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ORIGINAL RESEARCH

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An observational study of safety and clinical outcome measures across patient groups in the United Kingdom Medical Cannabis Registry

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ABSTRACT

Background: There is a paucity of high-quality data on patient outcomes and safety after initiating treatment with cannabis-based medicinal products (CBMPs). The aim of this study was to assess the clinical outcomes and safety of CBMPs by analyzing patient-reported outcome measures and adverse events across a broad spectrum of chronic conditions.

Research design and methods: This study analyzed patients enrolled in the UK Medical Cannabis Registry. Participants completed the EQ-5D-5L to assess health-related quality of life, Generalized Anxiety Disorder-7 (GAD-7) questionnaire to measure anxiety severity, and the Single-item Sleep Quality Scale (SQS) to rate sleep quality at baseline and follow-up after 1, 3, 6, and 12 months.

Results: A total of 2833 participants met inclusion criteria. The EQ-5D-5L index value, GAD-7, and SQS all improved at each follow-up ($p < 0.001$). There was no difference in EQ-5D-5L index values between former or current illicit cannabis consumers and naïve patients ($p > 0.050$). Adverse events were reported by 474 (16.73%) participants.

Conclusions: This study suggests that CBMPs are associated with an improvement in health-related quality of life in UK patients with chronic diseases. Treatment was tolerated well by most participants, but adverse events were more common in female and cannabis-naïve patients.

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Cannabis-based medicinal products; CBMPs; medical cannabis; cannabidiol; tetrahydrocannabi

1. Introduction

Since 2018, cannabis-based medicinal products (CBMPs) can be prescribed in the United Kingdom by specialist doctors for chronic illnesses where there has been insufficient response to licensed medications [1]. However, the National Institute for Health and Care Excellence currently only recommends CBMPs for intractable chemotherapy-induced nausea and vomiting, spasticity in adults with multiple sclerosis, and severe treatment-resistant epilepsy in Lennox-Gastaut and Dravet syndromes [1,2]. The reason for these narrow recommendations is that current evidence is limited and of low quality [2]. In particular, there is a paucity of randomized controlled trials, due to the challenges of investigating CBMPs in this setting [3]. The United Kingdom Medical Cannabis Registry (UKMCR) was designed to capture observational real-world data on CBMPs, and recent guidance by Medicines & Healthcare products Regulatory Agency has suggested that these datasets are valued in accelerating market authorization, in addition to randomized controlled trials [4–6]. The potential indications for CBMP therapy include a wide variety of conditions and diagnoses, many of which cause reduced health-related quality of life (HRQoL) [7]. Chronic diseases are also tightly linked to psychological and socio-economic burden, further emphasizing the need to address these conditions [8–10].

The most studied exogenous cannabinoids are (–)-trans-Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), both being recognized for a wide variety of pharmacological effects. Δ^9-THC, the psychotropic component of cannabis, mainly mediates its effects through partial agonism of cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) [11]. While CBD has low affinity for CB1 and CB2, studies suggest that it has a diverse range of pharmacological targets that are responsible for its resultant effects [12].

The suggested therapeutic properties of CBMPs include analgesic, anti-inflammatory, anti-emetic, anti-spasticity, anti-psychotic, anticonvulsant, anxiolytic, appetite-stimulating, and neuroprotective abilities [11,13–16]. This multitude of effects has been suggested as a mechanism for improvement of HRQoL with respect to chronic disease. An observational study of patients with chronic pain prescribed CBMPs, showed that, after 12 months, improvements were seen in pain intensity, pain disability, anxiety, and depression. However, the greatest improvement was seen between baseline and 3

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months [13]. In addition, earlier publications from the UKMCR, analyzing patient reported outcome measures (PROMs) after 1, 3, and 6 months, suggest that CBMPs may be associated with improvements in HRQoL for patients with various chronic conditions [4,5]. However, a 2017 systematic review investigating the relationship between medical cannabis and HRQoL was inconclusive, citing significant heterogeneity of the current literature [17].

1.1. Aim

The primary aim of this study is to investigate the clinical outcomes of CBMPs by analyzing HRQoL data from the UKMCR across all conditions. The secondary aim is to assess the incidence of adverse events in patients prescribed CBMPs.

2. Methods

This is an uncontrolled observational study of patients prospectively enrolled in the UKMCR. Patients were enrolled if they were prescribed CBMPs for any condition. In accordance with guidance from the Health Research Authority, no formal ethical approval was necessary for this study (Appendix A & B). All patients provided informed, written consent. Since conception in December 2019 by Sapphire Medical Clinics, the UKMCR has collected pseudonymized data of safety and efficacy in patients prescribed CBMPs in the United Kingdom and Channel Islands. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed during reporting of this study [18].

