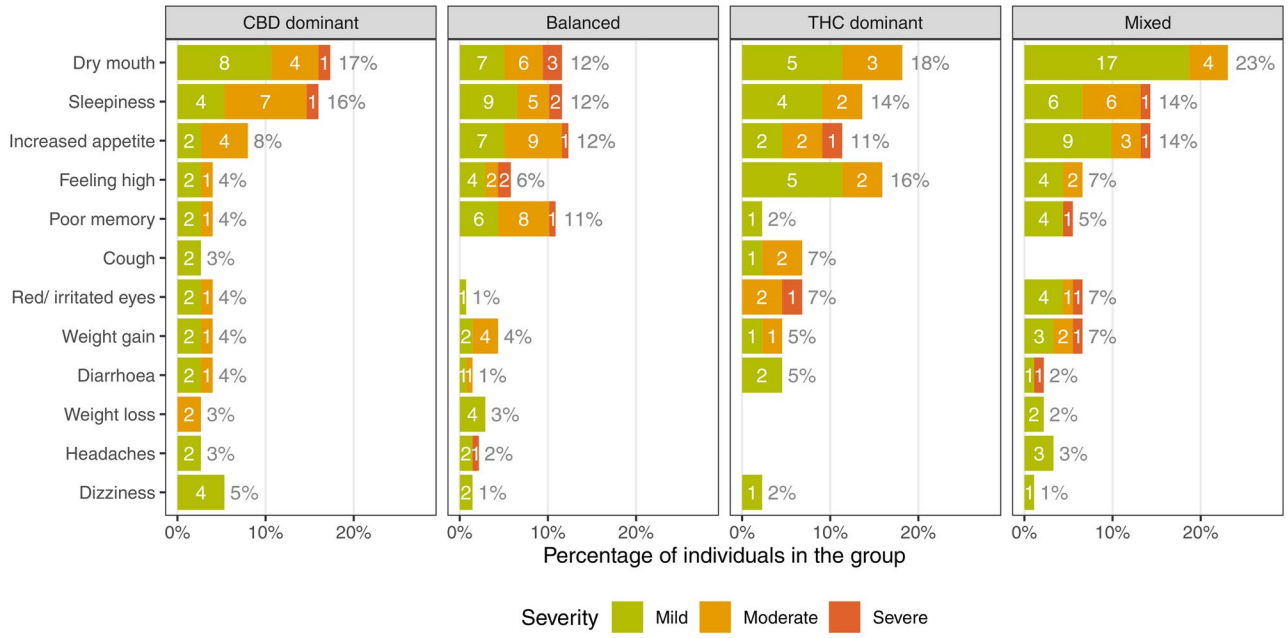

Figure 6. Twelve most frequent side effects experienced over the whole study period. The number of individuals in each group with a specific severity is indicated inside the bar corresponding to that severity. The percentage of individuals experiencing the side effect in each group is displayed in grey.

dry mouth, sleepiness and increased appetite, followed by 11% reporting poor memory. In the "THC dominant" group, 18% of the individuals reported a dry mouth as a side effect, with 16% experiencing feeling high, 14% sleepiness and 11% increased appetite. Finally, in the "Mixed" group, 23% of patients reported dry mouth and 14% experienced increased appetite and sleepiness. Overall, dry mouth was the most prevalent side effect across all groups, with sleepiness following closely. An increased appetite was observed more frequently in the "Balanced", "THC dominant" and "Mixed" groups. The feeling of being high was lowest in the "CBD dominant" group and increased with a heightened THC: CBD ratio. Across all time points, the majority of reported side effects were mild (55.6%), followed by moderate (30.8%) and severe (13.7%).

Discussion

In the context of increasing use of cannabinoid-based medicines, this study provides additional evidence relating to pain, mental health and sleep disorders for time periods up to 12-months. We identified clear associations between patient commencement of a prescribed medicinal cannabis product and improvements in pain, mental health and sleep difficulties, with the most pronounced therapeutic effects visible within the first 6 months of treatment. Furthermore, significant improvements were noted across diverse domains of symptom interference on daily functions, suggesting an improved quality of life for patients. In relation to pain management the majority of patients exhibited a notable decline in their use of both prescription and over-the-counter pain medications. This reduction in the use of other medications is consistent with the substantial improvements in pain severity reported by most patients.

However, by 12-months, the effectiveness of medicinal cannabis, in terms of pain severity and its interference with daily activities, appeared to wane. There was also a corresponding decline in the number of patients reporting reduced use of other prescription and OTC medications. Furthermore, the gradual reduction across the study in perceived improvement, from "very much better" to lesser degrees of improvement, and the presence of a few individuals who felt their condition worsened, shows the need for an improved understanding of the treatment's long-term effects on pain.

