


Clinical Outcome Data of First Cohort of Chronic Pain Patients Treated With Cannabis-Based Sublingual Oils in the United Kingdom: Analysis From the UK Medical Cannabis Registry

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Abstract

Cannabis-based medicinal products (CBMPs) are an emerging therapeutic option in the management of primary chronic pain, using the role of the endocannabinoid system in modulating central and peripheral pain processes. Despite promising preclinical data, there is a paucity of high-quality evidence to support the use of CBMPs for chronic pain. This study aimed to investigate the health-related quality-of-life outcomes of patients with chronic pain who were prescribed CBMP oil preparations (Adven, Curaleaf International, Guernsey, UK).

This study is a case series of patients from the UK Medical Cannabis Registry, who were treated with CBMP oils for an indication of chronic pain. The primary outcomes were the changes in Brief Pain Inventory short form, Short-Form McGill Pain Questionnaire-2, Visual Analog Scale Pain, General Anxiety Disorder-7, Sleep Quality Scale, and EQ-5D-5L, at 1, 3, and 6 months. One hundred ten patients were included. Significant improvements in Sleep Quality Scale, EQ-5D-5L pain and discomfort subscale, and Brief Pain Inventory Interference Subscale ($P < .05$) at 1, 3, and 6 months were demonstrated. There were no notable differences between cannabis-naïve and previous cannabis users in quality-of-life outcomes. The adverse event incidence was 30.0%, with most ($n = 58$; 92.1%) adverse events being mild or moderate in intensity. Treatment of chronic pain with Adven CBMP oils was associated with an improvement in pain-specific outcomes, health-related quality of life, and self-reported sleep quality. Relative safety was demonstrated over medium-term prescribed use. While these findings must be treated with caution considering the limitations of study design, they can inform future clinical trials.

Keywords

cannabinoids, chronic pain, health-related quality-of-life, medical cannabis

Chronic pain is defined as persistent or recurring pain lasting longer than 3 months, characterized by physical pain, disability, emotional disturbance, and social withdrawal.¹ The global burden of chronic pain is sizable, with an estimated global incidence of 20%.^{2,3} In the United Kingdom alone, 28 million people are thought to be affected by chronic pain.² Chronic pain can be accompanied by depression, anxiety, and sleeping difficulties, which contribute to decreased quality of life and increased incidence of suicide.^{4,5} In addition to the costs to the individual, chronic pain is associated with reduced work productivity, absenteeism, and unemployment. The cost to the UK economy from chronic back pain was estimated at £12.3 billion in 2000 (£21.2 billion, at 2021 inflation levels), with associated costs projected to have risen secondary to an aging population.⁶

While there is increasing recognition of the role of nonpharmacological therapies in the management of

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chronic pain, pharmacological therapies continue to be the mainstay of treatment, despite a paucity of high-quality evidence to support their use.⁷⁻⁹ For example, while opioid analgesics increased in usage in the early part of the 21st century, there is limited evidence to support their use in chronic pain.¹⁰⁻¹² This is despite increasing recognition of both short-term adverse effects and the associated risks of long-term use, including addiction, physical dependence, and increased risk of psychological comorbidity.^{11,13,14} Nonsteroidal anti-inflammatory drugs, which are commonly prescribed in the setting of musculoskeletal pain, similarly have an unclear role in chronic pain considering their association with gastrointestinal, cardiovascular, and renal adverse events.^{15,16} Gabapentinoids, originally developed for the treatment of epilepsy, have been used with increased frequency off-label for the treatment of chronic pain, partially driven by a desire to find a safer alternative to opioids.^{17,18} However, similar to opioids and nonsteroidal anti-inflammatory drugs, there is a paucity of evidence to support its current breadth of use in clinical practice, in addition to growing evidence of associated harms with chronic use, subversion, and abuse.¹⁸⁻²⁰

In view of the challenges in managing chronic pain, there is growing interest in the endocannabinoid system as a drug target due to its role in modulating central and peripheral pain processes. As such, cannabis-based medicinal products (CBMPs) are an emerging therapeutic option in the management of primary chronic pain of undefined origin, as well as chronic cancer pain and neuropathic pain.²¹⁻²³ CBMPs are a heterogeneous group of pharmaceuticals available as either isolate formulations of cannabinoids, or as broad-spectrum compounds containing other compounds from the cannabis flower with potential therapeutic properties, including terpenes, terpenoids, and flavonoids.²⁴ The 2 cannabinoids to which prescriptions are titrated and with the greatest preliminary research are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD).²⁴ THC is a partial agonist of the primary receptors of the endocannabinoid system, cannabinoid receptors type 1 and 2 (CB1 and CB2 receptors).^{25,26} CB1 receptors, located in the central nervous system, modulate glutamate and γ -aminobutyric acid neurotransmission.^{27,28} CB1 agonism by THC is thought to induce centrally acting analgesic effects, in addition to the psychotropic effects commonly associated with cannabis consumption.^{27,28} CB2 receptors, which are expressed in peripheral immune cells, modulate inflammatory cytokines.^{27,28} However, the extent to which this plays a role in nociception and pain processing is not clear. CBD has opposing effects at cannabinoid receptors. Its primary action is via inhibition of the enzyme fatty acid amino

