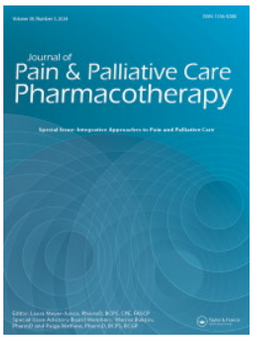

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UK Medical Cannabis Registry: An Analysis of Clinical Outcomes of Medicinal Cannabis Therapy for Cancer Pain

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ABSTRACT

Cancer pain (CP) is a prevalent condition with limited pharmacotherapeutic options. Cannabis-based medicinal products (CBMPs) have shown analgesic effects, but their efficacy in CP remains contentious. This study aims to evaluate the change in patient-reported outcome measures (PROMs) and adverse events (AEs) in CP patients treated with CBMPs. A case series was conducted using prospectively collected clinical data from the UK Medical Cannabis Registry. Primary outcomes were the changes in the Brief Pain Inventory (BPI), pain visual analogue scale (Pain-VAS), EQ-5D-5L, Generalized Anxiety Disorder-7 (GAD-7), Patient Global Impression of Change (PGIC) and Single-Item Sleep Quality Scale (SQS) questionnaires from baseline to 1, 3, and 6 months. AEs were recorded and graded. $p < 0.050$ was considered statistically significant. One hundred and sixty-eight participants were included. CBMPs were associated with improvements in all pain-specific PROMs at all follow-up periods ($p < 0.050$). Improvements in GAD-7, SQS, and EQ-5D-5L index scores were also observed ($p < 0.050$). Twenty-nine AEs (17.26%) were reported by five patients (2.98%), mostly mild-to-moderate (72.41%). Although the observational design means causality cannot be established, the findings support the development of future randomized controlled trials into CP management with CBMPs.

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KEYWORDS
Cancer pain; medical cannabis; cannabinoid; cannabidiol; tetrahydrocannabinol

Introduction

Cancer pain (CP) is defined by the International Classification of Diseases as pain arising from "the primary cancer itself or metastases" (1). Cancer is a prevalent disease, with more than 1.4 million cases recorded between 2017 and 2022 in the UK alone, and its incidence is expected to rise (2). As CP affects 45% of cancer patients (3), it is a growing public health concern.

Several guidelines recommend opioids for managing CP (4–7), but up to 20% of patients cannot tolerate their side effects (8), which include constipation, nausea, vomiting, and sedation (9). Moreover, long-term use risks serious adverse events (AEs) of addiction and overdose (10). The severity of these AEs is evident from the ongoing opioid crisis, reflecting a high prevalence of misuse and opioid-related mortality worldwide (11–13), particularly in the United States (14). There is also a paucity of high-quality evidence suggesting opioids are effective for CP (8, 15). Subsequently, there is a need for additional pharmacotherapeutic options for CP.

In this context, the potential of targeting the endocannabinoid system to manage CP has garnered attention. Activation of the cannabinoid-1 receptor (CB_1R) and cannabinoid-2 receptor (CB_2R) produces analgesic effects, evidenced by

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agonist activity of the endogenous cannabinoid anandamide (16–20). CB_1R activation in the superficial dorsal horn leads to heterodimer formation with μ-opioid receptors (21), reducing nociceptive firing and therefore, pain. CB_2R activation also exerts antinociceptive effects, but instead via the release of β-endorphins onto peripheral μ-opioid receptors (22).

Cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) are the most common cannabinoids derived from *Cannabis sativa L.* (23). THC is a partial CB_1R and CB_2R agonist (24, 25). CBD prevents anandamide breakdown by inhibiting fatty acid amide hydrolase, enhancing anandamide signaling and, thus, acts as an indirect CB_1R agonist to cause analgesic effects (26–28). CBD also exerts analgesic effects by inhibiting transient receptor potential vanilloid-1 (TRPV1) channels, decreasing inflammation through peroxisome proliferator-activated receptor-γ (PPARγ), and by interacting with the 5-hydroxytryptamine receptor 1 A ($5\text{-}HT_{1A}$) receptor (29–34).

Cannabis use in cancer patients is common, with over 40% having used it, often for pain (35). In the late 1970s, three double-blind, placebo-controlled RCTs demonstrated the effectiveness of THC or its analogues in reducing CP (36, 37). However, these studies were limited by low statistical power and only short-term monitoring of a few hours. Johnson *et al.* addressed this with a large, multicenter RCT of 177 CP patients, finding cannabis-based medicinal products (CBMPs) to reduce pain (38), and confirming longer-term efficacy in an extension study (39). There has been little improvement in the quality and quantity of the evidence base since this time. Consequently, the International Association for the Study of Pain (IASP) states that there is insufficient high-quality evidence to recommend CBMPs for this indication (40). The 2019 evidence review that shaped the National Institute for Health and Care Excellence (NICE) guidelines concluded that CBMPs reduced chronic pain but were not cost-effective based on quality-adjusted life year measures (41, 42). However, the study did not differentiate chronic pain by etiology. Wang *et al.* addressed this in their meta-analysis (43), which informed a recommendation to trial non-inhaled CBMPs for chronic pain if standard care is insufficient (44). While they found CBMPs to be associated with improvements in pain severity for non-cancer chronic pain, they did not find evidence of improvement in CP. Notably, the meta-analysis is limited in its generalizability as it contained no trials of inhaled CBMPs (43). However, up to 60% of chronic pain patients in the UK prescribed CBMPs administer it via an inhaled route (45). Considering the mixed findings in the literature (38, 46–48), there is a need for further research on the efficacy of CBMPs for CP.

The Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS) investigated the safety of CBMPs in 431 participants (49). The study found that CBMPs were not associated with an increased risk of serious AEs. Johnson *et al.* also reported that CBMPs have a favorable safety profile (38). Their randomized controlled trial (RCT) documented mostly mild-moderate AEs of nausea, dizziness, and somnolence and no treatment-related deaths. Longer-term safety was corroborated by an extension study (39). A case series of palliative care patients in the United Kingdom Medical Cannabis Registry (UKMCR) similarly found CBMPs to be well-tolerated. However, the small sample size limited analysis and the findings were inconclusive (50). This study will build on this, with a larger sample size, longer follow-up, and a focus on CP patients. The study will help provide evidence relating to CBMPs in CP in a naturalistic setting. It is an interim step to further evaluation of CBMPs against other medications for CP using the UKMCR. Furthermore, the outcomes can help identify the most appropriate CBMPs for CP and subsequently aid the design of RCTs. This study primarily aimed to evaluate the change in PROMs of patients enrolled in the UKMCR who are prescribed CBMPs for the management of CP. The secondary aim was to assess the incidence of AEs associated with CBMPs prescribed in the setting of CP.

Methods

Study design

This case series evaluated prospectively collected, pseudonymized clinical data from the UKMCR

for patients prescribed CBMPs for CP. Patients completed PROMs at baseline and follow-up intervals of 1, 3, and 6 months, and reported AEs.

Formal ethical approval was obtained for the UKMCR from the Health Research Authority (Central Bristol Research Ethics Committee reference: 22/SW/0145). The reporting of this study conforms with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations (51).

Settings and participants

The UKMCR is the UK's largest data platform for CBMP patient outcomes, privately managed and owned by Curaleaf Clinic (52). Participants are recruited from all areas of the United Kingdom and Crown Dependencies. All participants gave written, informed, consent, preceding their consecutive enrollment.

Patients were included if they met the following criteria: 1) Confirmation of a primary diagnosis of CP by a consultant physician; 2) Enrollment in the UKMCR for ≥ 6 months; 3) Completion of a minimum of one baseline PROM questionnaire. Patients were excluded if they were prescribed CBMPs for a primary indication that was not CP.

Cannabis-based medicinal products

CP patients are only eligible to be prescribed CBMPs if they have failed to gain sufficient improvement in symptoms from licensed therapies (53). All CBMP prescriptions adhered to the mandatory standards set by the Good Manufacturing Practice and the Medicines and Healthcare Products Regulatory Agency (54, 55).

Formats of CBMPs include medium-chain triglyceride oils or extracts formulated into capsules, pastilles, and lozenges, administered sublingually or orally. Dried flower was inhaled through a vaporization device. Patients were counseled to discontinue any non-prescribed cannabis at baseline.

Data collection

Clinicians collected baseline demographic data, including age, gender, height, weight, body mass index (BMI), occupation, comorbidities, and current medications. Additionally, Charlson-Comorbidity Index (CCI) values were generated for each patient using data on their age and comorbidities. Data was also collected on their tobacco, alcohol, and cannabis history. Alcohol consumption was quantified in units per week. Lifetime tobacco usage was quantified using pack years (56). Similarly, lifetime cannabis use was quantified using a novel metric called 'gram years', calculated by multiplying the daily consumption in grams by the number of years of consumption (57). Clinicians and specialist pharmacists documented specific details of the CBMPs prescribed.

Self-reporting of PROMs is the gold standard assessment for pain-specific outcomes in CP patients (58). All participants were sent baseline questionnaires upon enrollment. They were sent follow-up questionnaires at 1, 3, and 6 months (59). The baseline observation carried forward approach was used to handle missing PROM data. This methodology replaces missing data with that collected at baseline. This biases the results toward a null finding, assuming no change from baseline (60).

