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OBM Integrative and Complementary Medicine

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Original Research

Prescribed Medicinal Cannabis for the Treatment of Chronic Pain Comorbid with Depression: Real World Evidence from Project Twenty21

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Academic Editor: James D Adams

Special Issue: Topical Treatment of Pain: Perspectives on Complementary, Traditional, and Plant Medicine

OBM Integrative and Complementary Medicine
2024, volume 9, issue 2
doi:10.21926/obm.icm.2402032

Received: March 01, 2024
Accepted: May 23, 2024
Published: June 05, 2024

Abstract

Chronic pain is one of the most common conditions for which people seek treatment with cannabis-based medicinal products (CBMPs) and there is mounting real world evidence that CBMPs are safe and effective in treating pain. Many people with chronic pain also experience major depression and it is unknown whether pain patients with major depression derive equal benefit from CBMPs as those who are not depressed since comorbidities are usually an exclusion factor in RCTs. This study aimed to investigate whether patients with chronic pain with and without co-morbid depression experience the same improvement in pain and quality of life outcomes after three months of medical cannabis treatment. Data were derived from Project Twenty21 (T21), one of the largest observational studies in medicinal cannabis in the UK. Baseline data were available for 1816 chronic pain patients and three-month follow-up data were available for 1058 of these patients. Logistic regression models were used to

examine the relationship between chronic pain and comorbid depression after three months of medical cannabis treatment controlling for sociodemographic factors. Prescribed cannabis was associated with marked reductions in pain severity and interference and with improvements in aspects of general health and quality of life. A substantial portion (23.4%) of chronic pain patients reported comorbid depression. Patients with comorbid depression reported more pain interference at baseline (mean = 7.5 vs 6.8, $p < 0.01$) while there was no significant difference for pain severity (mean = 5.9 vs 6.0, $p > 0.05$). Depression status did not predict reduction in pain severity and interference at three months, while baseline scores, age and number of total comorbidities predicted some treatment outcomes. These results indicate that comorbid depression should not be a barrier to accessing treatment with CBMPs for chronic pain patients.

Keywords
Chronic pain; depression; Cannabis-Based Medicinal Products (CBMPs); comorbidity; Real-World Data (RWD); Project Twenty21 (T21)

1. Introduction

Chronic pain, defined as pain that persists or recurs for more than three months, is a leading cause of disability globally, affecting more than 30% of people worldwide [1]. In the UK, chronic pain affects between one third and one half of the population [2]. Chronic pain can negatively impact patients' quality of life (QoL) including mood and sleep [3]. Management of chronic pain presents an unmet clinical need, especially given the well-known adverse events associated with opioid medication [4]. The shift away from extended use of opioids for chronic pain has sparked growing interest in utilizing medical cannabis, which involves using the whole cannabis plant or its extracts, as an alternative treatment option.

Cannabis has a long history of use both medicinally and non-medicinally across several cultures [5]. Recently, there has been increasing availability of cannabis based medicinal products (CBMPs) worldwide due to changes in legislation. In the UK, the term CBMP is employed to refer to cannabis products that have been produced according to an approved standard (EU-GMP) and have received approval from the home office. This category encompasses flower, oil and other means of administration. Even though the National Institute for Care and Excellence (NICE) does not recommend the prescription of CBMPs for chronic pain [6], chronic pain is one of the most common conditions for which medicinal cannabis is prescribed in the UK [7, 8], and worldwide [9, 10] off label.

There is a perceived lack and inconsistency of data regarding the effectiveness of CBMPs for pain management. Existing Randomized Control Trials (RCTs) have mixed results of efficacy varying from slightly positive [11-14] to inconclusive [15-17] or negative [18]. However, there is a substantial amount of real-world evidence that supports the benefits of medical cannabis to treat the symptoms of a range of conditions [19, 20].