All prescribed CBMPs adhered to the criteria for Good Manufacturing Practice [6]. Patients were prescribed individual formulations (oil, capsules, lozenges, dried flower) according to clinical requirements in joint decision-making between clinician and patients. These could contain either isolated cannabinoids or be a broad/full spectrum extract. For broad/full spectrum extracts and dry flower, the chemovars were either *Cannabis sativa, Cannabis indica*, or a hybrid species. In accordance with the Medicines & Healthcare products Regulatory Agency, CBMPs were only initiated by specialist doctors [19].

Primary indication for treatment was identified and recorded by the responsible clinician, and where applicable, secondary, and tertiary indications were also reported.

2.1. Data collection

Patients attending Sapphire Medical Clinics between 1 December 2019 and 15 February 2022 were enrolled in the UKMCR and studied prospectively. The follow-up consisted of PROMs and adverse event questionnaires collected at baseline, and then at 1 month, 3 months, 6 months, and every 6 months thereafter. If enrollment was <1 month before data extraction, or baseline PROMs were incomplete, patients were excluded from the present analysis.

Relevant demographic and clinical information were added by medical staff at baseline. This included gender, age, occupation, and body mass index (BMI). Comorbidities were also recorded, including endocrine dysfunction, hypertension, anxiety, depression, epilepsy, and arthritis. The Charlson comorbidity index, a commonly used method to measure burden of disease and predicting mortality in data repositories, was also calculated [20].

Alcohol and tobacco status were extracted as units per week and pack years, respectively. Tobacco pack years are calculated by multiplying the length of tobacco consumption (years) with daily tobacco consumption (number of packs of cigarettes). Prior cannabis status, for either recreational or medical purposes, was described as 'never used,' 'current,' or 'ex-user,' and gram years were calculated to quantify the lifetime cannabis exposure. Gram years are calculated as the reported mean cannabis consumption in grams per day, multiplied by years of use, as previously described by our group [5]. This metric was developed to help quantify lifetime exposure and its potential effect on biological tolerance to cannabinoids, which has previously been described as a product of quantity of cannabis consumed and length of consumption [21,22].

Medications at baseline, including initial doses, were recorded. Changes in medications during treatment were recorded by patients and/or clinicians. Prescribed opioid medications were converted to oral morphine equivalents (OME) in accordance with recognized conversion factors stated by the British National Formulary [23].

Details of the prescribed CBMP – producer, formulation, method of administration, dose and concentration of Δ^9-THC, dose and concentration of CBD, and strain of plant – were recorded throughout treatment.

Quality-of-life PROMs included EQ-5D-5L, Single-Item Sleep Quality Scale (SQS), Generalized Anxiety Disorder Assessment (GAD-7), and Patient Global Impression of Change (PGIC) for all patients [24–27]. Patients completed PROMs electronically and were prompted to complete these utilizing electronic reminders.

The EQ-5D-5L is a validated questionnaire comprised a descriptive system that assesses HRQoL across five domains: Mobility, Self-care, Usual activities, Pain/Discomfort, and Anxiety/Depression. Every domain has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Each level corresponds to a number between 1 and 5, wherein no problems = 1, and extreme problems = 5. The patient is asked to choose the level best describing their state in each dimension. These values then combine to form one of 3125 health states [25]. A country-specific EQ-5D-5L index value can then be calculated from the combined health state, whereby 1 is equivalent to full health, while values below 0 represent health states where the health-related quality of life is deemed to be worse than that of deceased individuals [28].

The SQS is a validated single-item numerical rating scale of sleep quality over the past 7 days on a scale from 0 to 10, in which 0 implies 'terrible' and 10 indicates 'excellent' [25].

The GAD-7 is a validated questionnaire consisting of seven items, each representing a core symptom of generalized anxiety disorder. Patients respond according to how bothered they have been by each symptom during the past 14 days,

choosing one of the following options: 'not at all,' 'several days,' 'more than half days,' or 'nearly every day.' Every option scores accordingly as 0, 1, 2, or 3. Thus, a total score from 0 to 21 is generated. The cutoffs ≥5, ≥10, and ≥15 represent mild, moderate, and severe anxiety levels, respectively [26].

The PGIC is a validated 7-point scale for patients to rate their perceived health status compared to baseline, in which 0 points indicates 'very much worse' and 7 points signifies 'very much improved' [27].

Participants were prompted to report adverse events (AEs) prior to completing PROMs or during follow-up with a clinician. The AE was then classified and graded using the Common Terminology Criteria for Adverse Events version 4.0 [29]. All AEs were assessed independently of causality.

2.2. Statistical analysis

Extracted data were analyzed in IBM Statistical Package for Social Sciences (version: 28.0.0.0 SPSS Inc., [New York, IL], USA). Descriptive statistics were used to study the patient demographics. The Kolmogorov–Smirnov test was used to assess the distribution of the data. Results were presented as mean (± standard deviation [SD]) or median (interquartile range [IQR]). PROMs from baseline and follow-ups were compared using a paired t-test, considering the central limit theorem. Effect size was displayed as a Cohen's d value with respective 95% confidence interval values. These values were used to determine if effect size was small (d ≥ 0.2), medium (d ≥ 0.5), or large (d ≥ 0.8) [30]. To adjust for family-wise type I error, a Bonferroni adjustment was performed to correct p-values for multiple comparisons. A one-way ANOVA was performed to compare the change in EQ-5D-5L index value at each time point according to baseline cannabis exposure status. A logistic regression model was used to calculate odds ratios (ORs) and associated 95% confidence intervals (95% CI) for covariates to determine their prognostic value for experiencing an improvement in EQ-5D-5L index value and adverse events. The covariates were incorporated into a multivariate model to control for additional factors. Statistical significance was set to alpha <0.050.