AEs were directly recorded by the patient, either contemporaneously in an online form or just before completing PROMs via a bespoke electronic reporting platform. Alternatively, clinicians logged AEs during remote, follow-up consultations. AEs were then graded and classified in accordance with the Common Terminology Criteria for AEs Version 4.0 (61).

Outcome measures

The primary outcomes were changes in PROMs from baseline to 1, 3, and 6 months in all enrolled participants. The secondary outcome was the incidence of AEs in the same group. PROMs were divided into pain-specific and general categories.

Pain-specific PROMs

The Brief Pain Inventory short form (BPI) is a 2-part, 11-point scale, assessing pain severity and interference (62). Pain 'severity' ranges from 0 ("no pain") to 10 ("pain as bad as you can

imagine"). Pain 'interference' with daily life ranges from 0 ("does not interfere") to 10 ("completely interferes"). The minimum clinically important difference (MCID) is a decrease of 1 point in either severity or interference (63).

The pain visual analogue scale (VAS) is a visual analogue scale where patients mark their pain severity along a 10 cm line, with 0 cm representing "no pain" and 10 cm representing "worst pain" (64). The MCID for pain-VAS is a decrease by 1 cm (63).

General PROMs

The European Quality-of-Life 5 Dimension—5 Levels scale (EQ-5D-5L) evaluates patient problems in five health-related quality-of-life domains: anxiety/depression, mobility, pain/discomfort, self-care, and usual activities. Scores range from '1′ (no problems) to '5′ (extreme problems) (65). An index score is calculated from individual domain values, reflecting overall health, with '1′ representing "full health" and <0 indicating "worse than death".

The Generalized Anxiety Disorder-7 scale (GAD-7) measures the frequency of seven anxiety symptoms over the past two weeks. Anxiety severity is classified based on the total score: mild: 5–9; moderate: 10–14; severe: 15–21 (66).

Patient Global Impression of Change (PGIC) is a 7-point numerical rating scale for patients to report their improvement, with '1′ representing "no change or condition has worsened" and '7′ indicating "considerable improvement" (63).

The Single-Item Sleep Quality Scale (SQS) is a single-item numerical rating scale for patients to rate their overall sleep quality over the past week, scored from '0′ (terrible) to '10′ (excellent) (67).

Statistical analysis

Descriptive statistics were conducted on baseline patient demographics. Parametric data was presented as mean ± standard deviation (S.D.) and, non-parametric data as median [interquartile range (IQR)].

To examine the primary outcome of changes in PROMs, a repeated measures analysis of variance (ANOVA) was performed with Greenhouse-Geisser correction to adjust for lack of sphericity. For statistically significant values on repeated measures ANOVA, post-hoc multiple pairwise comparisons were conducted to compare each period, with Bonferroni correction to control for type I error. Descriptive statistics were used to examine the incidence of AEs.

Univariate and multivariate logistic regression analyses were used to assess patient and treatment-specific factors associated with clinically significant improvements in pain severity. For the univariate analyses, separate logistic regression models were fitted for each independent variable of interest against the binary outcome of achieving an MCID on pain-specific PROM scales. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated from the logistic regression coefficients to estimate the relative influence of each factor on achieving MCID. Due to variables being intrinsically linked, all variables were carried forward into a multivariate logistic regression analysis (68).

Statistical analyses were performed using the Statistical Packages for the Social Sciences version 29.0.2.0 (IBM SPSS Statistics v20) (IBM SPSS Statistics for Macintosh, Version 29.0.2.0 Armonk, NY: IBM Corp). Graphs were created in GraphPad Prism version 10.2.2. Statistical significance was defined as $alpha < 0.050$.

Results

Patient data

Data was extracted on December 13, 2023. At this time, there were 19,763 patients enrolled in the UKMCR. After inclusion and exclusion criteria were applied to this sample, 168 patients were included in the final analysis (Figure 1). Patients were excluded for not having a single complete baseline PROM ($n = 1{,}105$, 5.59%), being enrolled with the UKMCR for less than 6 months ($n = 5910$, 29.90%) and for a primary diagnosis that was not 'cancer pain' ($n = 12{,}580$, 63.65%).

Baseline demographics of study participants are shown in Table 1. There were 102 (60.71%) male participants and 66 (39.29%) female participants. The mean age was 54.20 ± 14.64 years ($n = 168$), and the mean BMI was 25.48 ± 5.78 kg/

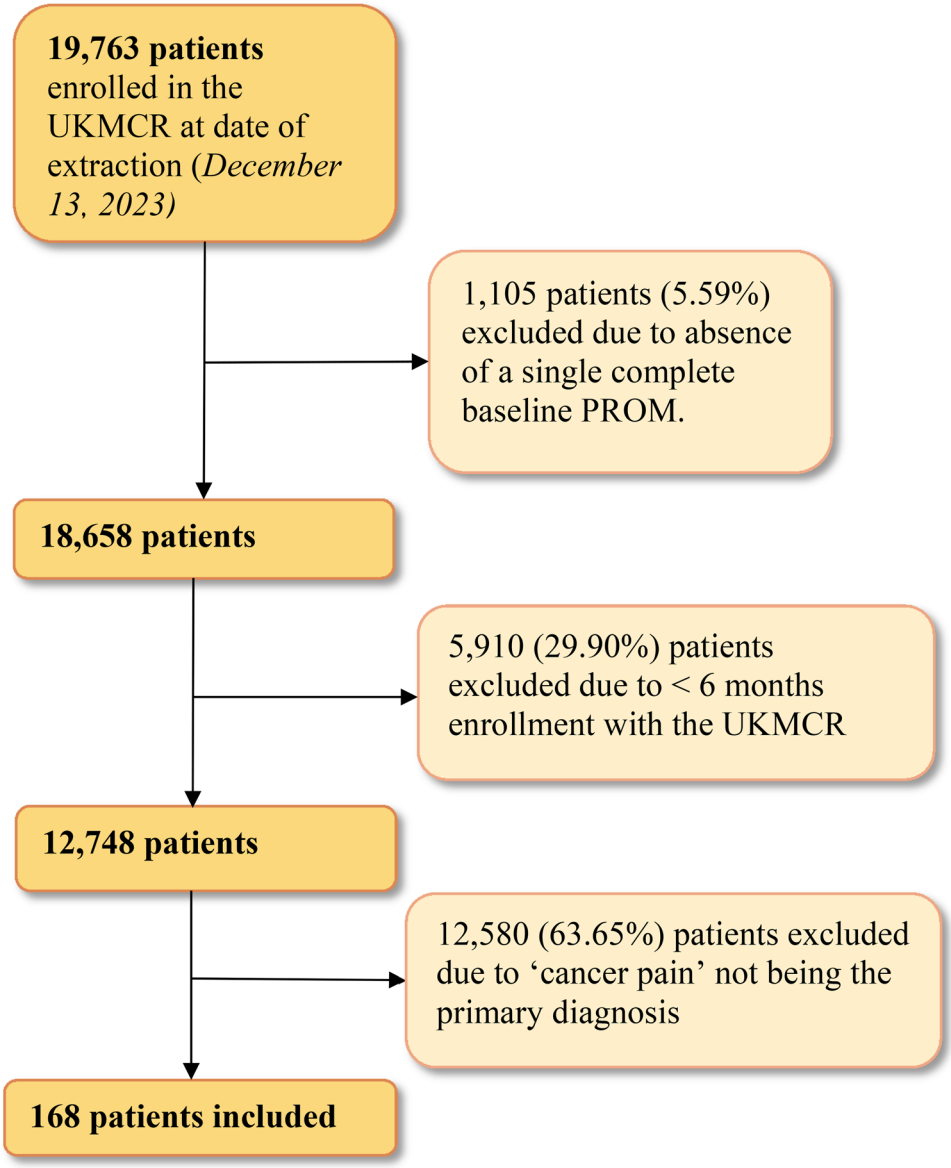

Figure 1. A Flowchart illustrating the inclusion and exclusion of patients.

m^2 ($n = 157$). The median CCI for all study participants ($n = 168$) was 8.00 [6.00–11.00]. Patient comorbidities are listed in Appendix A. The most common occupation status was employed ($n = 92$, 54.76%), followed by unemployed ($n = 70$, 41.67%), retired ($n = 3$, 1.79%) and unknown ($n = 3$, 1.79%).

Baseline alcohol, tobacco and cannabis consumption is also shown in Table 1. The median weekly alcohol consumption was 0 [0.00–2.00] units. Most participants were either ex-smokers ($n = 73$, 43.45%) or had never smoked ($n = 63$, 37.50%). A large proportion of participants had never used cannabis previously ($n = 71$, 42.26%). For those who were current users ($n = 69$, 41.07%) or ex-users ($n = 28$, 16.67%), the median lifetime cannabis consumption was 9.00 [1.00–9.00] gram years. Study participants originated from all areas of the United Kingdom and from the Crown Dependencies, with regional breakdown detailed in Appendix B.