There are several reasons for this apparent discrepancy between the promising results of medical cannabis from observational studies and the moderate effects from RCTs [21]. Using the gold

standard of randomized controlled trials to gather evidence for medical cannabis may be challenging as RCTs do not lend themselves well to the study of whole plants [22]. Medical cannabis can contain a variety of cannabinoids in varying ratios which differ in their pharmacology and may have different treatment effects [23]. Medicinal cannabis (containing THC and, or CBD) is different to cannabis-based medicines such as nabilone and nabiximols, which are licensed medications in the UK. Although some reviews examine evidence separately, others group them together. Synergistic and entourage effects further complicate the study of medical cannabis through RCTs [24]. Moreover, there are difficulties in maintaining effective blinding in the study of medical cannabis due to its psychoactivity [25]. Contrary to RCTs where there is a preference for cannabis naïve individuals, most patients in observational studies are either past or current cannabis users, complicating comparisons even further. Additionally, RCTs often prioritize the evaluation of pain measures over considering the overall quality of life of the patient or other patient-reported outcomes using PROMs. Finally, the discrepancy can partially be explained by poor study design or stringent inclusion and exclusion criteria that usually exclude any comorbidities and are not representative of patients in clinical care.

Pain comorbid with depression is frequently encountered in clinical settings, with up to 85% of chronic pain patients affected by depression [26]. Previous research demonstrated poorer physical, social and quality of life outcomes among patients with pain comorbid with depression in comparison with those with only pain or depression [27]. Dhanju et al., 2019 report that the combination of chronic pain and depression results in less favourable treatment outcomes and overall functioning compared to each condition in isolation [28]. Similarly, in a recent review on the differential antidepressant effectiveness in patients with depression comorbid with chronic pain, participants with both disorders reported fewer functional benefits from antidepressant use than those without chronic pain [29]. In preclinical animal models, Benamar [30] found cannabinoids have the potential to serve as analgesics while simultaneously addressing the major morbidities associated with chronic pain, depression, and anxiety.

There is little published research looking specifically at treatment with cannabis for pain patients with comorbid depression. However, an early paper looking at CBMPs for the treatment of painful diabetic neuropathy showed that patients with comorbid depression had higher baseline pain scores and were also more likely to respond favourably to intervention [31]. Another study confirmed that medicinal cannabis can significantly reduce both pain intensity and depression in fibromyalgia and neuropathic pain patients [32]. Bapir et al. examined the relationship between chronic pain and anxiety and found patients with comorbid anxiety reported greater improvements in health-related quality of life [33]. Poli et al. [34] found in a trial of 338 individuals with chronic pain that cannabis therapy, when used alongside conventional analgesic treatment, diminished pain intensity, enhanced daily functionality, and facilitated a decrease in symptoms of anxiety and depression.

Given the comorbid association between chronic pain and major depressive disorder (MDD) and the potential impact of CBMPs on both conditions, this study aims to compare the treatment outcomes of patients with chronic pain alone and those with comorbid depression following a three-month medical cannabis intervention. It will assess improvements not only in pain levels but also in quality of life, mood, and sleep quality, utilizing Patient-Reported Outcome Measures (PROMs) to gain comprehensive insights into patients' experiences. Data is derived from a large-scale observational study of individuals receiving medical cannabis in the UK (Project Twenty21) [35].

2. Materials and Methods

2.1 Project Twenty21 (T21)

The data used for this paper come from Project Twenty21 (T21) (https://www.drugscience.org.uk/t21/) a registry of people receiving prescribed cannabis established by Drug Science in 2019. There are no inclusion or exclusion criteria for participation in the registry, any patient with a diagnosed condition receiving a medical cannabis prescription from affiliated clinics in the UK can join. Patients are followed up every 3 months as long as they continue their treatment and up to 4 years. Detailed information on the project has been published elsewhere [35].

2.1.1 Primary and Secondary Conditions

Participants report the primary medical condition for which they are seeking medicinal cannabis treatment from a list of 38 options including pain, neurological and psychiatric conditions. Participants reporting any of the following as their primary condition are classified as seeking treatment for chronic pain: arthritis, back and/or neck pain, cancer-related pain, cluster headaches, complex regional pain syndrome, Ehlers Danlos Syndromes, endometriosis, fibromyalgia, migraines, musculoskeletal pain, neuropathic pain, palliative care pain or other condition that causes chronic pain.

In addition to reporting their primary medical condition, participants report whether they have any secondary or comorbid conditions. They are presented with a list of 54 possible conditions and, for the purposes of the analyses reported in this paper, they are classified as having comorbid depression if they report any of the following: major depressive disorder or mood disorders.