3. Results

There were 3546 patients enrolled on UKMCR on 15th of February 2022. From these, 443 were excluded for not having completed PROMs at baseline and another 270 for treatment duration of less than 1 month. The remaining 2833 patients were included in this analysis, of which 1219 (43.03%) were female and 1613 (56.94%) were male. The mean age was 42.24 ± 14.32 years, and the mean BMI was 27.27 ± 7.10 kg/m^2. Supplementary Table 1 outlines the occupations of participants in full. There were 2314 patients who had completed PROMs at 1 month, followed by 1598 at 3 months, 953 at 6 months, and 208 at 12 months. The mean follow-up was 226.24 ± 131.59 days.

The indication for treatment is outlined in Table 1. In total, there were 31 different diagnoses recorded. A secondary indication was reported in 1116 (39.39%) participants, of which 420 (14.82%) recorded a tertiary diagnosis as well. The median Charlson comorbidity index score was 0.00 (IQR 0.00–5.00).

Table 1. Primary, secondary, and tertiary indication for cannabis-based medicinal products.

Diagnosis	Primary n (%)	Secondary n (%)	Tertiary n (%)
Chronic non-cancer pain	914 (32.26%)	164 (5.79%)	34 (1.20%)
Anxiety	318 (11.22%)	294 (10.38%)	62 (2.19%)
Fibromyalgia	306 (10.80%)	106 (3.74%)	16 (0.56%)
Neuropathic pain	237 (8.37%)	85 (3.00%)	14 (0.49%)
Posttraumatic stress disorder	162 (5.72%)	45 (1.59%)	22 (0.78%)
Depression	129 (4.55%)	128 (4.50%)	102 (3.60%)
Migraine	82 (2.89%)	38 (1.34%)	14 (0.49%)
Ehlers-Danlos	81 (2.86%)	41 (1.45%)	14 (0.49%)
Autistic spectrum disorder	74 (2.61%)	26 (0.92%)	18 (0.64%)
Attention deficit hyperactivity disorder	72 (2.54%)	26 (1.02%)	17 (0.60%)
Multiple sclerosis	71 (2.51%)	4 (0.14%)	0 (0.00%)
Palliative care	70 (2.47%)	1 (0.04%)	0 (0.00%)
Insomnia	61 (2.15%)	61 (2.15%)	70 (2.47%)
Crohn's disease	51 (1.80%)	9 (0.32%)	2 (0.07%)
Epilepsy (adult)	40 (1.41%)	8 (0.28%)	3 (0.11%)
Epilepsy (child)	29 (1.02%)	0 (0.00%)	0 (0.00%)
Ulcerative colitis	25 (0.88%)	1 (0.04%)	2 (0.07%)
Cancer pain	15 (0.53%)	9 (0.32%)	0 (0.00%)
Parkinson's	15 (0.53%)	3 (0.11%)	0 (0.00%)
Rare and challenging skin condition	15 (0.53%)	0 (0.00%)	0 (0.00%)
Complex regional pain syndrome	12 (0.42%)	4 (0.14%)	3 (0.11%)
Tourette's syndrome	11 (0.39%)	4 (0.14%)	0 (0.00%)
Cluster headaches	9 (0.32%)	4 (0.14%)	1 (0.04%)
Obsessive-compulsive disorder	8 (0.28%)	12 (0.42%)	5 (0.18%)
Chemotherapy induced nausea and vomiting	7 (0.25%)	2 (0.07%)	1 (0.04%)
Headache	6 (0.21%)	12 (0.42%)	6 (0.21%)
Trigeminal neuralgia	6 (0.21%)	2 (0.07%)	0 (0.00%)
Eating disorder	3 (0.11%)	4 (0.14%)	8 (0.28%)
Agoraphobia	2 (0.07%)	10 (0.35%)	5 (0.18%)
Social phobia	2 (0.07%)	5 (0.18%)	1 (0.04%)
Panic disorder	0 (0.00%)	5 (0.18%)	0 (0.00%)

Anxiety or depression was reported in 1406 (49.63%) patients, while arthritis (n = 579; 20.44%), hypertension (n = 284; 10.02%), endocrine dysfunction (n = 200; 7.06%), epilepsy (n = 128; 4.52%), and venous thromboembolism (n = 76; 2.68%) were less common.