CBMP details

Specific details regarding CBMP treatment at baseline and follow-up at 6 months, including method of administration and dosage, are displayed in Table 2. Most patients administered CBMPs as oils only at baseline ($n = 133$, 79.17%) and at 6 months ($n = 115$, 68.45%). Over time, the use of oils alone decreased, while the use of both

oils and dry flower increased. Median CBD dosage increased from 21.00 [20.00–40.00] milligrams/day at baseline to 40.00 [20.00–40.00] milligrams/day at 1 month follow-up and remained stable thereafter. Median THC dosage continuously increased, from 4.20 [2.15–5.15] milligrams/day at baseline to 14.60 [8.20–100.90] milligrams/day at 6 months. Adven EMC1 50/<4 mg/ml CBD/THC (Curaleaf International, United Kingdom) and Adven EMT 20 mg/ml THC (Curaleaf International, United Kingdom) were the most frequently prescribed CBD- and THC-dominant oils. The most commonly prescribed dried flower was Adven EMT2 16%/<1% THC/CBD (Curaleaf International, United Kingdom).

Table 1. Demographic details are shown including gender split.

Baseline demographics	*n* (%)/mean ± S.D./median [IQR]
Gender	
Male	102 (60.71)
Female	66 (39.29)
Age (years)	54.20 ± 14.64
Height (cm)	171.09 ± 9.97
Weight (kg)	74.86 ± 18.55
BMI (kg/m^2)	25.48 ± 5.78
Charlson Comorbidity Index	8.00 [6.00–11.00]
Occupation Status	
Employed	92 (54.76)
Retired	3 (1.79)
Unemployed	70 (41.67)
Unknown	3 (1.79)
Weekly Alcohol Consumption (units)	0.00 [0.00–2.00]
Tobacco Status	
Current smoker	32 (19.05)
Ex-smoker	73 (43.45)
Never smoked	63 (37.50)
Lifetime tobacco consumption (pack years)	15.00 [7.25–30.00]
Cannabis Status	
Current user	69 (41.07)
Ex-user	28 (16.67)
Never used	71 (42.26)
Cannabis Daily Consumption (grams)	1.00 [1.00–2.00]
Frequency of Cannabis Consumption	
Daily	55 (32.74)
Every other day	8 (4.76)
1–2 times per week	5 (2.98)
>1 times per month	1 (0.60)
Lifetime cannabis consumption (gram years)	9.00 [1.00–9.00]

Abbreviations: BMI: body mass index; CCI: Charlson Comorbidity Index; n; number of participants; %: percentage; S.D.: standard deviation; IQR: interquartile range; cm: centimeters; kg: kilograms; m^2: meters squared of patients at baseline assessment.

Patient-reported outcome measures

Comparison of PROM scores across all time periods with repeated measures one-way ANOVA is displayed in Table 3. This is except for the PGIC score, which has no baseline score due to the nature of the scale. A change ($p < 0.050$) was found in all PROMs except EQ-5D-5L Selfcare ($p = 0.056$).

The repeated measures ANOVA results from Table 3 were further analyzed using post-hoc pairwise comparisons, with Bonferroni correction to account for multiple testing. This allowed for identifying changes in scores from baseline to each follow-up period, along with the corresponding p-values, as presented in Table 4. All pain-specific scales, including BPI-Severity, BPI-Interference and Pain-VAS, showed an improvement ($p < 0.010$) from baseline to follow-up at 1, 3 and 6 months. Regarding general health scales, there were improvements in GAD-7 and SQS from baseline to all follow-up periods ($p < 0.001$). The EQ-5D-5L Mobility domain was improved at 1 month ($p < 0.042$), but there was no change at 3 or 6 months compared to baseline ($p > 0.050$). The EQ-5D-5L anxiety and depression, pain and discomfort, and usual activities domains, as well as the index value, had all improved from baseline to all follow-up periods ($p < 0.010$) (Table 4). See Appendix C for further pairwise comparison.

Table 2. Details of cannabis-based medicinal products prescribed to patients at baseline and follow-up at 1 month ($n = 168$), 3 months ($n = 168$) and 6 months ($n = 167$).

	n (%)/ median [IQR]			
	Baseline	Follow up at 1 month	Follow up at 3 months	Follow up at 6 months
Administration[†]				
Oils	133 (79.17)	130 (77.38)	120 (71.43)	115 (68.45)
Dry Flower	19 (11.31)	18 (10.71)	18 (10.71)	18 (10.71)
Oils and Dry Flower	16 (9.52)	20 (11.90)	30 (17.86)	34 (20.24)
Dosage (milligrams/day)				
CBD	21.00 [20.00–40.00]	40.00 [20.00–40.00]	40.00 [20.00–40.00]	40.00 [20.00–40.00]
THC	4.20 [2.15–5.15]	8.20 [6.60–13.20]	11.20 [8.05–98.78]	14.60 [8.20–100.90]

Abbreviations: n: number of participants; IQR: interquartile range; CBD: Cannabidiol; THC: Delta-9-tetrahydrocannabinol. [†]data from one participant at 6 months removed to prevent re-identification from analysis.

Table 3. Patient-reported outcome measures (PROMs) at baseline, 1 month, 3 months and 6 months.

	PROM	Baseline	1 month	3 months	6 months	p-value
Pain-Specific Scales	BPI-Interference	6.08 ± 2.62	5.41 ± 2.73	5.21 ± 2.77	5.62 ± 2.75	<0.001***
	BPI-Severity	5.14 ± 2.18	4.57 ± 2.26	4.65 ± 2.33	4.81 ± 2.31	<0.001***
	Pain-VAS	6.09 ± 2.64	5.32 ± 2.79	5.33 ± 2.87	5.62 ± 2.79	<0.001***
General Health Assessment Scales	EQ-5D-5L Anxiety and Depression	2.63 ± 1.19	2.41 ± 1.12	2.31 ± 1.13	2.45 ± 1.15	< 0.001***
	EQ-5D-5L Mobility	2.74 ± 1.16	2.56 ± 1.17	2.61 ± 1.18	2.63 ± 1.19	0.018*
	EQ-5D-5L Pain and Discomfort	3.38 ± 1.16	2.96 ± 1.12	3.01 ± 1.16	3.16 ± 1.18	<0.001***
	EQ-5D-5L Self-Care	2.10 ± 1.04	2.00 ± 1.06	1.95 ± 1.05	2.04 ± 1.06	0.056
	EQ-5D-5L Usual Activities	3.18 ± 1.23	2.80 ± 1.22	2.83 ± 1.22	2.96 ± 1.26	<0.001***
	EQ-5D-5L Index Values	0.34 ± 0.35	0.45 ± 0.33	0.45 ± 0.35	0.40 ± 0.36	< 0.001***
	GAD-7	10.09 ± 6.76	7.42 ± 6.05	8.14 ± 6.49	8.82 ± 6.43	<0.001***
	PGIC		4.96 ± 1.48	5.21 ± 1.54	5.21 ± 1.47	0.031*
	SQS	3.90 ± 2.38	5.21 ± 2.55	4.87 ± 2.63	4.63 ± 2.54	<0.001***

Significance values are shown as: '***': $p < 0.001$; '**': $p < 0.010$; '*': $p < 0.050$. Abbreviations: BPI: brief pain inventory; VAS: visual analogue scale; EQ-5D-5L: European quality-of-life 5 Dimension - 5 levels; GAD-7: Generalized Anxiety Disorder scale; PGIC: patient global impression of change; SQS: single-item sleep quality scale.

Table 4. Pairwise comparison of patient-reported outcome measures (PROMs) taken at baseline and change in the PROM value at follow-up at 1 month, 3 months and 6 months.

	Patient-reported outcome measure	Mean baseline score ± S.D	n	Follow-Up (months)	n	Mean difference from baseline ± S.D	p-value
Pain-specific scales	Brief Pain Inventory Interference	6.08 ± 2.62	158	1	158	−0.67 ± 0.17	< 0.001***
				3	158	−0.87 ± 0.17	< 0.001***
				6	158	−0.46 ± 0.14	0.007**
	Brief Pain Inventory Severity	5.14 ± 2.18	158	1	158	−0.57 ± 0.12	< 0.001***
				3	158	−0.49 ± 0.12	< 0.001***
				6	158	−0.33 ± 0.10	0.006**
	Visual Analogue Scale - Pain	6.09 ± 2.64	159	1	159	−0.77 ± 0.16	< 0.001***
				3	159	−0.76 ± 0.17	< 0.001***
				6	159	−0.48 ± 0.13	0.003**
General health assessment scales	EQ-5D-5L Anxiety and Depression	2.63 ± 1.19	167	1	167	−0.22 ± 0.07	0.009**
				3	167	−0.32 ± 0.05	< 0.001***
				6	167	−0.19 ± 0.05	0.002**
	EQ-5D-5L Mobility	2.74 ± 1.16	167	1	167	−0.17 ± 0.06	0.042*
				3	167	−0.13 ± 0.05	0.089
				6	167	−0.11 ± 0.05	0.118
	EQ-5D-5L Pain and Discomfort	3.38 ± 1.16	167	1	167	−0.43 ± 0.07	<0.001***
				3	167	−0.38 ± 0.07	<0.001***
				6	167	−0.23 ± 0.06	<0.001***
	EQ-5D-5L Usual Activities	3.18 ± 1.23	167	1	167	−0.38 ± 0.08	<0.001***
				3	167	−0.35 ± 0.07	<0.001***
				6	167	−0.22 ± 0.07	0.005**
	EQ-5D-5L Index Values	0.34 ± 0.35	167	1	167	0.12 ± 0.02	<0.001***
				3	167	0.11 ± 0.02	<0.001***
				6	167	0.06 ± 0.02	<0.001***
	Generalized Anxiety Disorder scale	10.09 ± 6.76	168	1	168	−2.67 ± 0.42	< 0.001***
				3	168	−1.95 ± 0.35	< 0.001***
				6	168	−1.27 ± 0.29	< 0.001***
	Single-Item Sleep Quality Scale	3.90 ± 2.38	166	1	166	1.31 ± 0.19	< 0.001***
				3	166	0.98 ± 0.17	< 0.001***
				6	166	0.73 ± 0.14	< 0.001***

Significance values are shown as: '***': $p < 0.001$; '**': $p < 0.010$; '*': $p < 0.050$. Abbreviations: SD: standard deviation; n: number of participants; EQ-5D-5L: European quality-of-life 5 Dimension - 5 levels.

