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ORIGINAL RESEARCH

An Updated Analysis of Clinical Outcome Measures Across Patients From the UK Medical Cannabis Registry

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Abstract

Introduction: There is a growing body of literature supporting the efficacy of cannabis-based medicinal products (CBMPs). Despite an increase in prescribing globally, there is a paucity of high-quality clinical data on the efficacy of CBMPs for many conditions. This study aims to detail the changes in health-related quality of life (HRQoL) and associated clinical safety in patients prescribed CBMPs for any clinical indication from the UK Medical Cannabis Registry (UKMCR).

Methods: An uncontrolled prospective case series of the UKMCR was analyzed. Primary outcomes included change from baseline in patient-reported outcome measures collected across all patients (the Generalized Anxiety Disorder Scale [GAD-7], EQ-5D-5L, and Sleep Quality Scale [SQS]) at 1, 3, and 6 months. Secondary outcomes included the self-reported incidence and severity of adverse events. Statistical significance was defined as $p < 0.050$.

Results: Three hundred twelve patients were included in the final analysis, with a mean age of 44.8. The most common primary diagnoses were chronic pain of undefined etiology ($n = 102$, 32.7%), neuropathic pain ($n = 43$, 13.8%), and fibromyalgia ($n = 31$, 9.9%). Before enrolment, 112 (35.9%) patients consumed cannabis daily. The median cannabidiol and (−)-trans-Δ^9-tetrahydrocannabinol doses prescribed at baseline were 20.0 mg (0.0–510.0 mg) and 3.0 mg (0.0–660.0 mg), respectively. Statistically significant improvements were observed in GAD-7, EQ-5D-5L Index, EQ-5D Visual Analog Scale and SQS scores at 1, 3, and 6 months ($p < 0.050$). There were 94 (30.1%) reported adverse events, of which nausea ($n = 12$, 3.8%), dry mouth ($n = 10$, 3.2%), dizziness ($n = 7$, 2.2%), and somnolence ($n = 7$, 2.2%) were the most common.

Conclusion: This study demonstrated CBMP treatment to be associated with a relatively low incidence of severe adverse events in the medium-term. Positive changes following treatment were observed in general, as well as anxiety and sleep-specific, HRQoL outcomes. Randomized controlled trials are still awaited to assess causation; however, real-world evidence can help inform current clinical practice, future trials, and is an important component of pharmacovigilance.

Keywords: cannabinoid; CBD; quality of life; tetrahydrocannabinol; THC

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Introduction

The frequency of prescriptions for cannabis-based medicinal products (CBMPs) has risen worldwide.[1–3] The United Kingdom has followed suit following legislative change in 2018.[4] It is therefore timely for physicians, policymakers, and patients to understand the potential therapeutic and adverse effects of CBMPs, particularly in light of the paucity of high-quality randomized controlled trials.[5–7] CBMPs are defined in the United Kingdom as "cannabis-based products for medicinal use in humans," which "contain cannabis, its resin, cannabinol, or a cannabinol derivative."[8]

The cannabis plant contains over 144 different phytocannabinoids, which act predominantly via endogenous cannabinoid system receptors.[6,9,10] Two phytocannabinoids, (−)-trans-Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), have been the focus of most cannabis-related research.[11] THC is a partial agonist of the G-protein coupled receptors—cannabinoid type 1 (CB1R) and type 2 (CB2R) receptors.[12] THC's agonism of CB1R, which is found in the cerebellum, hippocampus, and basal ganglia, results in downregulation of other neurotransmitters.[13,14] This mechanism is utilized therapeutically due to its role in emotion regulation and processing—important in psychological disease and chronic pain.[13,14] CBD's predominant effect is via indirect inhibition of fatty acid amide hydrolase, increasing the concentration of endocannabinoids present at synaptic junctions. However, it is thought to also modulate both the effects of THC, as a noncompetitive negative allosteric modulator of CB1R.[15–17]

A key factor in determining clinical efficacy is through examination of the effects on health-related quality of life (HRQoL). In the United Kingdom, results have been published from an interim analysis of the UK Medical Cannabis Registry (UKMCR) at 3 months, containing 129 patients with various conditions showing an improvement in HRQoL in addition to anxiety-specific and sleep specific outcomes.[18] A smaller analysis of patients from a separate UK-based registry, Project Twenty21, also showed an improvement in HRQoL across a similar period.[19]

It is not yet known what the associated effects are in respect to HRQoL and adverse outcomes in a UK-based population prescribed CBMPs for >3 months. Herein, the primary aim of this consecutive case series of UK patients was to analyze safety and the change in HRQoL outcomes for all patients enrolled in the UKMCR who were prescribed CBMPs. Supplementary aims included evaluation of dosage regimens.

Methods

This study details an uncontrolled case series of patients with any condition treated with CBMPs from the UKMCR. This observational study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[20] The NHS Health Research Authority and Research Ethics Committees advised that formal ethical approval was not required for this study. Written informed consent was completed by all patients. The registry was established in December 2019 to capture pseudonymized outcomes and adverse events of patients prescribed CBMPs in the United Kingdom and Channel Islands, the first of its kind in the United Kingdom.