2.1.2 Use of Prescribed Medications

The current pharmacological medications and CBMPs that patients were prescribed at baseline and follow up are reported. The total number of products is calculated and the mean number of medications used reported. CBPMs are categorized based on their form (oil or flower) as well as their THC and CBD ratios (THC dominant, balanced and CBD dominant). The proportion of prescriptions falling into each of these six categories is presented.

2.2 Self-Reported Symptomatology

Patients complete at least one condition-specific questionnaire and 4 general questionnaires at baseline and at each of the three-monthly follow-ups.

2.2.1 Pain Severity and Interference

Patients with a primary condition of chronic pain complete the Brief Pain Inventory (BPI) which assesses the severity of pain and its impact on daily function [36]. The BPI is widely used in clinical care and research with Cronbach alpha reliability ranges between 0.81 and 0.95 [37]. For the analyses reported here we evaluate two scales: pain severity, consisting of 4 items and pain interference, the extent to which pain interferes with daily activities, assessed using 7 items.

2.2.2 Quality of Life

All patients, regardless of primary condition, complete the EuroQol-5D-5L questionnaire which evaluates quality of life based on 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). A weighted scale was calculated in this sample as per the weights in Table 2 of Devlin et al. 2017, with minimum of -0.285 and maximum of 1 (optimal health) [38].

2.2.3 General Health

General health was also evaluated using the visual analogue scale of the EQ-5D-5L (EQ VAS) which asks individuals to rate, on a scale of 0-100, their general health with '100' representing the best health imaginable [39]. The EQ-5D-5L is a valid and reliable instrument, widely used across countries [38-40].

2.2.4 Depressed Mood

All patients complete the Patient Health Questionnaire (PHQ-9) which comprises 9 items assessing mood and severity of depression with higher scores indicating worse mood. It has been validated in diverse populations [41]. The criteria reported by Kroenke and Spitzer were used to classify PHQ-9 scores to five categories: no depressive symptoms (0-4), mild depressive symptoms (5-9), moderate depressive symptoms (10-14), moderately severe depressive symptoms (15-19) and severe depressive symptoms (20-27) [42].

2.2.5 Sleep Quality

All patients answer an adapted version of the Pittsburgh Sleep Quality Index [43], which includes 4 items assessing sleep interference, duration, intensity of sleep and daytime sleepiness. Each of these items is assessed on a 5-point scale (with '5' representing severe problems) and for the current analyses all items are summed to form a single measure of sleep quality. Mention that we've previously shown this scale to have excellent reliability and/or calculate alpha for this sample.

2.2.6 Comorbidities

Participants were asked to report whether they had any secondary (comorbid) conditions. They were presented with a list of 54 possible conditions which were summed up and the total number of comorbidities present was used as a covariate (excluding depression and mood disorders).

2.2.7 Gender

Self-reported gender included 3 categories: male, female and non-binary.

2.2.8 Age

Age was assessed in years.

2.3 Statistical Analysis

By the 1st of April 2023, 3557 patients had been enrolled into T21 and had completed their baseline assessment. Patients who reported a primary condition of chronic pain were further divided into two groups based on their self-reports of whether or not they had a history of major depression or mood disorders. Differences in the sociodemographic characteristics, pain and health of these two groups were assessed using Pearson's chi-squared test for categorical measures (gender) and t-test for mean differences in continuous measures (age, pain severity etc). To test whether changes in symptoms between baseline and three months differed between the two groups we used multiple linear regression. Depression status was the dependent variable, the outcome was three-month scores and covariates used in the regression included baseline scores, total number of comorbidities, gender and age. All analyses were conducted using R Statistical Software (v4.2.2) [44].

According to the National Health Service Health Research Authority, Project Twenty21 is classified as research; however, based on the Medical Research Council decision tools, Research Ethics Committee review and approval is not required. All individuals did, however, provide signed informed consent for their data to be used for research purposes.

3. Results

3.1 Depression in Chronic Pain Patients

The majority (51.3%) of the sample reported chronic pain as their primary medical condition and reason for seeking treatment with medicinal cannabis. A substantial proportion of these (23.4%) also reported depression (including major depressive disorder and mood disorders). Table 1 compares sample characteristics of chronic pain patients with and without comorbid depression.

Table 1 Baseline characteristics of chronic pain patients with and without comorbid depression.