Figure 2 shows an improvement from baseline to 1 month follow-up in all pain-specific scales, including BPI-Interference, BPI-Severity and Pain-VAS. There is a plateau in improvement from 1 month follow-up ($p > 0.050$), but improvement from baseline was maintained ($p < 0.010$).

At 6 months, 31 patients (18.56%) met the MCID for BPI-Interference ($n = 157$). Twenty-four patients (14.37%) met the MCID of BPI-Severity ($n = 157$). Thirty patients (17.96%, $n = 158$) met the MCID for Pain-VAS ($n = 158$). The MCID for each of the BPI scales is a 1 point decrease, and for Pain-VAS it is a 1 cm decrease.

Adverse events

Twenty-nine (17.26%) AEs were reported by five patients (2.98%) during the study, all of whom

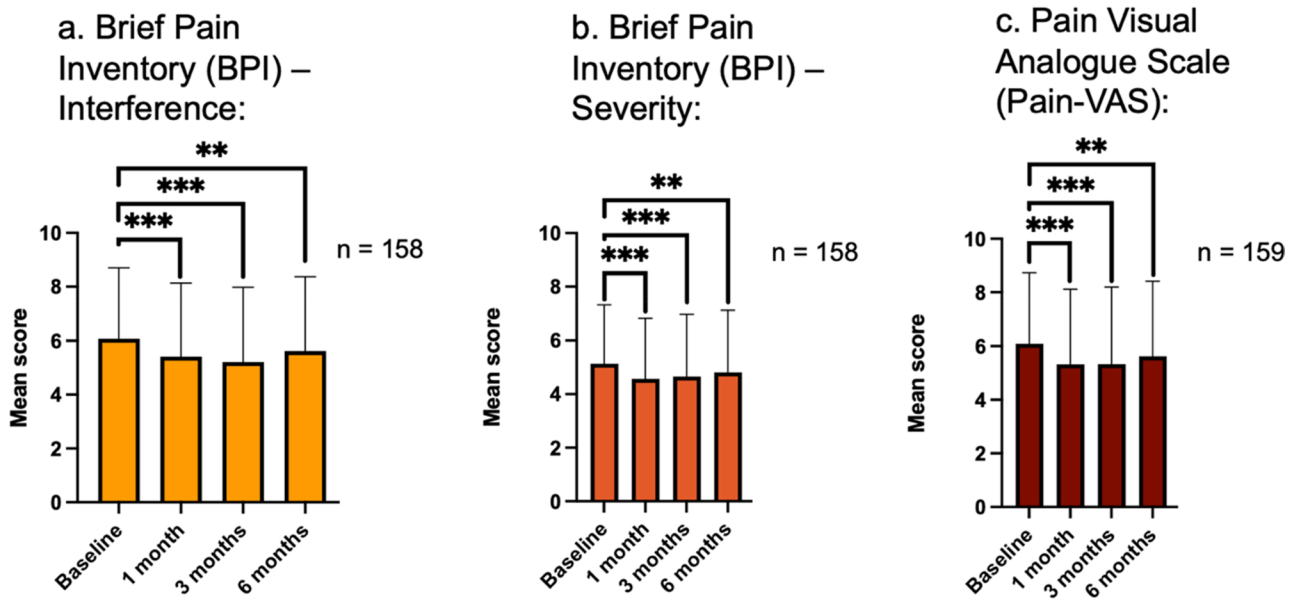

Figure 2. Comparison of mean pain-specific patient reported outcome measures (PROMs), including a) BPI-Interference; b) BPI-severity; c) pain-VAS taken at baseline, and follow-up at 1 month, 3 months and 6 months. Statistical significance is shown as '***': $p < 0.001$ and '**': $p < 0.010$. *Abbreviations: n: number of participants.*

were cannabis naïve, meaning they had never used cannabis previously. Twelve AEs (41.38%) were classified as mild severity, nine as moderate (31.03%) and eight as severe (16.41%). No life-threatening AEs were reported. There were twenty different AEs, and the most common AEs were fatigue ($n = 3$) and lethargy ($n = 3$). The mean duration of all AEs was 6.93 ± 5.04 days (Appendix D).

Univariate and multivariate logistic regression

Univariate logistic regression revealed increased odds of achieving minimum clinically important differences (MCID) on BPI-Severity (Appendix E), BPI-Interference (Appendix F) and Pain-VAS (Appendix G) amongst patients who administered CBMPs as both oils and dry flower ($p < 0.003$) and, who were prescribed higher doses of THC (>14.6 mg/day) ($p < 0.004$). Male gender increased the odds of an MCID on the BPI-interference scale ($p = 0.045$), while greater CBD doses (>40 mg/day) increased the odds of an MCID on the Pain-VAS ($p = 0.011$).

Subsequent multivariate analysis identified higher THC doses as a predictor of achieving an MCID only on the BPI-Severity scale (OR = 9.72; 95% CI: 1.54–61.51; $p = 0.016$) (Appendix H). Administering CBMPs as combined oils and dry flower was associated with an increased likelihood of an MCID on the BPI-Interference scale only (OR = 5.81; 95% CI: 1.09–30.85; $p = 0.039$) (Appendix I). Male gender and greater CBD doses were no longer associated with this effect (Appendix H-J). Conversely, low baseline EQ-5D-5L scores (≤0) were associated with reduced likelihood of achieving an MCID on BPI-Interference (OR = 0.12, 95% CI: 0.02–0.75; $p = 0.023$).

Discussion

This prospective case series investigated the reported change in validated PROMs and AEs in individuals prescribed CBMPs for CP using data from the UKMCR. CBMPs were associated with improved validated pain-specific and general health-related quality of life PROMs from baseline to all follow-up periods within 6 months. The AE incidence was relatively low at 17.26%, with most AEs classified as mild-to-moderate severity.

Patient-reported outcome measures

The observed improvements in pain-specific PROMs are corroborated by prior studies on the effectiveness of CBMPs in treating CP. Johnson *et al.* in a multicenter RCT also identified an

improvement in pain severity with THC-containing extracts (38). Portenoy *et al.* reported similar findings with nabiximols measured using the Pain-VAS tool (46). In particular, low doses of nabiximols, a CBMP administered as an oromucosal spray containing THC and CBD, reduced reported daily worst and average pain. However, contrary to the present study's findings, there was no significant difference in the BPI scores (46). Another RCT by Lichtman *et al.* conversely found that nabiximol was not more effective than placebo in reducing pain severity (47). Notably, both RCTs suffered from high attrition, limiting the conclusiveness of their findings (46, 47). The use of different CBMP formulations, including oils and dried flower, which were most associated with a positive change in pain severity in the present study, might contribute to these conflicting findings. Ultimately the lack of concordance across the literature highlights the need to identify the optimal regimen to take forward into future RCTs of CBMPs for CP, rather than limiting research to licensed preparations, such as nabiximols.

The analgesic effects of CBMPs were sustained at short- and medium-term follow-ups in this study. Following the trend of Figure 2, it is reasonable to predict the benefit would continue with a longer-term follow-up. This is supported by a similar prospective, observational study in Canada that found significant improvements in BPI-Severity and BPI-Interference at 12 months (69). However, the present study observed a plateau in PROM scores from 1 month follow-up, potentially indicating a ceiling effect wherein pain cannot be relieved further after the initial response. Preclinical research has found that repeated exposure to cannabinoids can lead to down-regulation and sensitization of the cannabinoid receptors (70), explaining this phenomenon.

The improvements in pain-specific PROMs align with previous UKMCR studies of chronic pain and palliative care (50, 71). However, the improvement in those studies was greater than in the present cohort. This may be attributed to the limited number of CP patients included in their cohorts, thereby limiting the generalizability of their findings to this specific population. The present study addresses this gap by evaluating the largest UKMCR cohort of CP patients to date, encompassing a diverse population with patients from each region of the UK and from the Crown Dependencies.