The effects of prescribed CBMP products were studied in patients who attended Sapphire Medical Clinics. All CBMP products met Good Manufacturing Practice guidelines and were one of two possible formulations: dry plant or oil (isolate phytocannabinoids or full spectrum products containing cannabinoids, flavonoids, and terpenes). As per national guidance, a specialist in the respective condition prescribed each CBMP, following discussion with a multidisciplinary team.[21]

CBMPs were prescribed to patients with the conditions detailed in Figure 1. Those with chronic pain, which could not be defined by cancer pain, complex regional pain syndrome, Ehlers–Danlos syndrome, fibromyalgia, or neuropathic pain, were named "chronic pain of undefined etiology" for the purpose of the registry. Palliative care was defined using the definition previously given by the World Health Organization.[22]

Data collection

As previously described, the UKMCR is designed for remote data collection via an online web-based platform utilizing automated reminders.[18] Patients completed patient-reported outcome measures (PROMs) and adverse event questionnaires before treatment and at 1-, 3-, and 6-month follow-ups. If the questionnaires were incomplete at the end of each period, patients were contacted by a member of the Sapphire Medical Clinics team to complete outstanding information.

Patients were excluded from analysis if baseline PROMs were incomplete, or if enrolment was <1 month before data extraction.

Demographic data recorded at the initial assessment included age, sex, body mass index (kg/m^2), and occupation. Primary diagnosis in addition to comorbidities was also recorded. The Charlson Comorbidity Index

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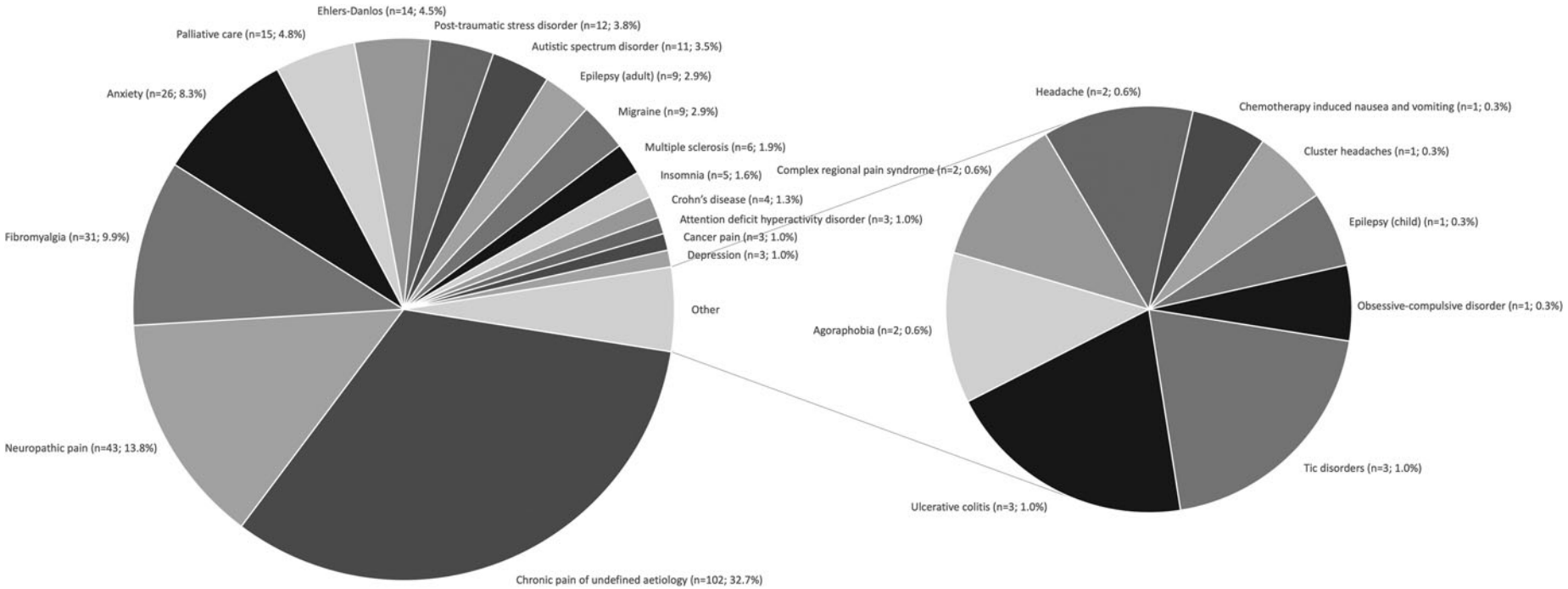


FIG. 1. The distribution of primary diagnoses ($n = 312$). For ease of reading, the figure can be viewed online.