Characteristics	Pain patients without comorbid depression	Pain patients with comorbid depression	Significance
Total number of patients reporting chronic pain	1399 (76.6%)	427 (23.4%)	
Gender	Female 41.0% Male 58.5% Non-binary 0.5%	Female 42.2% Male 56.2% Non-binary 1.6%	χ^2 =7.265, df = 2, p < 0.05
Average age	45.0 (SD = 12.9)	42.2 (SD = 12.3)	T = 3.97, p < 0.001
Average number of total comorbidities per patient (excluding depression)	2.9 (SD = 2.7)	5.7 (SD = 3.4)	T = -16.66, p < 0.001
Average number of current pharmacological medications per patient	3.9 (SD = 3.0)	5.1 (SD = 3.6)	T = -6.67, p < 0.001
Average number of CBMPs prescribed per patient	1.6 (SD = 0.7)	1.6 (SD = 0.7)	T = 0.54, p > 0.05
Baseline measures			

Pain interference (BPI) (0-10)	6.8 (0-10, SD = 2.0)	7.5 (0.9-10, SD = 1.9)	T = -5.83, p < 0.001
Pain severity (BPI) (0-10)	5.9 (0-10, SD = 1.7)	6.0 (0.8-10, SD = 1.7)	T = -1.18, p > 0.05
Mood/depression (PHQ-9) (0-27)	11.5 (0-27, SD = 6.5)	16.3 (0-27, SD = 6.0)	T = -13.15, p < 0.001
Quality of life (EQ-5D-5L) (weighted scores -0.285-1)	0.5 (-0.2-1, SD = 0.3)	0.3 (-0.3,0.9, SD = 0.3)	T = 7.94, p < 0.001
General Health Index (EQ-5D-5L VAS) (0-100)	47.2 (0-100, SD = 20.5)	42.3 (0-95, SD = 19.1)	T = 4.36, p < 0.001
Sleep Quality (0-20)	12.5 (4-20, SD = 4.0)	14.1 (4-20, SD = 3.5)	T = -7.37, p < 0.001

As shown in Table 1, the chronic pain group and the chronic pain with comorbid depression group differed in gender ratios ($\chi^2 = 7.3$, df = 2, $p < 0.05$) but did not differ in the mean number of medical cannabis medications prescribed, 1.6 for both groups ($p > 0.05$). The patient group with comorbid depression had a lower mean age (mean 42.3 vs 45.0, $p < 0.05$), more comorbidities (mean 5.7 vs 2.9, $p < 0.05$) and were currently prescribed a higher number of pharmacological medications (mean 5.1 vs 3.9, $p < 0.05$) than the group without comorbid depression.

3.2 Do Chronic Pain Patients with Comorbid Depression Experience More Severe Pain and Worse Quality of Life?

There was no significant difference in baseline scores for pain severity (mean = 5.9 vs 6.0, $p > 0.05$) but chronic pain patients with comorbid depression reported more pain interference (mean = 7.5 vs 6.8, $p < 0.01$).

Consistent with their classification of experiencing depression, current self-reported mood, as assessed by the PHQ-9 was worse in those who reported comorbid depression (mean = 16.3 vs 11.5, $p < 0.01$). Using the cut-off point of ≥20 as described above, 34.6% of the depression group classified as severely depressed vs 13.6% in the no-depression group. In addition, patients in the depressed group reported worse QoL (0.3 vs 0.5, $p < 0.01$), general health assessed using the VAS of the EQ5D (42.3 vs 47.2, $p < 0.01$) and poorer sleep (14.1 vs 12.5, $p < 0.01$).

3.3 Improvements at Three Months

At 3 months' follow-up quality of life score had improved by a mean of 0.12 (decrease in scores) and general health by 8 points (increase). Mean sleep score had decreased by 2.3 and mood/depression by 3.5 points.

3.4 Do Chronic Pain Patients with Depression Experience the Same Benefits from Medicinal Cannabis as Those without Depression?