hydrolase, which typically breaks down endogenous cannabinoid receptor agonists (anandamide and 2-arachidonoylglycerol).²⁹⁻³¹ Consequently, CBD leads to increased activation of CB1 and CB2. In clinical studies, CBD and fatty acid amino hydrolase inhibitors appear to have similar clinical effects.^{32,33} However, CBD is also a negative allosteric modulator of CB1 receptors reducing the overall effects of THC and other agonists.³⁴ THC, CBD, and other cannabinoids also act at other receptors implicated in pain pathways, including opioid, transient receptor potential cation channel subfamily V member 1, and serotonin 5-HT₃ receptors, each potentially contributing to the overall clinical effects.³⁵

Despite promising preclinical data, there is a paucity of high-quality evidence to support the use of CBMPs. The evidence base, while broad, is inconclusive, variable across chronic pain types, and thus insufficient to inform guidelines, funders, and licensing agencies. For cancer-related pain, placebo-controlled trials have shown clinically significant reduction in pain scores in those using nabiximols, an oromucosal spray containing THC and CBD in a 1.1:1.0 ratio. However, a large trial (n = 397) has shown the difference in effect to be nonsignificant.³⁶⁻³⁸ Systematic reviews of nabiximols in chronic non-cancer and neuropathic pain and CBMPs in musculoskeletal pain have also been inconclusive.^{39,40} However, clinical trials in CBMPs to date have largely been underpowered, performed in acute settings, and failed to account for the heterogeneity of available CBMPs.^{30,41} Observational studies could be complementary to clinical trials in this field, as they provide insights across a broad spectrum of medicines to guide clinical trials and practice while trial results are awaited.

The UK Medical Cannabis Registry, set up in 2019, captures longitudinal data of patients prescribed CBMPs in the United Kingdom outside of the National Health Service (NHS) and has published outcomes related to health-related quality of life (HRQoL) across all conditions.⁴² Following legalization of medical cannabis in the United Kingdom in 2019, many doctors have preferred sublingual oil as a mode of administration of CBMPs. This study aims to investigate the safety and clinical outcomes of patients with chronic pain enrolled in the UK Medical Cannabis Registry who were treated with cannabis-based medium-chain triglyceride oils (Adven, Curaleaf International, Guernsey, UK).

Methods

Study Overview

This study is an uncontrolled case series of patients identified from the UK Medical Cannabis Registry, and

reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology statement.⁴³ In accordance with the NHS Health Research Authority and Research Ethics Committees guidance, this study did not require formal ethical approval. All participants completed formal, written consent before enrollment in the registry.

Setting and Participants

The UK Medical Cannabis Registry was established in December 2019 and is the first prospective registry launched in the United Kingdom, capturing pseudonymized data on patients treated with CBMPs. It is privately owned and managed by Sapphire Medical Clinics. To date, it is the only clinic that enrolls patients into the registry. Patients are recruited from the United Kingdom and the Channel Islands. Clinicopathological information, comorbidities, drug and alcohol history, and medication information were collected prospectively by clinical staff. Patient-reported outcome measures (PROMs) and adverse event questionnaires were electronically administered to patients at baseline, 1 month, 3 months, and 6 months and the 6 monthly intervals thereafter.

Patient and Data Selection

For this analysis, data were extracted for the initial participants of the UK Medical Cannabis Registry who were prescribed cannabis-based oil preparations (Adven) for the indication of chronic pain and had recorded PROMs at baseline with at least 1 follow-up datum (1, 3, and/or 6 months). In the United Kingdom, prescriptions of CBMPs are only prescribed once other treatments have proven ineffective or inappropriate. Only patients who were prescribed exclusively Adven CBMPs in the form of oil preparation and no other CBMPs and modes of administration were included in this analysis. Data regarding demographic details, including age, sex, and occupation, were recorded. Participant body mass index (BMI) was also extracted. Data on the relevant comorbidities contributing to the Charlson Comorbidity Index, a widely used prognostic scoring model for 10-year mortality, was collected and a score calculated for each patient.⁴⁴ While not wholly representative of typical comorbidities that accompany chronic pain, the Charlson Comorbidity Index was chosen to be collected across the UK Medical Cannabis Registry, as it is the most commonly used comorbidity scoring system used in registry studies, allowing for direct comparison of comorbid status between cohorts.⁴⁵

Drug and alcohol data on patients were extracted and analyzed, including smoking status, smoking pack-years, alcohol units per week, and cannabis status. For

those who had previously or were presently taking nonprescription cannabis, a novel metric of “gram years” was calculated as previously described by our group.⁴² All CBMP prescriptions were recorded and analyzed, including company, formulation, method of administration, CBD concentration, THC concentration, and strain.