The percentage of individuals meeting the MCID for BPI-Interference, BPI-Severity, and Pain-VAS was low. On a population basis, between 1 to 2 in 10 individuals prescribed CBMPs for CP reported a clinically significant improvement at 6 months. This may be explained by the high proportion (57.74%) of current or previous cannabis users at baseline who may have been self-medicating with cannabis for their CP, underestimating the change in outcomes. This is supported by subgroup analysis in a UKMCR study, which found cannabis-naïve patients to have greater improvements in pain-specific PROMs compared to current or previous users (71). Wang et al. mention patients have previously suggested that a 10% likelihood of experiencing a clinically significant improvement is acceptable for a new medication trial if they have failed to benefit from other medications (43), similar to those in the present study.

Patients who administered CBMPs as both oils and dry flower had greater odds of reaching an MCID for BPI-Interference. Oils are ingested orally or sublingually, leading to a lower but sustained rise in plasma cannabinoid concentrations. In contrast, inhaled CBMPs have a much faster onset of action but are shorter-lived (72). Hence, a combination of these methods may optimize pain improvement. Additionally, higher THC doses led to greater odds of reaching an MCID for BPI-Severity. Similarly, an RCT found that 20 milligrams of THC reduced CP significantly, but this effect was not seen with 10 milligrams of THC (36).

Managing sleep is an essential component of holistic care for CP patients, as pain increases sleep disturbance, reduces sleep quality, and increases daytime somnolence (73). Anxiety is interlinked, as the 5-HT_{1A} receptor involved in anxiety is also involved in chronic pain (29, 31). Participants reported improvements in the SQS and GAD-7 at all short-term and medium-term follow-ups. Also, there were improvements in the EQ-5D-5L index at all short-term and medium-term follow-ups. This concurs with findings from registry studies of patients with insomnia and anxiety (74, 75).

Adverse events

The all-cause AE incidence at 17.26% reported in the present study is lower than other UKMCR studies (57, 76). This inconsistency can be explained by the fact that the specific CBMP formulation, administration method and CBD:THC split affects the AE profile (77). The most common AEs were lethargy and fatigue, similar to a UKMCR study on osteoarthritis patients (78). The COMPASS study also found that most AEs from CBMPs were mild-to-moderate (49). Furthermore, the present study observed no life-threatening AEs, supported by a systematic review by Wang *et al.* that noted 96.6% of AEs to be non-serious (77). All patients who experienced AEs were cannabis-naïve, concurring with literature that AEs are more common amongst cannabis-naïve patients (79). Following the same reasoning, the low proportion of cannabis-naïve patients may explain the small proportion (2.98%) of patients reporting AEs.

Limitations

As an observational case series, causality cannot be determined as the observed effects could be secondary to external factors or phenomena, such as regression to the mean. Although the study's naturalistic setting improves its ecological validity, it may introduce confounding factors, such as concurrent treatments or lifestyle changes. Furthermore, the lack of a comparator arm is particularly significant due to cancer's poor prognosis, with an expectation that symptoms will worsen over time (80). In this dynamic clinical setting, maintaining baseline control is difficult, potentially underestimating the improvement in outcomes and overestimating any deterioration. Patients were non-blinded and may exaggerate the mean difference in PROMs, especially due to positive media coverage of CBMPs (81, 82).

There may be sampling bias, as a large proportion of participants (57.74%) were current or former cannabis users. This subset may have already experienced benefits from cannabis in managing their CP and sought enrollment in the UKMCR to access regulated CBMPs under clinical supervision, overestimating an improvement in outcomes. These may have also resulted in other demographic biases within the dataset, for example, over 60% of patients being male. Moreover, patients were enrolled from a private clinic, introducing selection bias. However, 41.67% of patients were unemployed, suggesting socioeconomic status may not affect access to treatment. Individuals were recruited from across the UK and from the Crown Dependencies. The highest proportion was from Scotland, which may not be representative of other cohorts from across the UK, limiting generalizability nationally and internationally.

PROMs are the gold-standard method of assessing improvement in CP patients (58), but are prone to recall bias. There are also limitations in the delivery of PROMs questionnaires. As questionnaires are completed online, this may have limited the inclusion of individuals less proficient in technology. In terms of AEs, clinicians did not assess them to confirm whether they were treatment-related. Whilst there were multiple opportunities for participants to report AEs, there is a possibility of under-reporting, given the very low number of patients reporting AEs. This may have been due to a social desirability bias, where patients feel pressure to report more favorable outcomes. Moreover, patients may have attributed adverse events to their cancer diagnosis or treatment and therefore not reported adverse events as frequently as other condition groups. Classification bias may have occurred if patients were mislabeled as having CP when their pain was secondary to surgery, chemotherapy, radiotherapy, or other treatments, which should be categorized separately as cancer-treatment pain (1). This study was unable to collect data on specific cancer-types or cancer-related treatment in the population. Considering the different symptomatology associated with different cancer types, stage and treatment, it is important that future research attempts to address these issues.

Conclusion

This study found that initiation of CBMPs is associated with improvements in pain-specific and general health-related quality of life outcomes in CP patients over six months, with a relatively low incidence of mild-to-moderate AEs and no life-threatening AEs. However, the study is

limited by its observational, uncontrolled design, meaning that causality cannot be determined. More RCTs and longer observational case series are warranted, but this study can help inform their rollout, serving as a valuable pharmacovigilance tool for the use of CBMPs in CP, either as an alternative therapeutic option or as one part of multimodal treatment.

Disclosure statement

Madhur Varadpande is a medical student at Imperial College London. Madhur Varadpande has no shareholdings in pharmaceutical companies.

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Ross Coomber is a consultant orthopedic surgeon at St George's Hospital, London, and Operations Director at Curaleaf Clinic. Ross Coomber has no shareholdings in pharmaceutical companies.

James Rucker is a consultant psychiatrist at Curaleaf Clinic. James Rucker is an honorary consultant psychiatrist at The South London & Maudsley NHS Foundation Trust, and an NIHR Clinician Scientist Fellow at the Center for Affective Disorders at King's College London. James Rucker is funded by a fellowship (CS-2017-17-007) from the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. James Rucker leads the Psychedelic Trials Group at King's College London. King's College London receives grant funding from COMPASS Pathways PLC to undertake phase 1 and phase 2 trials with psilocybin. COMPASS Pathways PLC has paid for James Rucker to attend trial related meetings and conferences to present the results of research using psilocybin. James Rucker has undertaken paid consultancy work for Beckley PsyTech and Clerkenwell Health. Payments for consultancy work are received and managed by King's College London and James Rucker does not benefit personally. James Rucker has no shareholdings in pharmaceutical companies.

Michael Platt is a consultant in pain services at Curaleaf Clinic. Michael Platt has no shareholdings in pharmaceutical companies.

Shaheen Khan is a consultant in palliative care at Guy's and St Thomas' NHS Foundation Trust and Curaleaf Clinic. Shaheen Khan has no shareholdings in pharmaceutical companies.

Mikael Sodergren is a consultant hepatopancreatobiliary surgeon at Imperial College NHS Trust, London, a senior clinical lecturer at Imperial College London, and the chief medical officer of Curaleaf International. Mikael Sodergren has no shareholdings in pharmaceutical companies.

Ethical approval

Provided by South West–Central Bristol Research Ethics Committee (Reference: 22/SW/0145).

Patient consent statement

All study participants gave formal, informed, and written consent, preceding their consecutive enrollment into the database.

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Data availability statement

Data that support the findings of this study are available from the UK Medical Cannabis Registry. Restrictions apply to the availability of these data. Data specifications and applications are available from the corresponding author. All authors contributed to and approved the final article. All work was conducted at Curaleaf Clinic, London, UK.

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Appendix A

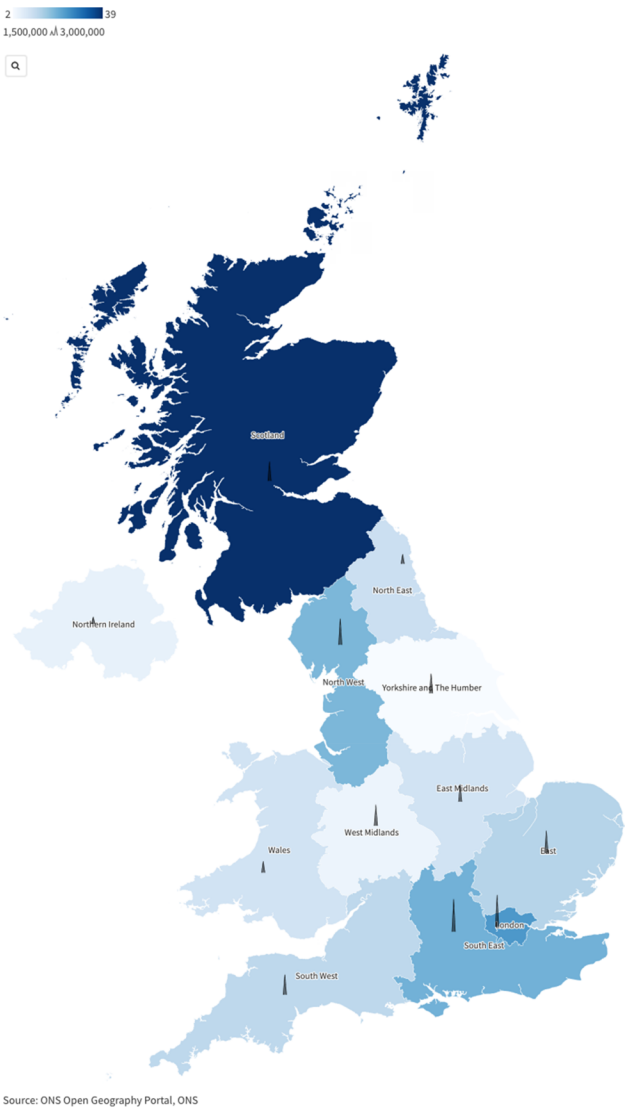
Table A1. Prevalence of comorbidities in participants at baseline.