3.1. Drug and alcohol status

Table 2 outlines the exposure of tobacco, alcohol, and cannabis among study participants at baseline. About two-thirds of participants were current or previous tobacco smokers (n = 1922; 67.84%), and the median pack year was 10.00 (IQR: 3.60–20.00). Likewise, most patients were current or previous consumers of cannabis (n = 2021; 71.34%). The median alcohol consumption was 0.00 (IQR: 0.00–5.00) units/week.

3.2 Patient-reported outcome measures (PROMs)

Table 3 outlines the outcome of PROMs at baseline and each follow-up. HRQoL was improved compared to baseline after 1, 3, 6, and 12 months, as shown by EQ-5D-5L index value, GAD-7, and SQS ($p < 0.001$). Improvement was also seen separately in each subscale of EQ-5D-5L, including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, at 1 month, 3 months, and 6 months ($p < 0.050$). At 12 months, improvement was seen in all subscales except self-care ($p = 0.078$). Additional comparison of follow-ups of EQ-5D-5L index value, GAD-7, and SQS demonstrated significant improvement in each PROM between 1 month and 3 months ($p < 0.050$), while no difference was recorded in any PROM between 3 months and 6 months, nor 6 months and 12 months ($p > 0.050$). Lastly, a positive change in PGIC was seen at each follow-up.

Subgroup analysis with respect to cannabis status demonstrated a significant improvement in EQ-5D-5L index value for current consumers at 1 month (n = 1307; 0.43 [± 0.32] vs 0.57 [± 0.27]; $p < 0.001$), 3 months (n = 954; 0.46 [± 0.32] vs 0.59 [± 0.28]; $p < 0.001$) 6 months (n = 558; 0.49 [± 0.31] vs 0.61 [± 0.27]; $p < 0.001$), and 12 months (n = 109; 0.51 [± 0.34] vs 0.61 [± 0.30]; $p < 0.001$). Likewise, significant improvement was seen for previous consumers at 1 month (n = 353; 0.42 [± 0.31] vs 0.57 [± 0.29]; $p < 0.001$), 3 months (n = 242; 0.45 [± 0.30] vs 0.58 [± 0.29]; $p < 0.001$), and 6 months (n = 133; 0.50 [± 0.29] vs 0.61 [± 0.24]; $p < 0.001$), but not 12 months (n = 19; 0.50 [± 0.27] vs 0.58 [± 0.19]; $p = 0.373$). Naïve cannabis users showed a significant improvement at 1 month (n = 586; 0.38 [± 0.31] vs 0.50 [± 0.29]; $p < 0.001$), 3 months (n = 365; 0.42 [± 0.31] vs 0.54 [± 0.28]; $p < 0.001$), 6 months (n = 233; 0.45 [± 0.30] vs 0.54 [± 0.27]; $p < 0.001$), and 12 months (n = 66; 0.42 [± 0.31] vs 0.50 [± 0.28]; $p = 0.009$). The mean change in EQ-5D-5 L was greatest in current (0.14 ± 0.23) and previous cannabis consumers (0.15 ± 0.24), compared to cannabis naïve patients (0.11 ± 0.22; $p < 0.001$) at 1 month. There were no statistically significant differences between the three groups at 3, 6, and 12 months ($p > 0.050$).

3.2. Dosing and administration of cannabis-based medicinal products

Dose of cannabinoids and route of administration at most recent follow-up were reported in 2614 (92.27%) participants. The median dose of CBD and THC per 24 hours was 20.00 (IQR: 5.00–40.50) mg and 110.00 (IQR: 20.00–200.00) mg, respectively. About a third of patients (n = 858, 30.29%) used solely

Table 2. Tobacco, alcohol, and cannabis status.

Tobacco, alcohol, and cannabis status	n (%)/median (IQR)
Tobacco status	
Current smoker	851 (30.04%)
Ex-smoker	1071 (37.80%)
Never used	911 (32.16%)
Tobacco pack years	
Current smoker	10.00 (5.00–20.00)
Ex-smoker	10.00 (3.00–20.00)
Alcohol status	
Nondrinkers	1559 (55.03%)
Drinkers	
Male	745 (26.30%)
Units/week	6.00 (3.00–14.00)
Female	489 (17.26%)
Units/week	5.00 (2.00–10.00)
Cannabis status	
Current consumer	1584 (55.91%)
Ex-consumer	437 (15.43%)
Never consumed	812 (28.66%)
Cannabis gram years	
Current consumer	7.50 (2.10–20.00)
Ex-consumer	3.00 (1.00–10.00)
Cannabis gram per day for current consumers	1.00 (1.00–2.00)
Cannabis use frequency for current consumers	
< 1 time per month	11 (0.39%)
> 1 time per month	16 (0.56%)
1–2 times per month	86 (3.04%)
Every other day	131 (4.62%)
Every day	1324 (46.73%)

Table 3. Paired baseline and follow-up patient-reported outcome measures.