All participants are administered quality-of-life PROMs questionnaires, including EQ-5D-5L, General Anxiety Disorder-7 (GAD-7), and Single-Item Sleep Quality Scale (SQS). Fibromyalgia patients were administered the Fibromyalgia Severity Scale, while all patients with other chronic pain etiologies were administered the Visual Analog Scale (VAS) Pain, Brief Pain Inventory Short Form (BPI), and Short-Form McGill Pain Questionnaire-2.⁴⁶⁻⁵¹

The BPI is a validated scale that assesses pain at its “worst,” “least,” “average,” and “now” (current pain) to produce a severity score from 0 to 10, as well as measuring interference score, which measures how much pain has interfered with 7 daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep.

The McGill Pain Questionnaire includes pain-specific descriptors, which patients score the intensity of, as a number from 1 to 5, in which each number is associated with the following words: 1, “mild”; 2, “discomforting”; 3, “distressing”; 4, “horrible”; and 5, “excruciating.” The descriptors fall into 5 major groups: continuous, intermittent, affective, neuropathic, and overall, for which the total scores are calculated.

The Fibromyalgia Severity Scale is derived from the 2016 diagnostic criteria for fibromyalgia.⁵¹ It ranges from 0 to 31 and is a sum of the widespread pain index, a value measuring the areas of pain experienced by a patient with fibromyalgia, and the symptom severity score, a measure of the severity of symptoms associated with fibromyalgia including fatigue, waking feeling unrefreshed, cognitive symptoms, headaches, lower abdominal pain, and depression.

The EQ-5D-5L is a 2-part tool that measures the quality of life across 5 domains (mobility, self-care, usual activities, pain or discomfort, anxiety or depression) with 5 levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems). These 5 domains and levels correspond to 1 of 3125 health states, which are mapped to EQ-5D-5L index values according to a technique described by van Hout et al.⁵² An index value of <0 represents a health state worse than death, while a score of 1 indicates perfect HRQoL. This is the preferred method of measuring HRQoL by the National Institute for

Health and Care Excellence.⁵³ The second part of the EQ-5D-5L is the EQ-VAS, which consists of a vertical scale of 0 to 100, whereby “100” corresponds to the “best health you can imagine” and “0” corresponds to the “worst health you can imagine.”⁴⁶

For the GAD-7 score, registry participants are asked about how often over the past 2 weeks they had been bothered by the core symptoms of generalized anxiety disorder, generating a score from 0 to 21, where a higher score is consistent with worse anxiety symptoms.⁴⁷

The SQS is a validated question of sleep quality over the past 7 days only with sleep quality rated from 0 to 10, wherein “10” signifies “excellent” and “0” denotes “terrible.”⁴⁸

Patients were also asked to rate their pain on a VAS of 0 to 10, where “0” is “no pain at all” and “10” is the “worst pain that they can imagine.”

Participants reported adverse events at 1, 3, and 6 months from baseline, either through self-reporting or during routine follow-up with a clinician. Adverse events were recorded in accordance with the common terminology criteria for adverse events version 3.0.⁵⁴

Outcomes

Primary outcome measures for this analysis were changes in BPI, Short-Form McGill Pain Questionnaire-2, VAS Pain, GAD-7, SQS, and EQ-5D-5L PROMs, at 1, 3, and 6 months. Secondary outcomes included analysis of adverse effects in terms of severity and incidence.

Statistical Analysis

Data from PROMs were analyzed compared to baseline at 1, 3, and 6 months. Normality was tested via a Shapiro-Wilk test. Parametric data were presented as a mean \pm standard deviation, while nonparametric data were presented as median (interquartile range [IQR]). A preplanned subgroup analysis comparing patients who have self-identified as active cannabis users before starting CBMP therapy with a subgroup composed of cannabis-naïve and ex-cannabis users was conducted. Baseline PROM data and change scores (calculated as a difference between baseline and follow-up data) were compared between subgroups. An adverse events profile was also analyzed.

Statistical analysis was performed with a *t*-test or Wilcoxon rank-sum test depending on whether the data were parametric or nonparametric, respectively. Statistical significance was defined using *P* value $<$.05. (R version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) was used for data visualization and analysis.