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was calculated for each patient as it is the most ubiquitously used tool in comorbidity assessment in registry studies.[23,24] Alcohol, cannabis, and smoking consumption were also recorded at baseline. A novel metric of "cannabis gram years" was devised to calculate the amount of illicit cannabis consumed if a patient had history of use.[18]

The following information was recorded for each CBMP prescription at baseline and follow-up intervals: licensed producer, formulation, THC dose per 24 h (mg), CBD dose per 24 h (mg), other active ingredients, and their doses per day (mg), and strain (*Sativa*, *Indica*, or hybrid).

The PROMs collected for all patients were the Generalized Anxiety Disorder Scale (GAD-7), EQ-5D-5L, and Sleep Quality Scale (SQS). Most conditions also have condition-specific PROMs, although the results for these will be outlined in future condition-specific studies. The scoring and interpretation of each PROM has been previously outlined in previous analysis by our group.[18]

The incidence of adverse events was captured synchronously with the completion of PROMs or during routine clinician follow-up. The adverse event severity was recorded using the Common Terminology Criteria for Adverse Events v4.0.[25]

Statistical analysis

Demographic data were analyzed using descriptive statistics, using mean (±standard deviation [±SD]) or frequency (%) as appropriate. The Shapiro–Wilk test was used to test the distribution of all other data. Parametric data and nonparametric data are presented with mean (±SD) and median (interquartile range [IQR]) values, respectively. Differences in PROMs from baseline assessment at each time point were analyzed using paired *t*-test (parametric data) or the Wilcoxon rank sum test (nonparametric data). All statistical analyses were conducted using Statistical Package for Social Sciences (IBM Statistics version 27; SPSS Inc., New York, IL). Statistical significance was defined as p-value <0.050.

Results

Three hundred twelve individual patients were identified from the UKMCR at the time of data extraction who had completed a baseline PROM. The mean age of patients was 44.77±15.39. One hundred forty (44.9%) patients were female. The largest occupation category for patients was unemployed ($n=100$, 32.0%). Full demographic details are detailed in Table 1.

Figure 1 details the primary diagnosis for all patients. The most prevalent conditions were chronic pain of undefined etiology ($n=102$, 32.7%), neuropathic pain ($n=43$, 13.8%), fibromyalgia ($n=31$, 9.9%), and generalized anxiety disorder ($n=26$, 8.3%).

A large proportion of patients were current cannabis users before initiation of treatment ($n=133$, 42.6%). One hundred twelve (35.9%) patients were daily cannabis users (Table 2). The median daily cannabis consumption was 1.00 g/day [0.33–1.88 g]. The median oral morphine equivalent for prescribed medications was 0.00 mg [$n=208$; 0.00–24.00 mg] at baseline, 0.00 mg [$n=46$; 0.00–14.00 mg] at 1 month, 0.00 mg [$n=51$; 0.00–0.00 mg] at 3 months, and 0.00 mg [$n=25$; 0.00–0.00 mg] at 6 months.

CBMP dosing. Patients were prescribed a median of two CBMPs at baseline and at each follow-up interval. Most patients ($n=292$, 93.9%) were prescribed both THC and CBD on initiation of therapy (Table 3). The median CBD dose at baseline was 20.00 mg (10.00–22.00 mg), while the median THC dose was 3.00 mg (1.00–21.00 mg).

Patient-reported outcome measures. Seventy-eight patients did not have follow-up PROMs recorded.

Table 1. Demographic Details of Patients ($n=312$)

Demographic details	All conditions ($n=312$), *n* (%)
Sex	
Female	140 (44.9)
Male	172 (55.1)
Age (years), mean (±SD)	44.77±15.39
Body mass index (kg/m^2), mean (±SD)	25.99±7.23
Occupation	
Armed forces occupations	0 (0.0)
Clerical support workers	4 (1.3)
Craft and related trades workers	8 (2.6)
Elementary occupations	12 (3.8)
Managers	14 (4.5)
Plant and machine operators, and assemblers	5 (1.6)
Professional	61 (19.6)
Service and sales workers	10 (3.2)
Skilled agricultural, forestry and fishery workers	3 (1.0)
Technicians and associate professionals	17 (5.4)
Other occupations[a]	160 (51.3)
Unemployed	100 (32.0)
Retired	14 (4.4)
Student	5 (1.6)

[a]Other occupations—the occupations for six patients (1.9%) were not described to avoid indirect personal identification. The occupation was undefined for 35 patients (11.2%).

n, number of patients; SD, standard deviation.