Patient-reported outcome measures and time to follow-up	Number of patients	Score at baseline	Score at follow-up	Cohen's d	p-value
EQ-5D-5L mobility					
1 month	2248	2.36 ± 1.22	2.20 ± 1.15	0.21 (0.17–0.25)	<0.001
3 months	1563	2.33 ± 1.21	2.14 ± 1.15	0.24 (0.19–0.29)	<0.001
6 months	925	2.33 ± 1.21	2.14 ± 1.14	0.24 (0.17–0.31)	<0.001
12 months	194	2.47 ± 1.24	2.32 ± 1.20	0.19 (0.04–0.33)	0.022
EQ-5D-5L self-care					
1 month	2248	1.95 ± 1.06	1.85 ± 1.02	0.15 (0.11–0.19)	<0.001
3 months	1563	1.93 ± 1.05	1.80 ± 1.00	0.17 (0.12–0.22)	<0.001
6 months	925	1.89 ± 1.04	1.79 ± 0.98	0.14 (0.08–0.21)	<0.001
12 months	194	1.94 ± 1.08	1.83 ± 0.98	0.15 (0.01–0.21)	0.078
EQ-5D-5L usual activities					
1 months	2248	2.76 ± 1.18	2.35 ± 1.08	0.41 (0.37–0.45)	<0.001
3 months	1563	2.70 ± 1.19	2.28 ± 1.10	0.40 (0.35–0.45)	<0.001
6 months	925	2.59 ± 1.18	2.22 ± 1.08	0.36 (0.29–0.43)	<0.001
12 months	194	2.61 ± 1.19	2.36 ± 1.09	0.25 (0.11–0.39)	0.001
EQ-5D-5L pain and discomfort					
1 month	2248	3.15 ± 1.20	2.65 ± 1.11	0.54 (0.50–0.59)	<0.001
3 months	1563	3.05 ± 1.19	2.50 ± 1.07	0.59 (0.54–0.64)	<0.001
6 months	925	2.94 ± 1.17	2.48 ± 1.03	0.50 (0.43–0.56)	<0.001
12 months	194	3.03 ± 1.17	2.58 ± 1.09	0.47 (0.32–0.62)	<0.001
EQ-5D-5L anxiety and depression					
1 month	2247	2.64 ± 1.25	2.22 ± 1.08	0.42 (0.38–0.47)	<0.001
3 months	1561	2.55 ± 1.24	2.16 ± 1.06	0.38 (0.32–0.43)	<0.001
6 months	924	2.37 ± 1.19	2.05 ± 0.99	0.31 (0.25–0.38)	<0.001
12 months	194	2.27 ± 1.13	1.88 ± 0.95	0.40 (0.25–0.55)	<0.001
EQ-5D-5L index value					
1 month	2247	0.42 ± 0.32	0.55 ± 0.28	0.58 (0.54–0.63)	<0.001
3 months	1561	0.45 ± 0.32	0.58 ± 0.28	0.56 (0.50–0.61)	<0.001
6 months	924	0.48 ± 0.31	0.59 ± 0.27	0.48 (0.41–0.55)	<0.001
12 months	194	0.47 ± 0.32	0.57 ± 0.29	0.42 (0.27–0.57)	<0.001
GAD-7					
1 month	2268	8.79 ± 6.57	6.04 ± 5.38	0.52 (0.48–0.57)	<0.001
3 months	1576	8.41 ± 6.49	5.48 ± 5.02	0.53 (0.48–0.59)	<0.001
6 months	936	7.40 ± 6.25	5.13 ± 4.81	0.42 (0.35–0.48)	<0.001
12 months	201	6.35 ± 6.04	4.75 ± 4.95	0.30 (0.16–0.44)	<0.001
SQS					
1 month	2219	4.13 ± 2.47	5.62 ± 2.49	0.56 (0.51–0.60)	<0.001
3 months	1539	4.33 ± 2.51	5.88 ± 2.49	0.59 (0.54–0.64)	<0.001
6 months	907	4.78 ± 2.57	5.96 ± 2.52	0.43 (0.36–0.50)	<0.001
12 months	181	4.81 ± 2.59	6.02 ± 2.48	0.49 (0.34–0.64)	<0.001
PGIC					
1 month	2205	-	5.10 ± 1.55	-	-
3 months	1543	-	5.50 ± 1.30	-	-
6 months	937	-	5.69 ± 1.20	-	-
12 months	207	-	5.82 ± 1.24	-	-

Outcome from EQ-5D-5L, Generalized Anxiety Disorder Assessment (GAD-7), Single-Item Sleep Quality Scale (SQS), and Patient Global Impression of Change (PGIC) reported as means (± standard deviation). Effect size displayed as Cohen's d value (95% confidence interval). Scores from baseline and follow-ups were compared separately by applying paired t-test.

oral/sublingual formulations, while less than a quarter (n = 671, 23.69%) vaporized dried flower as their only method of administration. A combination of the two was the most prescribed regimen (n = 1081, 38.16%). The most common CBMP therapies were THC oil (20 mg/ml), CBD oil (50 mg/ml), and cannabis flower (THC 19%, CBD < 0.1%).