Table 1. Participants' Demographic and Clinical Characteristics

Baseline Characteristics	No. (%) / Mean \pm SD
Age, y	52.1 \pm 15.4
Female	56 (50.90)
Male	54 (49.10)
Body mass index, kg/m ²	28.00 \pm 5.56
Occupation	
Elementary occupations	5 (4.55)
Professional	19 (17.27)
Retired	7 (6.36)
Unemployed	34 (30.91)
Other occupation	41 (37.27)
Undisclosed	4 (3.64)
Cannabis status	
Never used	71 (64.55)
Current user	26 (23.64)
Ex-user	13 (11.81)
Smoking status	
Never smoked	55 (50.00)
Current smoker	14 (12.72)
Ex-smoker	41 (37.27)
Charlson Comorbidity Index	1.69 \pm 1.94
Mean alcohol consumption per week, units	6.39 \pm 10.51
Mean pack-years	11.96 \pm 11.72
Mean cannabis lifetime use, gram years	9.44 \pm 24.58

SD, standard deviation.

Results

Data extraction included the first 831 patients who had been registered on the UK Medical Cannabis Registry. When restricted to patients who had received treatment for $>$ 1 month, 737 patients remained. Out of 737 patients, 449 had received CBMPs for chronic pain (primary diagnosis) and 257 received only Adven oil preparation, with no other CBMPs prescribed. From these, 148 had completed baseline PROM data and 110 of those had completed at least 1 follow-up data point. Of these, 100 patients had recorded PROMs at 1 month, while 54 patients had recorded PROMs at 3 months and 20 patients had PROMs at 6 months.

Demographic details are presented in Table 1. The mean age of patients was 52.07 (\pm 15.43). Nearly half ($n = 54$; 49.1%) of the patients were female. The mean BMI of participants was 28.02 (\pm 5.66). The majority of the patients have never used cannabis ($n = 71$; 64.55%), with nearly a quarter being current users ($n = 26$; 23.64%) and the rest being ex-users ($n = 13$; 11.81%). The mean cannabis lifetime use was 9.44 gram-years.

Table 2 outlines the primary diagnosis for which treatment was initiated. The most common primary diagnosis was chronic noncancer pain ($n = 53$; 48.2%), followed by neuropathic pain ($n = 26$; 23.6%) and fibromyalgia ($n = 18$; 16.3%). Fifty-two (47.3%) and 14 (12.7%) patients, respectively, also had a secondary or tertiary indication for CBMP therapy.

Table 2. Distribution of Indications for CBMP Therapy

Diagnosis	Primary, n (%)	Secondary, n (%)	Tertiary, n (%)
Chronic noncancer pain	53 (48.2)	18 (13.4)	2 (1.8)
Neuropathic pain	26 (23.6)	7 (6.3)	2 (1.8)
Fibromyalgia	18 (16.2)	12 (10.9)	0 (0.0)
Ehlers-Danlos	6 (5.4)	5 (4.5)	1 (0.9)
Complex regional pain syndrome	4 (5.4)	0 (0.0)	0 (0.0)
Cancer pain	3 (2.7)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	3 (2.7)	0 (0.0)
Migraine	0 (0.0)	2 (1.8)	3 (2.7)
Depression	0 (0.0)	1 (0.9)	2 (1.8)
Agoraphobia	0 (0.0)	0 (0.0)	1 (0.9)
Anxiety	0 (0.0)	2 (1.8)	0 (0.0)
Autism spectrum disorder	0 (0.0)	2 (1.8)	1 (0.9)
Eating disorder	0 (0.0)	0 (0.0)	1 (0.9)
PTSD	0 (0.0)	0 (0.0)	1 (0.9)

CBMP, cannabis-based medicinal product; PTSD, posttraumatic stress disorder.

CBMP Dosing and Mode of Administration

The majority of patients had 2 cannabis-based oil preparations prescribed ($n = 105$; 95.5%), with the rest of patients being prescribed a single CBMP ($n = 5$; 4.5%). Two hundred five CBMPs were prescribed across the whole cohort. Sativa strains were the most commonly prescribed ($n = 109$; 53.2%), followed by hybrid strains ($n = 98$; 47.8%). Fifty-nine patients (53.6%) were prescribed the same combination of 20 mg of CBD oil (sativa strain) and 1 mg of THC oil (hybrid strain). The median CBD dose at baseline was 20.0 mg per day (IQR, 20.0-20.0 mg), while the median THC dose at baseline was 1.00 mg per day (IQR 1.0-2.0 mg). The majority of oils were prescribed for oral admission ($n = 167$; 81.5%).