Baseline Patient Comorbidities	*n* (%)
Myocardial Infarction	10 (5.95)
Congestive Heart Failure	0 (0)
Leukemia	3 (1.79)
Peripheral Vascular Disease	0 (0)
Endocrine Thyroid Dysfunction	13 (7.74)
Depression or Anxiety	15 (8.93)
Venous Thromboembolism	10 (5.95)
Epilepsy	1 (0.60)
Hypertension	16 (9.52)
Arthritis	20 (11.90)
AIDS	0 (0)
Lymphoma	7 (4.17)
Cerebrovascular Accident or Transient Ischemic Attack	3 (1.79)
Connective Tissue Disease	1 (0.60)
Peptic Ulcer Disease	3 (1.79)
Moderate to Severe Chronic Kidney Disease	9 (5.36)
Hemiplegia	0 (0)
Dementia	0 (0)
Chronic Obstructive Pulmonary Disease	4 (2.38)
Diabetes	
- End organ damage	3 (1.79)
- None or diet-controlled	157 (93.45)
- Uncomplicated	8 (4.76)
Liver disease	1 (0.60)
Solid tumor	161 (95.83)
Localised	59 (35.12)
Metastatic	102 (60.71)

Abbreviations: AIDS: acquired immunodeficiency syndrome; n: number of participants.

Appendix B

A map of the United Kingdom (UK), showing the highest tier of Sub-national division and colored according to the frequency of participants originating from that region. Not displayed are the crown dependencies: Guernsey and Jersey ($n = 2$). Color coding is displayed by the legend at the top. The following regions are colored: East Midlands ($n = 9$), east of England ($n = 13$), london ($n = 24$), North East of England ($n = 10$), North West of England ($n = 19$), Northern Ireland ($n = 5$), Scotland ($n = 39$), South East of England ($n = 20$), South West of England ($n = 12$), Wales ($n = 9$), west Midlands (4) and yorkshire and the humber ($n = 2$). Created in flourish.studio



Appendix C

Table C1. Displays the results of pairwise comparisons of all patient-reported outcome measures (PROMs) between various time points: Baseline, 1 month, 3 months and 6 months.

BPI-Interference	Baseline	1 month	3 months	6 months
Baseline		−0.67 ± 0.17; *p* < 0.001	−0.87 ± 0.17; *p* < 0.001	−0.46 ± 0.14; *p* = 0.007
1 month	0.67 ± 0.17; *p* < 0.001		−0.20 ± 0.15; *p* = 1.000	0.21 ± 0.16; *p* = 1.000
3 months	0.87 ± 0.17; *p* < 0.001	0.20 ± 0.15; *p* = 1.000		0.41 ± 0.13; *p* = 0.012
6 months	0.46 ± 0.14; *p* = 0.007	−0.21 ± 0.16; *p* = 1.000	−0.41 ± 0.13; *p* = 0.012	
BPI-Severity	**Baseline**	**1 month**	**3 months**	**6 months**
Baseline		−0.57 ± 0.12; *p* < 0.001	−0.49 ± 0.12; *p* < 0.001	−0.33 ± 0.10; *p* = 0.006
1 month	0.57 ± 0.12; *p* < 0.001		0.08 ± 0.12; *p* = 1.000	0.24 ± 0.13; *p* = 0.403
3 months	0.49 ± 0.12; *p* < 0.001	−0.08 ± 0.12; *p* = 1.000		0.16 ± 0.11; *p* = 0.850
6 months	0.33 ± 0.10; *p* = 0.006	−0.24 ± 0.13; *p* = 0.403	−0.16 ± 0.11; *p* = 0.850	
Pain-VAS	**Baseline**	**1 month**	**3 months**	**6 months**
Baseline		−0.77 ± 0.16; *p* < 0.001	−0.76 ± 0.17; *p* < 0.001	−0.48 ± 0.13; *p* = 0.003
1 month	0.77 ± 0.16; *p* < 0.001		0.01 ± 0.16; *p* = 1.000	0.30 ± 0.16; *p* = 0.417
3 months	0.76 ± 0.17; *p* < 0.001	−0.01 ± 0.16; *p* = 1.000		0.28 ± 0.15; *p* = 0.322
6 months	0.48 ± 0.13; *p* = 0.003	−0.30 ± 0.16; *p* = 0.417	−0.28 ± 0.15; *p* = 0.322	
EQ-5D-5L Anxiety and Depression	**Baseline**	**1 month**	**3 months**	**6 months**
Baseline		−0.22 ± 0.07; *p* = 0.009	−0.32 ± 0.05; *p* < 0.001	−0.19 ± 0.05; *p* = 0.002
1 month	0.22 ± 0.07; *p* = 0.009		−0.10 ± 0.06; *p* = 0.679	0.04 ± 0.07; *p* = 1.000
3 months	0.32 ± 0.05; *p* < 0.001	0.10 ± 0.06; *p* = 0.679		0.14 ± 0.05; *p* = 0.002
6 months	0.19 ± 0.05; *p* = 0.002	−0.04 ± 0.07; *p* = 1.000	−0.14 ± 0.05; *p* = 0.002	
EQ-5D-5L Mobility	**Baseline**	**1 month**	**3 months**	**6 months**
Baseline		−0.17 ± 0.06; *p* = 0.042	−0.13 ± 0.05; *p* = 0.089	−0.11 ± 0.05; *p* = 0.118
1 month	0.17 ± 0.06; *p* = 0.042		0.05 ± 0.06; *p* = 1.000	0.07 ± 0.06; *p* = 1.000
3 months	0.13 ± 0.05; *p* = 0.089	−0.05 ± 0.06; *p* = 1.000		0.02 ± 0.05; *p* = 1.000
6 months	0.11 ± 0.05; *p* = 0.118	−0.07 ± 0.06; *p* = 1.000	−0.02 ± 0.05; *p* = 1.000	
EQ-5D-5L Pain Discomfort	**Baseline**	**1 month**	**3 months**	**6 months**
Baseline		−0.43 ± 0.07; *p* < 0.001	−0.38 ± 0.07; *p* < 0.001	−0.23 ± 0.06; *p* < 0.001
1 month	0.43 ± 0.07; *p* < 0.001		0.05 ± 0.06; *p* = 1.000	0.20 ± 0.07; *p* < 0.001
3 months	0.38 ± 0.07; *p* < 0.001	−0.05 ± 0.06; *p* = 1.000		0.15 ± 0.05; *p* = 0.034
6 months	0.23 ± 0.06; *p* < 0.001	−0.20 ± 0.07; *p* < 0.001	−0.15 ± 0.05; *p* = 0.034	
EQ-5D-5L Usual Activities	**Baseline**	**1 month**	**3 months**	**6 months**
Baseline		−0.38 ± 0.08; *p* < 0.001	−0.35 ± 0.07; *p* < 0.001	−0.22 ± 0.07; *p* = 0.005
1 month	0.38 ± 0.08; *p* < 0.001		0.04 ± 0.08; *p* < 0.001	0.16 ± 0.07; *p* = 0.153
3 months	0.35 ± 0.07; *p* < 0.001	−0.04 ± 0.08; *p* < 0.001		0.13 ± 0.06; *p* = 0.240
6 months	0.22 ± 0.07; *p* = 0.005	−0.16 ± 0.07; *p* = 0.153	−0.13 ± 0.06; *p* = 0.240	
EQ-5D-5L Index Value	**Baseline**	**1 month**	**3 months**	**6 months**
Baseline		0.12 ± 0.02; *p* < 0.001	0.11 ± 0.02; *p* < 0.001	0.06 ± 0.02; *p* < 0.001
1 month	−0.12 ± 0.02; *p* < 0.001		0.00 ± 0.02; *p* = 1.000	−0.06 ± 0.2; *p* = 0.019
3 months	−0.11 ± 0.02; *p* < 0.001	0.00 ± 0.02; *p* = 1.000		−0.05 ± 0.02, *p* = 0.005
6 months	−0.06 ± 0.02; *p* < 0.001	0.06 ± 0.2; *p* = 0.019	0.05 ± 0.02, *p* = 0.005	
GAD-7:	**Baseline**	**1 month**	**3 months**	**6 months**
Baseline		−2.67 ± 0.42; *p* < 0.001	−1.95 ± 0.35; *p* < 0.001	−1.27 ± 0.29; *p* < 0.001
1 month	2.67 ± 0.42; *p* < 0.001		0.71 ± 0.38; *p* = 0.367	1.39 ± 0.39; *p* = 0.003
3 months	1.95 ± 0.35; *p* < 0.001	−0.71 ± 0.38; *p* = 0.367		0.68 ± 0.28; *p* = 0.096
6 months	1.27 ± 0.29; *p* < 0.001	−1.39 ± 0.39; *p* = 0.003	−0.68 ± 0.28; *p* = 0.096	
PGIC	**1 month**	**3 months**	**6 months**	
1 month		0.25 ± 0.12; *p* = 0.124	0.25 ± 0.07; *p* = 0.002	
3 months	−0.25 ± 0.12; *p* = 0.124		0.00 ± 0.11; *p* = 1.000	
6 months	−0.25 ± 0.07; *p* = 0.002	0.00 ± 0.11; *p* = 1.000		
SQS	**Baseline**	**1 month**	**3 months**	**6 months**
Baseline		1.31 ± 0.19; *p* < 0.001	0.98 ± 0.17; *p* < 0.001	0.73 ± 0.14; *p* < 0.001
1 month	−1.31 ± 0.19; *p* < 0.001		−0.34 ± 0.17; *p* = 0.295	−0.58 ± 0.17; *p* = 0.004
3 months	−0.98 ± 0.17; *p* < 0.001	0.34 ± 0.17; *p* = 0.295		−0.25 ± 0.13; *p* = 0.398
6 months	−0.73 ± 0.14; *p* < 0.001	0.58 ± 0.17; *p* = 0.004	0.25 ± 0.13; *p* = 0.398	