3.3. Adverse events

In total there were 5176 (182.70%) AEs reported by 474 (16.73%) patients. The mean number of AEs reported per patient was 1.83 ± 6.82. When categorized by severity, most AEs were mild (n = 2201; 77.69%) or moderate (n = 2239; 79.03%), in contrast to severe (n = 730; 25.77%), and life threatening/disabling (n = 6; 0.21%). The most frequently reported AEs were fatigue (n = 409; 14.42%) and dry mouth (n = 347; 12.25%), followed by somnolence (n = 312; 11.01%), lethargy (n = 308; 10.87%), insomnia (n = 299; 10.55%), headache (n = 297; 10.48%), concentration impairment (n = 286; 10.10%), nausea (n = 242; 8.54%), and dizziness (n = 228; 8.05%). The adverse events are described in full in Supplementary Table 2.

3.4. Prognostic factors for improvement in EQ-5D-5 L

Supplementary Table 3 outlines all variables analyzed within a univariate analysis to identify prognostic factors for experiencing an improvement in EQ-5D-5L index value after 6 months. A subsequent multivariate analysis found female gender (OR = 1.42 [95% CI: 1.03–1.96]; p = 0.033), BMI 30–35 kg/m^2 (OR = 1.66 [1.05–2.64]; p = 0.032), and BMI > 35 kg/m^2 (OR = 2.01 [95% CI: 1.12–3.62]; p = 0.020) to be associated with increased probability of improvement (Table 4).

Table 4. Multivariate analysis of prognostic factors for Increased EQ-5D-5L Index Score at 6 months.

Variable	n	OR (95% CI)	p-value
Age			
0–17	2	-	-
18–30	115	1	
31–40	214	0.73 (0.45–1.21)	0.221
41–50	226	0.75 (0.46–1.22)	0.244
51–60	147	0.93 (0.55–1.60	0.801
61–70	58	0.85 (0.42–1.70)	0.638
71–80	19	1.81 (0.58–5.64)	0.310
80+	2	-	-
Gender			
Male	454	1	
Female	328	1.42 (1.03–1.96)	0.033
BMI (kg/m^2)			
≤20	75	0.97 (0.56–1.69)	0.922
20–25	246	1	
25–30	252	1.12 (0.77–1.62)	0.554
30–35	132	1.66 (1.05–2.64)	0.032
35+	78	2.01 (1.12–3.62)	0.020
Cannabis exposure			
Naïve	194	1	
Ex-consumer	113	1.66 (0.98–2.82)	0.062
Current consumer	476	1.46 (0.97–2.20)	0.068
CBD dosage (mg/24 h)			
0	126	1	
0–20	324	0.74 (0.47–1.17)	0.195
>20	333	0.83 (0.53–1.31)	0.427
THC dosage (mg/24 h)			
0	14	1	
0–110	312	1.03 (0.34–3.12)	0.954
>110	457	1.28 (0.43–3.88)	0.658

BMI, Body Mass Index; CBD, Cannabidiol; THC, (–)-trans-Δ9-tetrahydrocannabinol. Prognostic factors for experiencing an improvement in EQ-5D-5L index value compared to baseline after 6 months. All factors were included in the multivariate analysis to adjust for coexisting variables.

3.5. Prognostic factors for AEs

Supplementary Table 4 presents all variables analyzed utilizing a univariate analysis to identify prognostic factors for experiencing an AE during treatment. Subsequent multivariate analysis found female gender (OR = 1.77 [95% CI: 1.41–2.24], $p < 0.001$) to be associated with increased probability of experiencing an AE, while current consumption of cannabis (OR = 0.45 [95% CI: 0.34–0.60]; $p < 0.001$) was associated with a reduced risk of experiencing an AE (Table 5).

4. Discussion

This study investigated the safety and HRQoL in patients prescribed CBMPs by using data from the UKMCR. The findings suggest an association with improvements in HRQoL and related symptoms across various chronic conditions. Improvements demonstrated at 1 month were maintained throughout follow-up. Female gender and BMI > 30 kg/m^2 were associated with higher likelihood of having a positive improvement after 6 months. There was no difference in change in HRQoL according to prior cannabis exposure. Although some participants experienced several, and in some cases severe, AEs, CBMPs were generally well tolerated, and most patients (n = 2359; 83.27%) did not report any AEs across the study period. Females were at increased risk of AEs, while cannabis consumption prior to baseline was a protective factor.

Findings from the present study build upon previous interim analysis from the UKMCR, which identified an association between initiating CBMP treatment and improved HRQoL in chronically ill patients [4,5]. These results are in line with findings from several other studies [31,32]. A study by Rapin et al. similarly observed improvement in pain, anxiety, depression, and wellbeing after using CBD-rich products in a diverse cohort of patients. However, these results were only found in those with moderate/severe symptoms, with patients with mild symptoms failing to show any benefit [32]. The present study did not compare outcomes stratified by initial symptom severity. However, in the UK, patients may only be treated with CBMPs if they have failed to achieve sufficient clinical benefit from conventional licensed medications [1]. This suggests that patients included in the present analysis are those with the most significant health effects from their illnesses. Consequently, further analysis of patients from broad spectrum of severity, particularly through randomized controlled trials, will be necessary to explore this effect further.