Patient-Reported Outcome Measures

Table 3 outlines full paired results from baseline to 1 month, 3 months, and 6 months (where data are available). Statistically significant improvements in HRQoL were demonstrated at 1, 3, and 6 months in SQS, EQ-5D-5L pain and discomfort subscale, and Brief Pain Inventory Interference Subscale ($P < .05$). Statistically significant improvements were also demonstrated at 1 and 3 months only in the EQ-5D-5L Index, VAS Pain, and EQ-5D-5L VAS ($P < .05$). It is worth noting that due to the bimodal distribution of the data, some comparisons were significant, despite the median baseline score and follow-up score being the same.

Effect of Previous Cannabis Use

The majority of current users declared using cannabis daily ($n = 24$; 88.5%), with median daily usage of 0.75 g (IQR, 0.35-2.00 g). On subgroup analysis, no statistical significance difference between cannabis-naïve and current users was found at baseline for all the PROMs ($P > .05$). When the change scores were considered,

the cannabis-naïve group had a significantly larger difference in scores at 1 month (median, -0.52 vs $+0.22$; $P = .044$). Moreover, at 3-month follow-up, the current cannabis user subgroup had a larger difference in McGill's Continuous Pain Subscale scores (median, -3.42 vs 0.50 , $P = .036$). Full subgroup analysis results can be found in Table S1.

Adverse Events

Reported adverse events are described in full in Table 4. There were 63 total reported adverse events reported by 33 patients (30.0%). The most commonly experienced adverse events were nausea ($n = 9$; 14.3%) and dizziness ($n = 7$; 11.1%). The majority of adverse events were mild or moderate ($n = 58$; 92.1%), with only 2 events being described as severe and 1 as disabling. Only 1 of the 63 adverse events (1.6%) was reported by a current cannabis user, with the rest being reported by patients who were either ex-users ($n = 4$, 6.3%) or cannabis naïve ($n = 58$; 92.1%).

Discussion

This analysis presents the short-term outcomes of the first cohort of patients prescribed CBMP oils for chronic pain in the United Kingdom. Significant improvements in HRQoL were demonstrated in SQS, EQ-5D-5L pain and discomfort subscale, and Brief Pain Inventory Interference Subscale ($P < .05$) at all follow-up points recorded to date (at 1, 3, and 6 months). There were no notable differences between cannabis-naïve and previous cannabis users in terms of quality-of-life outcomes. The adverse event incidence was 30.0%, with the majority of adverse events being either mild or moderate in intensity ($n = 58$; 92.1%).

Registries have already been established for monitoring of CBMP prescriptions in chronic pain globally. A recent analysis of German pain e-Registry in 2017, which investigated the effectiveness and safety of THC/CBD spray for chronic pain management in a cohort of 800 patients found that 56% of patients had $>50\%$ improvement in >5 of 9 aggravated symptom relief-9 scale domains. These included improvements in pain intensity (67.5%), depression (66.5%), overall well-being (61.3%), anxiety (57.6%), disabilities in daily life (56.3%), sleep (47.0%), and physical (42.1%) and mental quality-of-life (17.4%).⁵⁵ This is in line with the findings of the present study, in terms of improvements in pain intensity, overall HRQoL, and sleep quality, all of which were significant at 1, 3, and 6 months in our analysis. However, in the present study, there was no detectable improvement in the EQ-5D-5L domains of mobility, self-care, and usual activities. This may suggest that CBMP oils may be associated with improved perception of pain without resulting