Three-month follow-up data were available for 1058 pain patients (244 with depression and 814 without). Rates of follow-up did not differ ($\chi^2 = 0.98$, df = 1, $p > 0.05$) between those with (58.3%) vs without depression (61.2%). A series of multiple linear regression analyses was conducted to test whether outcomes (pain levels, quality of life, mood/anxiety and sleep) assessed at three months

differed between those with versus without depression. These analyses included the corresponding assessment of each baseline outcome and other socio-demographic and health related measures to adjust for the differences between those with or without depression documented above. These analyses, summarized in Table 2 lead to the following conclusions:

1. Those with and without depression experienced equal levels of improvement in both pain severity and pain interference.
2. Those with depression experienced a greater improvement in general health and sleep, assessed using the VAS of the EQ-5D and the SQQ respectively, but there were no differences between the two groups in terms of their improvement in quality of life or mood once gender, age and total number of comorbid conditions had been taken into account.
3. Baseline scores significantly predicted outcomes at 3 months for all measures.

Table 2 Outcomes at 3 months based on depression status, baseline scores, gender age and number of comorbidities.

Outcome measure	**Depression**	**Baseline score**	**Gender**	**Age**	**Total comorbid conditions**
Pain interference (BPI) (0-10)	-0.211 (0.162) p > 0.05	0.636 (0.033) p < 0.00	F: -0.094, (0.114), p > 0.05 M: -0.113, (0.131), p > 0.05 N-B: -0.072, (0.840), p > 0.05	0.009 (0.005) p > 0.05	0.079 (0.022) p < 0.00
Pain severity (BPI) (0-10)	-0.137 (0.119) p > 0.05	0.658 (0.029) p < 0.00	F: -0.172, (0.087), p > 0.05 M: -0.191, (0.097), p > 0.05 N-B: -0.231, (0.619), p > 0.05	0.010 (0.004) p < 0.05	0.028 (0.016) p > 0.05
Mood/depression (PHQ-9) (0-27)	0.4236 (0.407) p > 0.05	0.522 (0.025) p < 0.00	F: -0.093, (0.184), p > 0.05 M: -0.662, (0.318), p > 0.05 N-B: -0.598, (0.498), p > 0.05	0.023 (0.013) p > 0.05	0.099 (0.056) p > 0.05
Quality of life (EQ-5D-5L) (weighted scores -0.285-1)	-0.259 (0.230) p > 0.05	0.423 (0.027) p < 0.00	F: -0.054, (0.296), p > 0.05 M: -0.068, (0.184), p > 0.05 N-B: -0.081, (0.149), p > 0.05	-0.123 (0.045) p < 0.00	0.098 (0.031) p < 0.01

General Health Index (EQ-5D-5L VAS) (0-100)	-1.783 (1.400) $p < 0.05$	0.390 (0.029) $p < 0.00$	F: 1.592, (1.185), $p > 0.05$ M: 1.629, (1.124), $p > 0.05$ N-B: 8.524, (7.219), $p > 0.05$	-0.174 (0.047) $p < 0.00$	-0.345 (0.187) $p > 0.05$
Sleep Quality (0-20)	-0.514 (0.261) $p < 0.05$	0.578 (0.026) $p < 0.00$	F: -0.199, (0.222), $p > 0.05$ M: -0.183, (0.209), $p > 0.05$ N-B: -0.880, (0.136), $p > 0.05$	0.003 (0.008) $p > 0.05$	0.149 (0.035) $p < 0.01$

There were no gender differences in outcomes at three months for any of the measures. Age significantly influenced pain severity outcomes at 3 months with younger patients improving more. Age also significantly influenced quality of life and general health in a similar fashion, with younger patients improving more. The greater the number of comorbidities the more pain interference, the worse quality of life and worse sleep quality. Gender, age and depression had no significant effect on changes in sleep quality.

3.5 Product Characteristics

Participants reported receiving an average of 1.6 (range = 1-6) products at the start of treatment and 1.98 (range = 1-8) CBMPs at three months. These numbers did not differ between the depressed and non-depressed groups. 31.2% reported using one product, 46.5% reported using two products and 22.3% reported using three or more products. The majority of these CBPMs were for products that were classified as THC-dominant flower (67.7% of all prescriptions), with other prescriptions being classified as balanced flower (20.5%), balanced oil (6.5%), THC-dominant oil (4.1%), CBD dominant oil (4.5%), and CBD dominant flower (1.2%).