Table 2. Smoking, Alcohol, and Cannabis Status of Patients ($n = 312$)

Smoking, alcohol, and cannabis status	*n* (%)/ median [IQR]
Smoking status	
Current smoker	71 (22.8)
Pack years	10.00 [5.00–20.00]
Ex-smoker	88 (28.2)
Pack years	5.00 [2.50–14.00]
Nonsmoker	146 (46.8)
Weekly alcohol consumption (units)	1.00 [0.00–5.50]
Cannabis status	
Current user	133 (42.6)
Lifetime quantity of cannabis consumption (gram years)	3.75 [1.00–10.00]
Current quantity of cannabis consumption (g/day)	1.00 [0.33–1.88]
Ex-user	45 (14.4)
Lifetime quantity of cannabis consumption (gram years)	1.00 [0.40–1.00]
Nonuser	127 (40.7)
Frequency of cannabis use for current users	
Every day	112 (35.9)
Every other day	6 (1.9)
1–2 times per week	5 (1.6)
>1 times per month	2 (0.6)
<1 times per month	2 (0.6)

IQR, interquartile range.

The reasons for loss to follow-up were not collected. The results show statistically significant improvement at each of the follow-up dates in matched analysis to baseline assessment, according to reported GAD-7, EQ-5D Index value, EQ Visual Analog Scale (EQ-VAS), and SQS outcomes ($p < 0.050$; Table 4). There were also statistically significant improvements, as determined by EQ-5D-5L Self-Care subscale at 1 month, EQ-5D-5L Mobility subscale at 1 and 3 months, and the EQ-5D-5L Usual Activities, EQ-5D-5L Pain and Discomfort, and EQ-5D-5L Anxiety and Depression subscales at the 1-, 3-, and 6-month follow-ups ($p < 0.050$).

Difference in outcome measures based on prior cannabis use. At baseline, there was a significantly larger EQ-5D-5L pain and discomfort score for the cannabis-naive group analyzed at the 1- and 6-month follow-ups, while there was a significantly larger EQ-5D-5L Index score at the 3-month follow-up and EQ-VAS score at the 1-month follow-up for those who were consuming cannabis at baseline. On analysis of change in scores from baseline, the cannabis consuming group had a larger change in the GAD-7 score at the 1-month (median, −1.00 vs. 0.00, $p = 0.002$) and the 6-month follow-up (median, −5.00 vs. 0.00, $p = 0.035$), EQ-5D-5L anxiety and depression at the 1-month follow-up (median, 0.00 vs. 0.00, $p < 0.001$) and the 3-month follow-up (median, −1.00 vs. 0.00, $p = 0.043$), as well as the EQ-VAS at the 6-month follow-up (median, 12.50 vs. 2.50, $p = 0.012$). Full analysis of outcomes according to cannabis consumption at baseline is detailed in Supplementary Table S1.

Adverse events. Ninety-four (30.1%) adverse events were reported (Table 5). The most commonly reported adverse events were nausea ($n = 12$, 3.8%), dry mouth ($n = 10$, 3.2%), dizziness ($n = 7$, 2.2%), and somnolence ($n = 7$, 2.2%). The most common severity of adverse events was mild ($n = 46$, 14.7%), while only 1 event, being insomnia, was deemed as disabling. No adverse events were deemed life-threatening. The most reported "other" adverse events were diarrhea ($n = 3$, 1.0%), depression ($n = 2$, 0.6%), and anxiety ($n = 2$, 0.6%). Patients who were consuming cannabis at baseline reported 26 (8.3%) adverse events, while prior cannabis users and cannabis-naive patients reported 18 (5.8%) and 47 (15.1%), respectively. Three (1.0%) patients who experienced an adverse event did not have a baseline cannabis status recorded.

Discussion

This study presents an updated analysis from the UKMCR of patient outcomes for those prescribed CBMPs across a range of indications. The results demonstrate that CBMPs may be associated with an

Table 3. Cannabis-Based Medicinal Product Dosing for Patients

Medication status	Baseline	1 Month	3 Month	6 Month
Number of patients recorded with a prescription	311	101	50	25
Median [IQR] CBD dose (mg)	20.00 [10.00–22.00]	20.00 [5.00–37.00]	20.00 [6.50–32.25]	10.00 [2.50–35.00]
Median [IQR] THC dose (mg)	3.00 [1.00–21.00]	12.00 [6.50–86.50]	13.00 [6.00–72.50]	16.00 [4.50–38.00]
Number of patients prescribed both THC and CBD (%)	292 (93.9)	85 (84.2)	40 (80.0)	19 (76.0)
Number of patients prescribed THC products only (%)	10 (3.2)	14 (13.9)	8 (16.0)	5 (20.0)
Number of patients prescribed CBD products only (%)	9 (2.9)	2 (2.0)	2 (4.0)	1 (4.0)

CBD, cannabidiol; THC, (−)-trans-Δ^9-tetrahydrocannabinol.