There was no difference between the likelihood of experiencing an improvement in HRQoL, as demonstrated by EQ-5D-5L index value, regardless of cannabis status at baseline. In addition, subgroup analysis shows cannabis consumers at baseline experienced an improvement at all follow-up periods. This indicates that despite the potential to develop tolerance to the effects of cannabis, patients still received additional benefit from initiating CBMPs under medical supervision [33]. This suggests that there are supplementary benefits from accessing

Table 5. Multivariate analysis of prognostic factors for experiencing an adverse event across the study period.

Variable	n	OR (95% CI)	p-value
Age			
0–17	26	0.37 (0.10–1.32	0.125
18–30	484	1	
31–40	682	0.90 (0.64–1.24)	0.510
41–50	595	0.77 (0.54–1.08)	0.131
51–60	350	1.15 (0.80–1.65)	0.462
61–70	146	0.97 (0.60–1.56)	0.886
71–80	69	0.91 (0.48–1.73)	0.766
80+	25	1.19 (0.47–3.05)	0.715
Gender			
Male	1014	1	
Female	1336	1.77 (1.41–2.24)	<0.001
BMI (kg/m^2)			
≤20	232	0.97 (0.65–1.46)	0.884
20–25	768	1	
25–30	713	1.11 (0.83–1.48)	0.487
30–35	360	1.34 (0.96–1.87)	0.089
35+	278	1.07 (0.74–1.55)	0.724
Cannabis exposure			
Naïve	641	1	
Ex-consumer	372	0.76 (0.54–1.07)	0.121
Current consumer	1338	0.45 (0.34–0.60)	<0.001
CBD dose (mg/24 h)			
0	333	1	
0–20	1049	1.01 (0.69–1.47)	0.97
>20	969	1.42 (0.98–2.07)	0.063
THC dose (mg/24 h)			
0	86	1	
0–110	1137	0.74 (0.44–1.25)	0.263
>110	1128	0.87 (0.51–1.49)	0.623

BMI, Body Mass Index; CBD, Cannabidiol; THC, (–)-trans-Δ9-tetrahydrocannabinol. Prognostic factors for experiencing an adverse event across the study period. All factors were included in the multivariate analysis to adjust for coexisting variables.

consistent supply of CBMPs manufactured according to GMP criteria. Conversely, the improvements could be secondary to enhancement of the placebo effect of CBMPs through accessing cannabis in a medical setting. Moreover, through no longer having to access cannabis through illicit settings, this may have resulted in additional psychosocial benefits which are represented in improvements in health-related quality of life [34].

This study demonstrated modest improvements in anxiety symptoms across all participants treated with CBMPs. This is pertinent as anxiety levels were at a pathological level at baseline. However, despite improvement, the mean GAD-7 score was still pathological at all follow-ups except after 12 months. While preclinical evidence supports the role of cannabinoids in modulating anxiety, there is a paucity of high-quality clinical studies. In examining patients with other health conditions, a meta-analysis by Black et al. concluded that CBMPs and cannabinoids may reduce anxiety when studied as a secondary outcome [35]. In contrast, there are several observational studies suggesting that medicinal cannabis does not affect anxiety [31,36]. A reason for the divergence in outcomes may be heterogeneity in the studied population. In addition, the current study utilized the GAD-7 to measure improvements in anxiety, different to the PROMs used in other studies.

The mean number of AEs across the observation period was 1.83, while only 16.73% of participants experienced an AE. Thus, it appears a minority of patients are experiencing AEs, however those who experience AEs are likely to experience multiple AEs. Furthermore, there was a high number of severe AEs (n = 730; 25.77%) recorded in our population [37,38]. This may be secondary to the frequency in which patients are asked to record AEs in the present study, resulting in higher detection of AEs that are otherwise undetected in other published literature. Another explanation may be that patients were treated with various concentrations and combinations of cannabinoids [12,39,40]. In randomized controlled trials of pediatric patients treated with oral CBD for treatment-resistant epilepsy, one of the most common adverse events was elevated liver enzymes [41]. However, the proposed incidence of these adverse events in the studied population is very low. The likely reason for this is that the doses of CBD per body weight used in these studies are larger than the mean CBD dose of patients enrolled on the UK Medical Cannabis Registry. Finally, the mean observation period (226.24 ± 131.59 days) was longer than most previous studies; therefore, there is more time for AEs to occur [37,38]. This highlights the importance of a long-term pharmacovigilance strategy, such as the UK Medical Cannabis Registry.