Abbreviations: GAD-7: Generalized anxiety disorder scale; SQS: single-item sleep quality scale; BPI: brief pain inventory; VAS: visual analogue scale; EQ-5D-5L: European quality-of-life 5 dimension - 5 levels; PGIC: patient global impression of change.

Appendix D

Table D1. An overview of adverse events observed during the study.

Adverse Event	Frequency by severity			Overall frequency (%)	Mean ± S.D Duration (days)
	Mild	Moderate	Severe		
Amnesia	1	0	0	1 (0.60)	7
Anorexia	0	0	1	1 (0.60)	7
Cognitive disturbance	1	0	0	1 (0.60)	2
Concentration impairment	1	1	0	2 (1.19)	6 ± 1.41
Constipation	1	0	1	2 (1.19)	5
Dizziness	1	0	0	1 (0.60)	3
Dry mouth	2	0	0	2 (1.19)	6 ± 1.41
Dysgeusia	1	0	0	1 (0.60)	7
Dyspepsia	0	0	1	1 (0.60)	7
Fatigue	0	2	1	3 (1.79)	4.67 ± 2.52
Generalized muscle weakness	0	1	0	1 (0.60)	7
Insomnia	0	0	2	2 (1.19)	18.5 ± 16.26
Lethargy	2	1	0	3 (1.79)	5.67 ± 1.15
Nausea	1	0	1	2 (1.19)	6 ± 1.41
Pharyngitis	0	1	0	1 (0.60)	15
Somnolence	0	2	0	2 (1.19)	5
Vomiting	1	0	1	2 (1.19)	7.5 ± 3.54
Weight loss	0	1	0	1 (0.60)	7
Total	12 (7.14)	9 (5.36)	8 (4.76)	29 (17.26)	6.93 ± 5.04

Abbreviations: %: percentage; S.D.: standard deviation.

Appendix E

Table E1. Univariate logistic regression of the minimum clinically important difference for the brief pain inventory (severity) with multiple different variables.

	n	Odds ratio (95% Confidence Interval)	p-value
Gender			
Female	66	Ref	Ref
Male	91	1.936 (0.753–4.978)	0.170
Age (years)			
18–40	32	Ref	Ref
41–50	27	1.23 (0.32–4.79)	0.768
51–60	47	1.11 (0.33–3.75)	0.870
61–70	25	0.23 (0.03–2.06)	0.187
70 +	26	1.29 (0.33–5.03)	0.718
Body Mass Index (kg/m^2)			
<18.5	10	1.40 (0.260–7.58)	0.696
18–5-24.9	66	Ref	Ref
25.0–29.9	45	1.03 (0.36 – 2.948)	0.954
≥ 30.0	26	0.49 (0.10–2.40)	0.376
Cannabis Status			
Never used	66	Ref	Ref
Current user	64	1.173 (0.443–3.108)	0.748
Ex-user	27	1.439 (0.434–4.773)	0.552
CBMP Method of Administration			
Oils	111	Ref	Ref
Flower	15	2.525 (0.609–10.470)	0.202
Both	31	5.555 (2.082–14.824)	<.001
Total THC Dosage (mg/day)			
≤ median dose (14.6)	82	Ref	Ref
> median dose (14.6)	75	7.091 (2.296–21.899)	<.001
Total CBD Dosage (mg/day)			
≤ median dose (40)	126	Ref	Ref
> median dose (40)	31	2.39 (0.92–6.25)	0.075
Sleep Quality Scale Baseline Score			
Sleep unimpaired (≥4)	82	Ref	Ref
Sleep impaired (≤3)	75	2.028 (0.829–4.959)	0.121
GAD-7 Baseline Score			
None (0–4)	41	Ref	Ref
Mild (5–9)	35	1.49 (0.413–5.377)	0.543
Moderate (10–14)	29	0.831 (0.182–3.790)	0.811
Severe (≥15)	52	1.714 (0.536–5.480)	0.363
EQ-5D-5L Index Value			
> 0	129	Ref	Ref
≤ 0	28	0.0617 (0.171–2.232)	0.462

Abbreviations: BPI: Brief pain inventory; n: number of participants; CBMP: cannabis-based medicinal product; THC: tetrahydrocannabinol; CBD: cannabidiol; GAD-7: Generalized anxiety disorder scale; EQ-5D-5L: European quality-of-life 5 dimension - 5 levels.

Appendix F

Table F1. Univariate logistic regression of the minimum clinically important difference for the brief pain inventory (interference) with multiple different variables.

	n	Odds ratio (95% Confidence Interval)	p-value
Gender			
Female	66	Ref	Ref
Male	91	2.45 (1.02–5.90)	0.045
Age (years)			
18–40	32	Ref	Ref
41–50	27	1.24 (0.35–4.41)	0.742
51–60	47	0.76 (0.23–2.51)	0.651
61–70	25	0.83 (0.21–3.31)	0.787
70 +	26	1.93 (0.57–6.51)	0.291
Body Mass Index (kg/m^2)			
<18.5	10	0.93 (0.18–4.87)	0.930
18–5-24.9	66	Ref	Ref
25.0–29.9	45	1.06 (0.42–2.66)	0.899
≥ 30.0	25	0.32 (0.07–1.54)	0.156
Cannabis Status			
Never used	66	Ref	Ref
Current user	64	1.57 (0.64–3.84)	0.325
Ex-user	27	1.96 (0.66–5.84)	0.227
CBMP Method of Administration			
Oils	111	Ref	Ref
Flower	15	2.52 (0.71–9.01)	0.155
Both	31	5.00 (2.02–12.40)	<.001
Total THC Dosage (mg/day)			
≤ median dose (14.6)	82	Ref	Ref
> median dose (14.6)	75	4.09 (1.70–9.86)	0.002
Total CBD Dosage (mg/day)			
≤ median dose (40)	126	Ref	Ref
> median dose (40)	31	1.56 (0.62–3.92)	0.347
Sleep Quality Scale Baseline Score			
Sleep unimpaired (≥4)	82	Ref	Ref
Sleep impaired (≤3)	75	1.42 (0.65–3.14)	0.380
GAD-7 Baseline Score			
None (0–4)	41	Ref	Ref
Mild (5–9)	35	1.22 (0.41–3.69)	0.722
Moderate (10–14)	29	0.66 (0.18–2.44)	0.534
Severe (≥15)	52	1.11 (0.40–3.07)	0.845
EQ-5D-5L Index Value			
> 0	129	Ref	Ref
≤ 0	28	0.63 (0.20–1.97)	0.427

Abbreviations: BPI: Brief pain inventory; n: number of participants; CBMP: cannabis-based medicinal product; THC: tetrahydrocannabinol; CBD: cannabidiol; GAD-7: Generalized anxiety disorder scale; EQ-5D-5L: European quality-of-life 5 dimension - 5 levels.