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Table 4. Paired Baseline and Follow-Up Patient-Reported Outcome Measures

Patient-reported outcome measure	Follow-up (months)	*n*	Scores at baseline	Scores at follow-up	*p*
GAD-7	1	234	6.00 [2.00–13.00]	5.00 [1.00–9.00]	< 0.001
	3	106	6.50 [3.00–14.25]	4.00 [1.00–8.00]	< 0.001
	6	68	7.00 [3.00–15.00]	4.50 [2.00–9.00]	< 0.001
EQ-5D-5L mobility	1	221	2.00 [1.00–3.00]	2.00 [1.00–3.00]	< 0.001
	3	103	2.00 [1.00–4.00]	2.00 [1.00–3.00]	0.035
	6	63	3.00 [1.00–4.00]	3.00 [1.00–3.00]	0.301
EQ-5D-5L self care	1	221	1.0 [1.00–3.00]	1.00 [1.00–2.50]	0.011
	3	103	1.00 [1.00–3.00]	1.00 [1.00–3.00]	0.279
	6	63	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.722
EQ-5D-5L usual activities	1	221	3.00 [2.00–4.00]	2.00 [1.00–3.00]	< 0.001
	3	103	3.00 [2.00–4.00]	2.00 [2.00–3.00]	< 0.001
	6	63	3.00 [2.00–4.00]	3.00 [2.00–3.00]	0.009
EQ-5D-5L pain and discomfort	1	221	3.00 [2.00–4.00]	3.00 [2.00–3.00]	< 0.001
	3	103	3.00 [3.00–4.00]	3.00 [2.00–3.00]	< 0.001
	6	63	3.00 [3.00–4.00]	3.00 [2.00–4.00]	0.001
EQ-5D-5L anxiety and depression	1	220	2.00 [1.00–3.00]	2.00 [1.00–3.00]	< 0.001
	3	103	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.004
	6	63	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.027
EQ-VAS	1	222	50.00 [34.75–71.00]	60.00 [41.00–75.00]	< 0.001
	3	104	50.00 [30.25–67.75]	64.00 [42.75–80.00]	< 0.001
	6	62	50.00 [30.00–65.00]	56.00 [38.75–71.25]	0.012
EQ-5D-5L index value	1	220	0.54 [0.24–0.72]	0.63 [0.38–0.74]	< 0.001
	3	103	0.48 [0.21–0.68]	0.62 [0.34–0.77]	< 0.001
	6	63	0.39 [0.11–0.65]	0.54 [0.27–0.68]	0.001
SQS	1	202	5.00 [3.00–7.00]	6.00 [4.00–8.00]	< 0.001
	3	89	4.00 [2.00–6.00]	6.00 [4.00–7.00]	< 0.001
	6	51	4.00 [2.00–6.00]	6.00 [4.00–8.00]	< 0.001

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

Table 5. Reported Adverse Events by Patients (*n* = 312)

	Severity of adverse events					
Adverse events	Mild	Moderate	Severe	Life-threatening/disabling	Not recorded	Total (%)
Abdominal pain	2	0	0	0	0	2 (0.6)
Amnesia	0	0	1	0	0	1 (0.3)
Anorexia	0	1	0	0	0	1 (0.3)
Cognitive disturbance	1	1	1	0	0	3 (1.0)
Concentration impairment	0	2	0	0	0	2 (0.6)
Constipation	2	1	0	0	0	3 (1.0)
Coordination/balance/speech impairment	1	0	0	0	0	1 (0.3)
Dizziness	3	2	1	0	1	7 (2.2)
Dry mouth	8	1	1	0	0	10 (3.2)
Dysgeusia	0	1	0	0	0	1 (0.3)
Dyspepsia	1	1	0	0	0	2 (0.6)
Fall	0	1	0	0	0	1 (0.3)
Fatigue	2	2	1	0	0	5 (1.6)
Headache	2	3	0	0	0	5 (1.6)
Increased seizures	0	1	0	0	0	1 (0.3)
Insomnia	2	0	0	1	0	3 (1.0)
Lethargy	1	1	1	0	1	4 (1.3)
Memory impairment	0	2	0	0	0	2 (0.6)
Muscular weakness	0	0	0	0	1	1 (0.3)
Nausea	11	1	0	0	0	12 (3.8)
Other	8	3	2	0	1	14 (4.5)
Somnolence	0	7	0	0	0	7 (2.2)
Spasticity	0	1	1	0	0	2 (0.6)
Tremor	0	0	1	0	0	1 (0.3)
Vertigo	1	0	0	0	0	1 (0.3)
Vomiting	1	1	0	0	0	2 (0.6)
Total (%)	46 (14.7)	33 (10.6)	10 (3.2)	1 (0.3)	4 (1.3)	94 (30.1)

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acceptable adverse event profile and improved HRQoL outcomes in chronic ill-health, as measured by improvements up to 6 months compared to baseline scores in the GAD-7, EQ-5D-5L Index Value, EQ-VAS, and SQS outcome measures. Adverse event incidence was 30.1%, with nausea being the most frequent (3.8%).