Table 3. Paired Baseline and Follow-Up Patient-Reported Outcome Measures

PROM	Follow-Up Interval	n	Scores at Baseline	Scores at Follow-Up	P
GAD-7	1 mo	98	4.00 (0.20-8.00)	2.50 (0.00-8.00)	.346
	3 mo	51	4.00 (0.50-9.00)	3.00 (1.00-8.00)	.663
	6 mo	20	5.00 (1.00-11.80)	6.00 (2.50-12.00)	.914
SQS	1 mo	88	5.06 ± 2.49	5.77 ± 2.33	.001**
	3 mo	47	4.83 ± 2.42	6.09 ± 2.47	<.001***
	6 mo	14	4.57 ± 2.34	6.29 ± 2.30	.024**
Pain VAS	1 mo	68	6.37 ± 1.84	5.97 ± 1.71	.016*
	3 mo	41	6.61 ± 1.64	5.56 ± 2.14	<.001***
	6 mo	12	6.33 ± 1.72	5.42 ± 2.50	.190
EQ-5D-5L Mobility	1 mo	92	3.00 (2.00-4.00)	3.00 (1.80-3.00)	.200
	3 mo	51	3.00 (2.00-4.00)	3.00 (2.00-4.00)	.655
	6 mo	19	3.00 (2.00-4.00)	3.00 (2.00-3.50)	.964
EQ-5D-5L Self-Care	1 mo	92	2.00 (1.00-3.00)	2.00 (1.00-5.00)	.997
	3 mo	51	2.00 (1.00-3.00)	1.00 (1.00-3.00)	.718
	6 mo	19	1.00 (1.00-3.00)	2.00 (1.00-3.00)	.514
EQ-5D-5L Usual Activities	1 mo	92	3.00 (2.00-4.00)	3.00 (2.00-3.00)	.073
	3 mo	51	3.00 (2.00-4.00)	2.00 (2.00-3.50)	.120
	6 mo	19	3.00 (2.00-4.00)	3.00 (2.50-3.50)	.575
EQ-5D-5L Pain and Discomfort	1 mo	92	3.00 (3.00-4.00)	3.00 (2.00-4.00)	.028*
	3 mo	51	3.00 (3.00-4.00)	3.00 (3.00-4.00)	.009**
	6 mo	19	4.00 (3.00-4.00)	3.00 (2.00-3.50)	.013*
EQ-5D-5L Anxiety and Depression	1 mo	92	2.00 (1.00-3.00)	2.00 (1.00-3.00)	.545
	3 mo	51	2.00 (1.00-3.00)	1.00 (1.00-2.00)	.135
	6 mo	19	2.00 (1.00-3.00)	2.00 (1.00-3.50)	.878
EQ-5D-5L Index	1 mo	92	0.447 ± 0.299	0.511 ± 0.290	.005**
	3 mo	51	0.401 ± 0.319	0.496 ± 0.299	.003**
	6 mo	19	0.357 ± 0.343	0.404 ± 0.345	.295
EQ-5D-5L VAS	1 mo	92	52.43 ± 21.43	56.72 ± 21.28	.028*
	3 mo	50	50.76 ± 21.60	57.46 ± 21.48	.030*
	6 mo	18	46.17 ± 23.55	49.83 ± 22.88	.480
Brief Pain Inventory—Severity Subscale	1 mo	68	5.09 ± 1.95	4.75 ± 1.85	.071
	3 mo	36	5.40 ± 1.76	4.37 ± 1.91	.014*
	6 mo	13	5.29 ± 2.13	4.15 ± 1.40	.012*
Brief Pain Inventory—Interference Subscale	1 mo	68	4.95 ± 2.12	4.38 ± 2.26	.0182*
	3 mo	36	5.24 ± 2.03	4.22 ± 2.33	.029*
	6 mo	13	5.78 ± 2.25	3.96 ± 1.85	<.001***
McGill's Pain Scale—Continuous Pain Subscale	1 mo	56	4.42 (2.29-6.4)	3.58 (1.79-5.71)	.255
	3 mo	33	4.33 (2.67-6.67)	3.67 (1.83-5.17)	.213
	6 mo	11	4.50 (2.92-6.08)	2.83 (1.00-5.42)	.211
McGill's Pain Scale—Intermittent Pain Subscale	1 mo	56	4.42 (1.33-5.71)	3.42 (1.25-5.04)	.343
	3 mo	33	4.67 (1.67-5.83)	2.83 (0.67-5.17)	.162
	6 mo	11	5.00 (1.17-5.50)	1.50 (0.17-3.83)	.129
McGill's Pain Scale—Affective Pain Subscale	1 mo	56	3.62 (1.75-5.75)	2.50 (1.25-4.31)	.124
	3 mo	33	3.75 (2.00-5.00)	2.25 (0.75-4.00)	.057
	6 mo	11	5.00 (2.38-6.00)	1.25 (0.25-4.12)	.030*
McGill's Pain Scale—Overall Score	1 mo	56	3.79 (2.22-5.31)	3.09 (1.63-4.71)	.195
	3 mo	33	3.98 (2.36-5.44)	2.94 (1.15-4.67)	.109
	6 mo	11	4.71 (2.58-4.17)	2.04 (0.73-4.77)	.065
McGill's Pain Scale—Neuropathic Pain Subscale	1 mo	56	3.08 (1.17-4.37)	2.75 (1.00-3.71)	.316
	3 mo	33	3.33 (1.83-4.67)	3.33 (0.67-4.50)	.445
	6 mo	11	3.67 (3.25-4.17)	2.83 (0.75-3.75)	.293
Fibromyalgia Severity Scale	1 mo	12	23.50 (18.50-25.00)	20.50 (15.25-23.75)	.340
	3 mo	9	18.00 (16.00-24.00)	18.00 (13.00-22.00)	.505

GAD-7, General Anxiety Disorder-7; SQS, Sleep Quality Scale; VAS, Visual Analog Scale.

* $P < .05$, ** $P < .01$, *** $P < .001$.