4. Discussion

In this paper we have described the characteristics of T21 pain patients with and without depression and examined whether depression status affects patient-reported outcomes at three months. The three month time point was selected to maintain statistical power of the study and extended follow-up will be explored in future research. Our sample of 1,816 pain patients is one of the largest studies of its kind to date. Major depression was common (23.4%) amongst patients with chronic pain. Patients with depression (versus without) were younger and reported more comorbidities. There was no difference in the severity of pain between the two groups but patients with comorbid depression experienced more pain interference. In addition, pain patients diagnosed with depression at baseline reported worse quality of life and general health, as well as worse mood and poorer sleep quality. A key finding was that chronic pain patients with or without comorbid depression experienced the same level of improvement in pain intensity and interference. However, those with depression experienced a greater improvement in general health and sleep. These

results suggest that medical cannabis may be equally effective in the treatment of comorbid chronic pain and depression.

Comorbid pain and depression are frequently encountered in clinical settings and should perhaps be addressed concurrently. Most pain trials so far either do not assess depression or exclude individuals with depression which limits the exploration of multimorbidity. An ideal treatment that effectively addresses the simultaneous occurrence of pain and depression has not yet been identified, though duloxetine is frequently employed as a therapeutic option in such cases [25]. In line with our findings, Ishak et al. have found that alternative pharmacotherapies like ketamine and cannabinoids seem to be both safe and effective in alleviating depressive symptoms as well as ameliorating pain [25]. Contrary to our findings, Selvarajah et al., demonstrated that depression could significantly influence chronic pain trials [31].

The emphasis in clinical practice guidelines and healthcare training and delivery often revolves around individual diseases, resulting in care that may be insufficient. Comorbidity can have implications for treatment provision. Polypharmacy heightens the risk of drug-drug interactions or drug-condition interactions, further exacerbating the extent of multimorbidity [45]. Medical cannabis could potentially solve such issues and revolutionise patient care, since a single medication/product can be effective across a range of conditions and comorbidities and exert positive effects on several symptoms simultaneously, as we have shown here. Clinicians should discuss the risks and benefits of medical cannabis with the patient especially in the light of the serious adverse effects that opiates and other common pharmacological medications can exert. Perhaps a different model for the provision of care needs to be developed, not based in specialisation and fragmentation of care but on holistic treatment. Patients in the “real world” such as clinical settings, usually present with various comorbidities and could benefit from a treatment that can address several complaints simultaneously. Our findings suggest that chronic pain patients with major depression treated with medical cannabis also experience improvements in depression, highlighting the importance of comprehensively and holistically assessing patients.

Our study findings, in line with other observational research on medicinal cannabis usage, indicate potential mood enhancement and depression reduction. This stands in contrast to investigations into the effects of recreational cannabis, especially among adolescents. Notably, Lev-Ran [46] suggests that heavy cannabis consumption, may be associated with an increased risk for developing depressive disorders. Discrepancies between conclusions drawn from general population studies and those focused on medicinal usage may stem from several factors. These include variations in product types, administration methods, user demographics between recreational and medicinal contexts, and the potential influence of social environments where recreational cannabis is consumed and evaluated.

4.1 Safety and Side-Effects

There are ongoing concerns in regards to cannabis safety and the development of cannabis use disorder (CUD), especially given the lack of long-term data. However, our own research [47] suggests that medical cannabis shows a good safety profile and that side effects are rare and mild in nature with only 2.9% of patients reporting any adverse events and the most common ones being dry mouth, feeling drowsy and having red/sore eyes. These results are consistent with previous reports demonstrating the safety and mild adverse effects of cannabis-based medications [48-50]. Schlag

[51] argues that concerns around dependence in recreational cannabis users, where most CUD research has focused, may not apply to prescribed medical users and that it may be unjustifiable to directly extrapolate findings from recreational use to medical use.

4.2 Strengths and Limitations

The primary limitation of this study stems from its observational nature, making it susceptible to selection and reporting biases due to the absence of randomization and a control group. Nonetheless, the study managed to attain large sample sizes, thanks to the same inherent observational approach. Around 15% of the 22,000 (MCCS figures) [52] people seeking medical cannabis treatment in the UK are taking part in T21. The sample is representative of the population who are seeking medical cannabis for the treatment of pain because no exclusion criteria have been applied as opposed to clinical trials. Importantly, unlike RCTs, observational studies allow the examination of patients with substantial comorbidities and a broader demographic representation. This enhances ecological validity, expands the participant pool, and leads to noteworthy cost savings [7].