There was an improvement in general HRQoL in this patient population following initiation of therapy, which was sustained at 6 months. This builds on a previous interim analysis from the UKMCR, which demonstrated similar outcomes at 3 months.[18] A study of patients in Canada receiving CBMPs registered with MedReleaf®, showed similar improvements as demonstrated by both the EQ-5D-5L Index Value and EQ-VAS in patients with chronic pain, anxiety, and posttraumatic stress disorder at 6-week follow-up.[26] However, this effect was not seen in those with rheumatic disorders or insomnia.[26] The patients in the present study had lower initial EQ-5D-5L index values indicating a lower initial HRQoL. This may be the reason why changes in HRQoL were seen, as a symptom-specific analysis from patients treated at a clinic in Canada found that only those with moderate and severe symptoms had a positive response to therapy.[27]

At present in the United Kingdom, CBMPs can only be prescribed in those with refractory symptoms despite best initial medical treatment.[28] If CBMPs are initiated in patients with less severe symptoms in the future, it will be important to capture any divergence of response.

Further studies have also shown an association between initiation of CBMP therapy and improvements in HRQoL. An analysis from patients with noncancer pain, mental health and neurological diagnoses, and cancer symptoms from New Zealand, who were treated with CBD oil (Tilray CBD100), found an improvement in self-reported HRQoL measured using the EQ-VAS.[29] A study which performed a focused evaluation found a subjective improvement in HRQoL using a Likert scale in an elderly population treated with medical cannabis.[30] Despite showing similar results to the present study, the treatment was predominantly containing high THC strains, compared to the median initiating THC dose of patients on the UKMCR being 3.0 mg.[30]

Modest changes were identified in anxiety scores using the EQ-5D-5L anxiety and depression subscale and GAD-7. This builds upon preclinical evidence supporting the role of the endocannabinoid system in the experience of anxiety.[7,31] Previous studies have also found that CBMPs induced a reduction in anxiety symptoms in the setting of provoked social anxiety.[32,33] There is evolving evidence to suggest the impact of improved anxiety symptoms in patients treated for other conditions as presented in the present study.

A small randomized controlled trial of smoked cannabis in patients with neuropathic pain found that increased concentrations of THC resulted in improved subjective anxiety as measured according to the anxiety and depression EQ-5D-5L subscale.[34] In patients from the UKMCR analysis, there were greater changes in GAD-7 scores at 3- and 6-month time periods. This may be secondary to increasing THC doses as the prescription is titrated to clinical response. A recent case series of 37 patients with chronic pain also found improvements in anxiety symptoms at 3 and 6 months.[35]

Moreover, improvements were found in self-reported sleep quality. While it has yet to be fully elucidated, the endocannabinoid system has been demonstrated to have a regulatory role in the sleep-wake cycle, with cannabinoid receptor agonists demonstrated to be hypnogenic.[35] A recent randomized clinical trial of a THC-dominant CBMP (ZTL-101) for the treatment of chronic insomnia over a 2-week period demonstrated improvement in insomnia symptoms and sleep-quality.[36] However, more long-term evidence on treatment outcomes for insomnia with CBMPs is awaited.

This study also sought to identify the differences in outcomes between cannabis naive and cannabis consumers at baseline before starting treatment. Interestingly, those who were already consuming cannabis had significant improvements in GAD-7, EQ-5D-5L anxiety and depression subscale, and the EQ-VAS at varying timescales. This contrasts with previous data from the UKMCR, which showed greater improvements in pain-specific PROMs in those who were previously naive to cannabis prescribed a specific group of oil-based CBMPs.[37] The reason for this discrepancy could represent the breadth of CBMPs studied within the present analysis, with previous cannabis consumers benefiting from more rapid titration of dose and initiation of treatment with flos alongside oils. Moreover, those who were previously consuming cannabis could be a self-selecting group of patients who respond to cannabis-based therapy but benefitted from improved, consistent quality and expert medical oversight.

This study identified an adverse event incidence of 30.1%. This represents an increased incidence compared to that reported in a previous interim analysis

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of the UKMCR (24.03%).[18] This may be representative of increased length of prescribing allowing for greater accumulation of adverse events over time, highlighting the importance of a continuous pharmacovigilance strategy to best inform clinicians and patients regarding the potential risks of prescribing CBMPs. The general adverse events incidence is similar to that reported by previous studies. For example, a postmarketing surveillance survey of patients prescribed nabiximols found an adverse event incidence of 40.9%.[38] This compares favorably to the adverse event incidence of opioids. For example, a systematic review found an adverse event incidence of 112% across the seven most commonly reported adverse events with a maximum follow-up of 8 weeks.[39]

There are notable limitations to this study. It is unable to determine causality between CBMP therapy and the observed effects because of its observational nature and lack of a control group or incorporation of external factors not captured by the UKMCR. It is notable that there are fewer patients at each follow-up and this change may introduce selection bias secondary to cessation of treatment due to lack of clinical efficacy. It is not possible to ascertain from the UKMCR if any decision to stop treatment was due to cost, clinical ineffectiveness, or inability to tolerate side effects.