Table 4. Adverse Event Profile

Adverse Events	Severity Mild	Moderate	Severe	Life Threatening/ Disabling	Unknown	Total, n (%)
Nausea	9	0	0	0	0	9 (14.3)
Dizziness	5	2	0	0	0	7 (11.1)
Headache	2	4	1	0	0	7 (11.1)
Constipation	5	1	0	0	0	6 (9.6)
Fatigue	5	0	0	0	0	5 (7.9)
Dry mouth	4	1	0	0	0	5 (7.9)
Other	1	3	0	0	1	5 (7.9)
Memory impairment	0	4	0	0	0	4 (6.3)
Vomiting	2	0	0	0	0	2 (3.2)
Concentration impairment	1	1	0	0	0	2 (3.2)
Upper abdominal pain	2	0	0	0	0	2 (3.2)
Somnolence (sleepy/ drowsy)	0	2	0	0	0	2 (3.2)
Amnesia	1	0	0	0	0	1 (1.6)
Dyspepsia	0	0	1	0	0	1 (1.6)
Insomnia	1	0	0	0	0	1 (1.6)
Lethargy	0	1	0	0	0	1 (1.6)
Coordination/Balance/Speech impairment	1	0	0	0	0	1 (1.6)
Vertigo (spinning/dizziness)	0	0	0	1	0	1 (1.6)
Total, n (%)	39 (61.9)	19 (30.2)	2 (3.2)	1 (1.6)	1 (1.6)	63 (100)

in functional change. The study was not designed to assess for differences in this subscale, and further evaluation of the role of CBMPs in effecting function in the setting of chronic pain will be required. The improvements in sleep quality, could be secondary to the endocannabinoid system's role in the regulation of the sleep-wake cycle, through modulation of circadian rhythm by acting on the suprachiasmatic nucleus.⁵⁶ Similar improvements in sleep quality in the context of chronic conditions, have further been shown in a recent meta-analysis of 8 placebo-controlled trials.⁵⁷

The present analysis has demonstrated a statistically significant improvement in health-related quality of life in a range of pain-related metrics (EQ-5D-5L pain and discomfort subscale, and Brief Pain Inventory Interference Subscale). This is consistent with the results of a prospective observational study of 751 patients in Canada, who were prescribed medical cannabis for chronic pain conditions, which found a decrease in both pain interference and severity subscale at 12 months.⁵⁸ This is also consistent with the initial analysis of patients from the UK Medical Cannabis Registry, which noted an improvement in HRQoL, as measured by the EQ-5D-5L index value, across all conditions.⁴² A 2017 systematic review and meta-analysis of HRQoL outcomes in those prescribed CBMPs or synthetic cannabinoids for all conditions failed to demonstrate an impact on HRQoL.⁵⁹ While formal analysis was not performed on pain-specific studies, it was notable that pain studies were more likely to have a positive impact on HRQoL. This review was also limited, as HRQoL was a secondary

outcome of most included studies. What is more, the heterogeneity in dose and consistency of cannabis regarding THC:CBD ratio and methods of intake prevents direct comparison between the studies. It should be noted that due to interpersonal differences in response to CBMPs, and variability between cannabis plant strains, a degree of variability between prescribed protocols will inevitably exist and generally limit the generalizability of studies on cannabinoids. In this study, analysis was focused on a single CBMP oil range to limit this variability where possible.

There was no noted improvement in any aspects of McGill's Pain Scale, except the affective pain scale at 6 months. This is in keeping with the latest Cochrane review of cannabis products in adult neuropathic pain, which concluded that there was no clinically significant difference in pain relief in those with neuropathic pain.⁶⁰ This review did find low-quality evidence of a difference in pain intensity and sleep, again corroborated by the present study. However, this study comprises only 35 (31.5%) participants with neuropathic pain, including secondary and tertiary diagnoses, and therefore may not reveal the outcomes for those with pain of a neuropathic origin. Preclinical studies have highlighted a potential role of THC and CBD in neuropathic pain models; however, this is not wholly supported at present by clinical data. In future studies, we aim to assess the effect of CBMPs in select patients from the UK Medical Cannabis Registry with neuropathic pain for better evaluation.⁶¹

While self-reporting of adverse events, which is used in the UK Medical Cannabis Registry can lead to

selection bias, the overall adverse event rate in this cohort was 30.0%, which is comparable to the incidence reported in the postmarketing safety analysis of nabiximols by Etges et al (31.3%)⁶² but higher than in the study by Oreja-Guevara et al (20.0%).⁶³ Interestingly, all but 1 adverse event was reported by patients who have self-reported never previously using cannabis, suggesting potential initial adjustment period in which dosing regimens are being optimized by patients, after which adverse events subside. Moreover, those who use cannabis before starting treatment with CBMPs are subject to selection bias with those with significant side effects unlikely to seek treatment. As the UK cannabis registry is expanded, a more in-depth analyses of adverse events rate over time should be conducted to elucidate the true incidence.