An additional possible limitation of the study may be that primary condition and the presence of comorbidities rely on patient reports without necessarily the confirmation of a clinical diagnosis. Nevertheless, the utilization of patient-reported outcome measures (PROMs) has provided insights into the patient's perspective of their symptoms, functioning, quality of life and sleep. The questionnaires used, such as the BPI and the PHQ-9, are standardised and well validated and are amongst the most frequently used in clinical and research settings. In conditions such as pain and depression, PROMs have a particular value in fully illustrating the patient perspective. An assessment focusing only on pain intensity does not fully capture the various impacts of cannabinoids. Thus, as argued by Balestra et al. [53], the effects of cannabinoid treatments should be assessed using a variety of Patient-Reported Outcome Measures (PROMs).

Another limitation is that our sample was not naïve to cannabis. Consequently, our sample is somewhat self-selected, as patients who have experienced positive outcomes with cannabis in the past are more likely to choose medical cannabis treatment.

A final limitation is the number of people lost to follow-up. By the 1st of April, 3381 patients would have been eligible for their three-month follow-up. There is available data only on 2094 patients which equates to a 61.9% retention rate overall in the project.

4.3 Recommendations

Clinical evidence reveals that chronic pain and depression often accompany each other. However, most clinical trials have rigorous exclusion criteria which would not allow patients with comorbid depression to take part in the trial. According to our results, depression status does not impact the benefit that patients can receive from medical cannabis treatment. Therefore, it could be proposed that future clinical trials consider including patients not only presenting with "pure" disorders but also with comorbidities. This would make results more generalisable to the patient population presenting in clinical care.

The National Institute for Health Research (NIHR) or other funding bodies should fund research on medical cannabis treatment as it is a novel and promising field. The National Institute for Health and Care Excellence (NICE) should add medical cannabis research into their research

recommendations and take into account findings from observational research such as T21, along with considering adjusting the current stringent recommendations in regard to CBMP prescribing.

Future studies should examine concerns about standardization, dosing precision, potential side effects, and long-term safety via extended follow-up.

5. Conclusion

Consistent with previous findings from T21, and with a growing body of RWE, prescribed cannabis was associated with marked reductions in pain severity and interference and with improvements in aspects of general health and quality of life. Our results compare with existing real world evidence studies [21] and support that medical cannabis treatment can have a significant effect in quality of life, sleep and mood. Individuals suffering from pain also frequently grapple with depression, and our research shows that they experience comparable levels of improvement following medical cannabis treatment. Addressing the presence of comorbid health conditions in clinical trials of treatments for chronic pain would increase the generalizability and real-world applicability of research. Tackling multimorbidity requires an approach centered on the individual, prioritizing the concerns of both the individual and their caregivers. This strategy ensures well-coordinated, minimally disruptive care that may better align with the patient's values. As the number of patient requests for medical cannabis rises, it is becoming increasingly clear that medical professionals will need to educate themselves on the benefits that it can provide. Our hope is that medical cannabis will become more widely available and will be accessible on the NHS in the near future.

Acknowledgments

We would also like to offer our gratitude to the patients who are providing their data to T21, and thus are helping to develop the scientific evidence base on medical cannabis.

Author Contributions

AAF contributed to the analysis of the results and to the writing of the manuscript. MTL contributed to the writing and editing of the manuscript. AKS and DJN contributed to the editing of this manuscript.

Funding

Drug Science receives an unrestricted educational grant from a consortium of medical cannabis companies to further its mission, that is the pursuit of an unbiased and scientific assessment of drugs regardless of their regulatory class. Current partners are Ethypharm, Somai Pharmaceuticals, 4CLabs and Blackpoint Biotech, while previous partners include Alta Flora, Cellen Biotech Ltd, JMCC Group, Khiron Life Sciences Corp., Lyphe Group, BOD Australia, Canopy Growth Corporation and Grow Pharma. These partners were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Competing Interests

All Drug Science committee members, including the Chair, are unpaid by Drug Science for their effort and commitment to this organization. AKS is a scientific advisor to Somai Pharmaceuticals and Evolve. None of the authors would benefit from the wider prescription of medical cannabis in any form.

Data Availability Statement

The data that support the findings of this study are available on reasonable request from the corresponding author, [AAF]. The data are not publicly available as they contain information that could compromise the privacy of research participants.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: Secondary conditions list.

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