Moreover, this study is affected by inherent selection bias. The included patients were all treated from one clinic, which is only accessible through self-funding. However, the clinic does cover the entire United Kingdom and Channel Islands, giving geographical variation. In addition, although the treatment is self-funded, a significant proportion of patients are unemployed (32.0%). There is also significant heterogeneity within the studied population regarding underlying medical conditions and prescribed medication, which is representative of real-world prescribing. A significant limitation is the number of patients who have missing baseline data and/or follow-up data. This must be accounted for when making inferences from the outcomes. Most notably, missing data prohibit the utilization of a repeated measures analysis of variance, which may result in lower *p*-values.

Finally, the observed outcomes may be exaggerated by the phenomenon "regression to the mean" whereby patients seek treatment while their symptoms are at their most severe and that their symptoms may have improved over repeat measurement without treatment. In addition, although patients are counseled about the consumption of cannabis recreationally alongside medicinal use, the registry is unable to assess whether this occurs and any subsequent effect on clinical outcomes or dosage considerations.

On the contrary, this presents both the largest analysis and the longest follow-up period of UK patients treated with CBMPs to date. This may represent an important contribution to pharmacovigilance and assessment of observed adverse events as prescribing continues to increase in the United Kingdom, and globally. As the UKMCR continues to enroll patients, it will be able to assess further long-term prescribing outcomes, with a focus on individual conditions and medications with stratification according to clinicopathologic criteria, including previous cannabis consumption. Despite this, good quality randomized controlled trials are still required in this field.

Conclusion

The results from this study suggest that treatment with CBMPs was associated with an acceptable safety profile and improved HRQoL outcomes across a broad spectrum of chronic conditions at 1-, 3-, and 6-month follow-ups compared to baseline before treatment. The incidence of adverse events was 30.1%, with 84.0% of these being mild or moderate, suggesting favorable tolerability relative to medications, such as opiates, that are prescribed more frequently. Given the numerous limitations of this open-label case series, these results must be interpreted with caution. In future, robust randomized controlled trials, built upon this case series, will be paramount for further exploration of CBMP outcomes.

Authors' Contributions

M.E., S.E., and M.H.S. conceived the study. M.E., S.E., M.H., M.K., D.N., O.S., K.L., R.A., A.U., M.S., S.B., J.H., S.A.K., M.W.W., M.P., and J.J.R. collected data. M.E., S.E., and M.H.S. analyzed and interpreted the data. S.B., J.H., S.A.K., M.W.W., M.P., and J.R.R. provided guidance on the study design and analysis. M.E., S.E., and M.H.S. drafted the article. All the authors read, edited, and approved the final version of the article. All authors had full access to all of the data in the study.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The raw data belonged to the

present study cannot be made publicly available because the disclosure of personal data was not included in the research protocol of the present study.

Ethics Approval

The NHS Health Research Authority and Research Ethics Committees advised that formal ethical approval was not required for this study. Written informed consent was completed by all patients.

Author Disclosure Statement

M.E., M.H., M.K., D.N., K.L., and R.A. are medical students at Imperial College London. M.E., S.E., M.H., M.K., D.N., O.S., K.L., R.A., C.H., R.C., A.U., M.S., S.B., J.H., S.A.K., M.W.W., M.P., and J.J.R. have no shareholdings in pharmaceutical companies.

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M.H.S. is a consultant hepatopancreatobiliary surgeon, a director, and a shareholder at Sapphire Medical Clinics and a consultant at Imperial College NHS Trust, London. He is a senior clinical lecturer at Imperial College London. He is the research director at EMMAC Life Sciences.

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Supplementary Material

Supplementary Table S1

References

1. Aguilar S, Gutiérrez V, Sánchez L, Nougier M. Medicinal cannabis policies and practices around the world. International Drug Policy Consortium. 2018. Available at https://idpc.net/publications/2018/04/medicinal-cannabis-policies-and-practices-around-the-world (Accessed April 17, 2021).
2. Freeman TP, Hindocha C, Green SF, et al. Medicinal use of cannabis based products and cannabinoids. BMJ. 2019;365:l1141.
3. European Monitoring Centre for Drugs and Drug Addiction. Medical use of cannabis and cannabinoids: questions and answers for policymaking. 2018. Available at https://www.emcdda.europa.eu/publications/rapid-communications/medical-use-of-cannabis-and-cannabinoids-questions-and-answers-for-policymaking_en (Accessed April 17, 2021).
4. UK Government. The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018. Available at https://www.legislation.gov.uk/uksi/2018/1055/made (Accessed April 17, 2021).
5. Mücke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018; 3:CD012182.
6. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313:2456–2473.
7. Sarris J, Sinclair J, Karamacoska D, et al. Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. BMC Psychiatry. 2020; 20:24.
8. UK Government. Rescheduling of cannabis-based products for medicinal use in humans. 2018. Available at https://www.gov.uk/government/