Appendix G

Table G1. Univariate logistic regression of the minimum clinically important difference for the pain visual analogue scale with multiple different variables.

	n	Odds ratio (95% Confidence Interval)	p-value
Gender			
Female	65	Ref	Ref
Male	93	1.26 (0.55–2.87)	0.581
Age (years)			
18–40	33	Ref	Ref
41–50	27	2.36 (0.67–8.31)	0.182
51–60	47	1.33 (0.40–4.39)	0.644
61–70	25	0.49 (0.09–2.75)	0.415
70 +	26	1.68 (0.45–6.28)	0.441
Body Mass Index (kg/m^2)			
<18.5	10	1.75 (0.40–7.69)	0.461
18–5-24.9	66	Ref	Ref
25.0–29.9	45	1.02 (0.39–2.63)	0.969
≥ 30.0	26	0.34 (0.07–1.63)	0.176
Cannabis Status			
Never used	65	Ref	Ref
Current user	66	1.08 (0.45–2.59)	0.857
Ex-user	27	1.00 (0.32–3.19)	0.995
CBMP Method of Administration			
Oils	110	Ref	Ref
Flower	17	2.11 (0.60–7.39)	0.243
Both	31	4.33 (1.74–10.81)	0.002
Total THC Dosage (mg/day)			
≤ median dose (14.6)	82	Ref	Ref
> median dose (14.6)	76	3.77 (1.56–9.10)	0.003
Total CBD Dosage (mg/day)			
≤ median dose (40)	127	Ref	Ref
> median dose (40)	31	3.13 (1.29–7.56)	0.011
Sleep Quality Scale Baseline Score			
Sleep unimpaired (≥4)	83	Ref	Ref
Sleep impaired (≤3)	75	1.13 (0.51–2.51)	0.758
GAD-7 Baseline Score			
None (0–4)	41	Ref	Ref
Mild (5–9)	35	1.09 (0.37–3.20)	0.880
Moderate (10–14)	28	0.28 (0.06–1.42)	0.125
Severe (≥15)	53	0.96 (0.36–2.59)	0.936
EQ-5D-5L Index Value			
> 0	130	Ref	Ref
≤ 0	28	0.67 (0.21–2.09)	0.487

Abbreviations: VAS: visual analogue scale; n: number of participants; CBMP: cannabis-based medicinal product; THC: tetrahydrocannabinol; CBD: cannabidiol; GAD-7: Generalized anxiety disorder scale; EQ-5D-5L: European quality-of-life 5 dimension - 5 levels.

Appendix H

Table H1. Multivariate logistic regression of the minimum clinically important difference for the brief pain inventory (severity) with multiple different variables.

	n	Odds ratio (95% Confidence Interval)	p-value
Gender			
Female	61	Ref	Ref
Male	85	2.41 (0.54–10.81)	0.249
Age (years)			
18–40	32	Ref	Ref
41–50	24	0.28 (0.04–1.98)	0.203
51–60	45	0.78 (0.15–3.93)	0.759
61–70	22	0.43 (0.03–5.81)	0.524
70 +	23	1.50 (0.19–12.04)	0.704
Body Mass Index (kg/m^2)			
<18.5	10	4.81 (0.51–45.83)	0.172
18–5-24.9	66	Ref	Ref
25.0–29.9	45	0.92 (0.23–3.63)	0.900
≥ 30.0	25	0.51 (0.08–3.31)	0.479
Cannabis Status			
Never used	59	Ref	Ref
Current user	61	0.16 (0.02–1.05)	0.057
Ex-user	26	0.81 (0.13–4.95)	0.817
CBMP Method of Administration			
Oils	103	Ref	Ref
Flower	15	4.12 (0.38–44.39)	0.243
Both	28	3.05 (0.54–17.30)	0.207
Total THC Dosage (mg/day)			
≤ median dose (14.6)	74	Ref	Ref
> median dose (14.6)	72	9.72 (1.54–61.51)	0.016
Total CBD Dosage (mg/day)			
≤ median dose (40)	116	Ref	Ref
> median dose (40)	30	1.79 (0.46–7.04)	0.402
Sleep Quality Scale Baseline Score			
Sleep unimpaired (≥4)	78	Ref	Ref
Sleep impaired (≤3)	68	3.09 (0.82–11.58)	0.095
GAD-7 Baseline Score			
None (0–4)	40	Ref	Ref
Mild (5–9)	32	2.53 (0.47–13.48)	0.278
Moderate (10–14)	26	1.13 (0.16–7.84)	0.903
Severe (≥15)	48	1.45 (0.27–7.78)	0.667
EQ-5D-5L Index Value			
> 0	121	Ref	Ref
≤ 0	25	0.10 (0.01–1.14)	0.063

Abbreviations: BPI: Brief pain inventory; n: number of participants; CBMP: cannabis-based medicinal product; THC: tetrahydrocannabinol; CBD: cannabidiol; GAD-7: Generalized anxiety disorder scale; EQ-5D-5L: European quality-of-life 5 dimension - 5 levels.

Appendix I

Table I1. Multivariate logistic regression of the minimum clinically important difference for the brief pain inventory (interference) with multiple different variables.

	n	Odds ratio (95% Confidence Interval)	p-value
Gender			
Female	61	Ref	Ref
Male	85	1.91 (0.55–6.66)	0.307
Age (years)			
18–40	32	Ref	Ref
41–50	24	0.58 (0.11–3.25)	0.538
51–60	45	0.71 (0.15–3.25)	0.656
61–70	22	2.85 (0.46–17.91)	0.263
70 +	23	5.53 (0.88–34.69)	0.068
Body Mass Index (kg/m^2)			
<18.5	10	1.52 (0.20–11.62)	0.684
18–5–24.9	66	Ref	Ref
25.0–29.9	45	1.01 (0.33–3.12)	0.989
≥ 30.0	25	0.28 (0.05–1.58)	0.148
Cannabis Status			
Never used	59	Ref	Ref
Current user	61	0.55 (0.12–2.47)	0.434
Ex-user	26	2.13 (0.45–10.12)	0.341
CBMP Method of Administration			
Oils	103	Ref	Ref
Flower	15	4.14 (0.54–32.03)	0.174
Both	28	5.81 (1.09–30.85)	0.039
Total THC Dosage (mg/day)			
≤ median dose (14.6)	74	Ref	Ref
> median dose (14.6)	72	4.07 (0.93–17.78)	0.062
Total CBD Dosage (mg/day)			
≤ median dose (40)	116	Ref	Ref
> median dose (40)	30	0.77 (0.21–2.86)	0.697
Sleep Quality Scale Baseline Score			
Sleep unimpaired (≥ 4)	78	Ref	Ref
Sleep impaired (≤ 3)	68	1.70 (0.56–5.18)	0.347
GAD-7 Baseline Score			
None (0–4)	40	Ref	Ref
Mild (5–9)	32	1.47 (0.34–6.30)	0.606
Moderate (10–14)	26	0.90 (0.17–4.83)	0.905
Severe (≥ 15)	48	0.93 (0.21–4.00)	0.917
EQ-5D-5L Index Value			
> 0	121	Ref	Ref
≤ 0	25	0.12 (0.02–0.75)	0.023

Abbreviations: BPI: Brief pain inventory; n: number of participants; CBMP: cannabis-based medicinal product; THC: tetrahydrocannabinol; CBD: cannabidiol; GAD-7: Generalized anxiety disorder scale; EQ-5D-5L: European quality-of-life 5 dimension - 5 levels.

Appendix J

Table J1. Multivariate logistic regression of the minimum clinically important difference for the pain visual analogue scale with multiple different variables.

	n	Odds ratio (95% Confidence Interval)	p-value
Gender			
Female	60	Ref	Ref
Male	87	1.24 (0.39–3.97)	0.717
Age (years)			
18–40	33	Ref	Ref
41–50	24	1.26 (0.27–5.96)	0.770
51–60	45	1.33 (0.32–5.50)	0.691
61–70	22	0.67 (0.09–5.18)	0.696
70 +	23	1.99 (0.34–11.52)	0.445
Body Mass Index (kg/m^2)			
<18.5	10	2.77 (0.47–16.35)	0.261
18–5-24.9	66	Ref	Ref
25.0–29.9	45	1.09 (0.36–3.32)	0.880
≥ 30.0	26	0.43 (0.08–2.43)	0.342
Cannabis Status			
Never used	58	Ref	Ref
Current user	63	0.42 (0.10–1.71)	0.223
Ex-user	26	0.70 (0.15–3.27)	0.647
CBMP Method of Administration			
Oils	102	Ref	Ref
Flower	17	3.67 (0.53–25.43)	0.188
Both	28	3.27 (0.72–14.99)	0.126
Total THC Dosage (mg/day)			
≤ median dose (14.6)	74	Ref	Ref
> median dose (14.6)	73	2.16 (0.54–8.60)	0.273
Total CBD Dosage (mg/day)			
≤ median dose (40)	117	Ref	Ref
> median dose (40)	30	1.86 (0.59–5.85)	0.291
Sleep Quality Scale Baseline Score			
Sleep unimpaired (≥ 4)	79	Ref	Ref
Sleep impaired (≤3)	68	1.45 (0.50–4.25)	0.499
GAD-7 Baseline Score			
None (0–4)	41	Ref	Ref
Mild (5–9)	32	1.31 (0.35–4.94)	0.686
Moderate (10–14)	25	0.40 (0.06–2.52)	0.331
Severe (≥15)	49	0.84 (0.21–3.33)	0.805
EQ-5D-5L Index Value			
>0	122	Ref	Ref
≤0	25	0.23 (0.04–1.49)	0.124

Abbreviations: VAS: visual analogue scale; n: number of participants; CBMP: cannabis-based medicinal product; THC: tetrahydrocannabinol; CBD: cannabidiol; GAD-7: Generalized anxiety disorder scale; EQ-5D-5L: European quality-of-life 5 dimension - 5 levels.