Our analysis also identified improvements in aspects of depression, anxiety and sleep

disturbances following the commencement of prescribed medicinal cannabis. This included sustained decreases in the DASS-21 depression, anxiety and stress subscales across the 12-month study period and corresponding sustained reductions in SAS distress scores associated with depression, as well as anxiety for the initial 6 months only. Distress caused by sleep problems showed improvements that were sustained through to the end of the study. Around a third to half of patients demonstrated reductions in the use of medications related to depression, anxiety and sleep during the initial 6 months. Concurrently, around half reported significant symptom alleviation for depression and anxiety, and around two-thirds for sleep-related symptoms that persisted throughout the study. While there was a trend of diminished change in both reduced medication use and patient perceived change in depression, the DASS-21 depression score itself showed sustained improvement. The medium to large effect sizes for pain severity and mental health outcomes indicate the potential therapeutic properties of medicinal cannabis in improving mental well-being alongside physical health.

Several factors could explain the observed decline in the effectiveness of medicinal cannabis during the last 6-month period. For example, chronic exposure to THC has been reported to lead to the desensitization and downregulation of CB_1 receptors, which may result in reduced CB_1 agonist activity and therefore, could contribute to the diminishing therapeutic effects of cannabis over time (22). Secondly, pain, depression and anxiety can be mediated by distinct pathways and receptor systems, which can lead to different outcomes when treated with medicinal cannabis. For instance, while CB_1 and CB_2 receptors are associated with analgesic effects (23), the 5-HT_{1A} receptor can regulate anxiety and depression (24, 25). Chronic use of medicinal cannabis may induce changes in these receptors systems, potentially resulting in different long-term effects on pain compared to mental health symptoms. Several receptors beyond $CB_{1/2}$ are also associated with analgesic effects, further complicating the overall picture (23). Moreover, chronic pain can have various origins and the effectiveness of medicinal cannabis may diminish if the underlying condition progresses (such as cancer) or changes, whereas it may respond more consistently to mental health symptoms. Additionally, psychological factors may play a role and patients might perceive the benefits as less pronounced over time.

Similar findings to this study have been reported in other recent observational studies, such as in one by O'Brien et al. (26) who reported medicinal cannabis use to be associated with significant reductions in self-reported pain intensity and interference at 3-months in patients with chronic pain. Longer-lasting improvements in patients with chronic pain, extending up to 6-months, were observed by Gruber et al. (27). This study showed improvements in pain, which were accompanied by enhanced sleep, mood, anxiety and quality of life. Similarly, in a study with elderly participants (28), the vast majority reported improvements in their condition and a reduction in pain at 6-months. Furthermore, enhancements in pain management, sleep quality and overall quality of life in patients with peripheral neuropathic pain after using THC/CBD spray was noted at the 9-month mark (29).

In longer-term observational assessments, a multicenter study demonstrated overall mild-to-modest long-term improvement in all investigated measures, including pain and associated symptoms over 12 months (30). Similarly, significant pain relief was documented in cancer patients at 3, 6, and 9-months, with an uptick at the 12-month mark in BPI worst pain and pain interference (31). Additionally, there was a slight increase in pain severity and overall pain, resulting in all these 12-month outcomes not being significantly different from the baseline. This 12-month study adds more evidence regarding efficacy of medicinal cannabis in managing chronic pain and provides additional insights into its long-term effects. Our results align with the 12-month study by Aprikian et al. (31), as we observed increases in BPI pain severity and interference, potentially highlighting the diminished long-term effectiveness of medicinal cannabis treatment. However, this contrasts with the 24-month registry-based study by Vickery et al. (32), which identified sustained improvements in pain severity and interference.

Limitations

A limitation of this study is its reliance on self-reported data and uncontrolled nature of the study, which can provide valuable insights into individual experiences but necessitates cautious interpretation due to the potential for subjective variations. The variability in medicinal cannabis products could affect the study's outcomes and their generalizability. The concurrent use of other medications by patients might have also influenced their evaluation of medicinal cannabis effectiveness. The small sample size prevented performing subgroup analyses within the cannabinoid group. Lastly, patient attrition during the study could have introduced additional bias, however, statistical methods were employed to control for this.

Conclusion

Considering the limited number of studies examining the effects of medicinal cannabis on pain over periods longer than 6 months, this study provides valuable additional insights in this area. Overall, we found that the use of medicinal cannabis was associated with reduced pain during the first 6 months and improved mental well-being over 12 months. Patients reported not only less pain but also experienced reduced interference from pain in their daily functions. Furthermore, they reported decreased use of pain medications and a large proportion felt that their pain symptoms had significantly improved, as reflected in their reported changes in the severity of pain. However, by the end of 12-months, some of these benefits appeared to wane. Overall, our results are encouraging in relation to the short term treatment of pain and mental health symptoms, but long-term effects, especially in terms of pain, appear uncertain. Further longitudinal and controlled studies are necessary to better understand the sustained effects of cannabis-based medications on pain and mental health.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Monash Health Human Research Ethics Committee (RES-18-0000524A). Patient consent was obtained from all subjects involved in the study.

Author contributions

R.C. and D.P. contributed to the design and implementation of the research. A.H. and D.P. contributed to the analysis of the results. A.H., R.C. and D.P. contributed to the writing of the manuscript.

Disclosure statement

DP and AH hold equity in a commercial entity, Psychae Therapeutics, which is undertaking research with psychedelic compounds and DP is a co-CEOs of the same organization.

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Data availability statement

The datasets presented in this article are not readily available because the ethical approval and consent signed by the patients were for data access by the research team members only.

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