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publications/circular-0182018-rescheduling-of-cannabis-based-products-for-medicinal-use-in-humans/rescheduling-of-cannabis-based-products-for-medicinal-use-in-humans-accessible-version (Accessed April 17, 2021).
9. Baron EP. Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it's been…. J Headache and Face Pain. 2015;55:885–916.
10. Hanuš LO, Meyer SM, Muñoz E, et al. Phytocannabinoids: a unified critical inventory. Nat Prod Rep. 2016;33:1357–1392.
11. Elsaid S, Kloiber S, Le Foll B. Effects of cannabidiol (CBD) in neuropsychiatric disorders: A review of pre-clinical and clinical findings. Progr Mol Biol Transl Sci. 2019;167:25–75.
12. Klumpers LE, Thacker DL. A brief background on cannabis: from plant to medical indications. J AOAC Int. 2019;102:412–420.
13. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci. 2018;19:833.
14. Ebbert JO, Scharf EL, Hurt RT. Medical cannabis. Mayo Clin Proceed. 2018; 93:1842–1847.
15. Englund A, Morrison PD, Nottage J, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol. 2013;27:19–27.
16. Dalton WS, Martz R, Lemberger L, et al. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. Clin Pharmacol Ther. 1976;19:300–309.
17. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 2010;35:764–774.
18. Erridge S, Salazar O, Kawka M, et al. An initial analysis of the UK Medical Cannabis Registry: outcomes analysis of first 129 patients. Neuropsychopharmacol Rep. 2021;41:362–370.
19. Sakal C, Lynskey M, Schlag AK, et al. Developing a real-world evidence base for prescribed cannabis in the United Kingdom: preliminary findings from Project Twenty21. Psychopharmacology (Berl). 2021.
20. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344–349.
21. Medicines and Healthcare products Regulatory Agency. The supply of unlicensed cannabis-based products for medicinal use in humans. 2020. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/869284/Cannabis_Guidance__unlicensed_CBPMs__updated_2020.pdf Accessed June 1, 2021.
22. World Health Organization. Integrating palliative care and symptom relief into primary health care: a WHO guide for planners, implementers and managers. 2018. Available at: https://apps.who.int/iris/handle/10665/274559 Accessed June 1, 2021.
23. Brusselaers N, Lagergren J. The Charlson Comorbidity Index in registry-based research: which version to use? Methods Inf Med. 2017;56:401–406.
24. Quan H, Li B, Couris CM, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173:676–682.
25. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003;13:176–181.
26. Cahill SP, Lunn SE, Diaz P, et al. Evaluation of patient reported safety and efficacy of cannabis from a survey of medical cannabis patients in Canada. Front Public Health. 2021;9:626853.
27. Rapin L, Gamaoun R, El Hage C, et al. Cannabidiol use and effectiveness: real-world evidence from a Canadian medical cannabis clinic. J Cannabis Res. 2021;3:19.
28. Case P. The NICE guideline on medicinal cannabis: keeping Pandora's box shut tight? Med Law Rev. 2020;28:401–411.
29. Gulbransen G, Xu W, Arroll B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. BJGP Open. 2020;4: bjgpopen20X101010.
30. Abuhasira R, Schleider LBL, Mechoulam R, et al. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. Eur J Intern Med. 2018;49:44–50.
31. Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry. 2019;6:995–1010.
32. Crippa JAS, Nogueira Derenusson G, Borduqui Ferrari T, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol. 2011;25:121–130.
33. Bergamaschi MM, Queiroz RHC, Chagas MHN, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-nave social phobia patients. Neuropsychopharmacology. 2011;36:1219–1226.
34. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. C Can Med Assoc J. 2010;182: E694.
35. Gruber SA, Smith RT, Dahlgren MK, et al. No pain, all gain? Interim analyses from a longitudinal, observational study examining the impact of medical cannabis treatment on chronic pain and related symptoms. Exp Clin Psychopharmacol. 2021;29:147–156.
36. Walsh JH, Maddison KJ, Rankin T, et al. Treating insomnia symptoms with medicinal cannabis: a randomized, cross-over trial of the efficacy of a cannabinoid medicine compared with placebo. Sleep. 2021;44:zsab149.
37. Kawka M, Erridge S, Holvey C, et al. 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. J Clin Pharmacol. 2021;61:1545–1554.
38. Etges T, Karolia K, Grint T, et al. An observational postmarketing safety registry of patients in the UK, Germany, and Switzerland who have been prescribed Sativex ® (THC:CBD, nabiximols) oromucosal spray. Ther Clin Risk Manag. 2016;12:1667–1675.
39. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Res Ther. 2005;7:R1046–R1051.

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Abbreviations Used

CB1R = cannabinoid type 1
CB2R = cannabinoid type 2
CBD = cannabidiol
CBMPs = cannabis-based medicinal products
EQ-VAS = EQ Visual Analog Scale
GAD-7 = Generalized Anxiety Disorder Scale
HRQoL = health-related quality of life
IQR = interquartile range
n = number of patients
NIHR = National Institute for Health Research
PROMs = patient-reported outcome measures
SD = standard deviation
SQS = Sleep Quality Scale
THC = (−)-trans-Δ^9-tetrahydrocannabinol
UKMCR = UK Medical Cannabis Registry

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