While registry studies provide a resource-efficient method to collect naturalistic data, this study has inherent limitations. Due to a lack of comparator arm or a control group, this introduces biases and limits the ability to make any statements regarding causation for the associations found. What is more, while efforts have been taken to reduce the selection bias, it is not eliminated, as all included patients were prescribed CBMP therapy via a private prescription. This limits access to CBMPs to those who cannot afford the costs associated with such therapy. Selection bias was compounded by the exclusion of patients who did not have baseline data or did not complete follow-up data and must be taken into account in interpreting the results. However, to limit the effect of incomplete or missing data, the study was restricted to those with complete baseline data. While the potential effect of previous cannabis use could have confounded the results, on subgroup analysis we have found no notable differences between cannabis-naïve and previous-user subgroups in terms of PROMs (Table S1). It is also worth noting that regression toward the mean phenomenon could have accounted for some of the differences observed, especially for patients with multiple repeated observations, such as those who had a 1-, 3-, and 6-month follow-up set of PROMs.

While there is heterogeneity in the etiology of chronic pain treated in the context of this study, this is the first study of its kind of patients from the United Kingdom. This study focuses on short-term outcomes, and medium- and long-term efficacy and safety outcomes of CBD/THC oils in the treatment of chronic pain are still unknown, as data were not sufficient to conduct the analysis at 12-month follow-up. Going forward, as more patients are being prescribed CBMPs in the United Kingdom, analyses of long-term outcomes are pertinent. A more in-depth study into specific prescribing protocols (dose, strain, mode of admission) and investigating dose-response relationship are needed

for establishing optimal dosing regimens. Interactions and potential synergistic effect of other analgesics with CBMPs should also be explored, as a single agent is unlikely to be used in isolation for chronic pain management.

Conclusion

These results suggest that treatment of chronic pain with selected prescription regimens of sublingual CBMP oils (Adven) is associated with an improvement in pain-specific outcomes in addition to HRQoL and self-reported sleep quality. Moreover, it details the incidence profile of adverse events, particularly highlighting how severe or disabling side effects are rare over medium-term treatment, which is in line with the previously published data. Due to notable limitations of this study, definite conclusions on specific prescription regimen efficacy cannot be drawn; however, the 20-mg CBD: 1-mg THC prescription protocol, which was most commonly used in the study, shows promising initial results. As the UK Medical Cannabis Registry increases in the number of participants and follow-up available, further product-specific analyses are planned across conditions, including oils and flower CBMPs.

Conflicts of Interest

M.K. is a medical student at Imperial College London. He has no shareholdings in pharmaceutical companies. S.E. is a junior doctor and undertakes paid consultancy work at Sapphire Medical Clinics. He is an honorary clinical research fellow at Imperial College London. He has no shareholdings in pharmaceutical companies. C.H. is chief clinical pharmacist at Sapphire Medical Clinics. He has no shareholdings in pharmaceutical companies. R.C. is a consultant orthopedic surgeon, a director, and a shareholder at Sapphire Medical Clinics and a consultant at St George's Hospital, London. He has no shareholdings in pharmaceutical companies. A.U. is a pain specialist at Sapphire Medical Clinics (London) and a consultant at Dartford and Gravesham NHS Trust. He has no shareholdings in pharmaceutical companies. M.S. is a pain specialist at Sapphire Medical Clinics (London) and a consultant at Dudley Group of Hospitals NHS Trust. He has no shareholdings in pharmaceutical companies. M.P. is a consultant in pain services and a director and a shareholder at Sapphire Medical Clinics (London). He has no shareholdings in pharmaceutical companies. J.R. is a consultant psychiatrist, a director, and a shareholder at Sapphire Medical Clinics (London). He is an honorary consultant psychiatrist at the South London & Maudsley NHS Foundation Trust, and a National Institute for Health Research (NIHR) Clinician Scientist Fellow at the Centre for Affective Disorders at King's College London. He is funded by a fellowship (CS-2017-17-007) from the NIHR. He 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 him to attend trial-related meetings and conferences to present the results of research using psilocybin. He 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 he does not benefit personally. He has no shareholdings in pharmaceutical companies. M.S. is a consultant hepatopancreatobiliary surgeon at Imperial College Healthcare NHS Trust, London, and a Senior Clinical Lecturer at Imperial College London. He is a founder, director, and a shareholder at Sapphire Medical Clinics and Research Director at Curaleaf International. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

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.

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Supplemental Information

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