This study found female gender and previous cannabis consumption to be prognostic factors for the tolerability of CBMPs. Frequent consumption of cannabis has previously been described as a protective factor against adverse reactions to cannabis due to the development of tolerance with prolonged exposure to cannabis [33]. It has also been demonstrated that female patients are more likely to experience adverse events [42,43]. This difference may be secondary to differences in pharmacokinetics and pharmacodynamics between male and female patients. A clinical trial previously demonstrated that females experienced the same acute

effects as males despite administering less cannabis and achieving lower blood concentrations of THC and 11-Nor-9--carboxy-Δ^9-tetrahydrocannabinol [44]. Moreover, sex hormones have been suggested to affect the expression of CB1 receptors in the central nervous system [45]. The divergence of outcomes between males and females is an important consideration to ensure safe prescribing.

4.1. Strengths and limitations

While this study benefits from a relatively long observation period and large study size compared to prior literature, it has several limitations. Most notably, there is no control group, which introduces several potential biases. Firstly, without a control group, it is not possible to assess whether the improvement in PROMs that was observed is secondary to the effects of CBMPs or due to another factor, such as regression to the mean. In addition, the placebo effect of CBMPs is enhanced due to the associated psychoactive and vasoactive effects [46]. Furthermore, the study is subject to selection bias. This is exacerbated by treatment being provided through a private healthcare route, whereby only those who could afford treatment would be able to access therapy. This study relied upon the collection and accuracy of patient-reported outcomes. Despite measures to optimize this process, there are incomplete data which likely bias our outcomes toward the null. Furthermore, the reliability of PROMs may not be impeccable, and this should be considered before interpreting the result of this study. Due to the different enrollment periods during the study, this limited the assessment of true dropouts and the ability to adjust for missing data with appropriate statistical methodologies, such as multiple imputation [47]. This precludes the utilization of a repeated measures ANOVA for analysis, further limiting the applicability of the data. Future analyses from the UKMCR should aim to limit analysis to those who have enrolled for a fixed period to limit the implicit bias this introduces. Another limitation in this study is the heterogeneity of the studied population. Further assessment of outcomes from the patients enrolled on the UKMCR shall focus on individual indications for prescription of CBMPs, such as those previously described for chronic pain, anxiety, and autism spectrum disorder [48–50]. Moreover, the type and dose of CBMPs were heterogenous throughout the studied population. Consequently, the route of administration, concentrations of cannabinoids, and daily use of CBMPs varied among participants. Lastly, there was no ability to assess whether adverse events were treatment related. This may lead to over-reporting of true side effects or those secondary to polypharmacy. Cannabinoids are known to cause potent inhibition of cytochrome P450 drug metabolism resulting in drug–drug interactions [51,52].

5. Conclusion

This observational study suggests that initiating treatment with CBMPs is associated with an improvement in general HRQoL, as well as sleep- and anxiety-specific symptoms up to 12 months in patients with chronic illness. Participants who were consuming illicit cannabis at baseline still experienced an improvement after initiating medicinal cannabis. Most patients tolerated the treatment well; however, the risk of AEs should be considered before initiating CBMPs. In particular, female and cannabis-naïve patients are at increased likelihood of experiencing adverse events. These findings may help to inform current clinical practice, but most importantly, highlight the need for further clinical trials to determine causality and generate guidelines to optimize therapy with CBMPs.

Abbreviations

AE, adverse event; BMI, body mass index; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; CBD, cannabidiol; CBMP, cannabis-based medicinal products;; CI, confidence interval; GAD-7, Generalized Anxiety Disorder Assessment; HRQoL, health-related quality of life; IQR, interquartile range;; OR, odds ratio; PGIC, Patient Global Impression of Change; PROM, patient reported outcome measure; SD, standard deviation; SQS, Single-Item Sleep Quality Scale;; UKMCR, United Kingdom Medical Cannabis Registry; Δ^9-THC, (–)-trans-Δ^9-tetrahydrocannabinol

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Declaration of interests

S Erridge, C Holvey, R Coomber, S Beri, J Hoare, SA Khan, MW Weatherall, M Platt, JJ Rucker, and M Sodergren are the founding clinicians of Sapphire Medical Clinics, which is the first clinic registered with the CQC to evaluate patients for medical cannabis in England. Additionally, JJ Rucker is funded by a fellowship (CS-2017-17-007) from the National Institute for Health Research (NIHR). JJ 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 JJ Rucker to attend trial related meetings and conferences to present the results of research using psilocybin. JJ 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 JJ Rucker does not benefit personally. M Sodergren is Chief Medical Officer at Curaleaf International. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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Ethics statement

In the UK, ethics approval is not required for purely registry-based studies. The study was performed following the principles of the Declaration of Helsinki. All participants completed written, informed consent prior to enrolment in the registry.

Author contributions

The authors confirm that the PI for this paper is MH Sodergren and that he had direct clinical responsibility for patients.

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Data availability statement

Data that support the findings of this study are available from the UK Medical Cannabis Registry (https://ukmedicalcannabisregistry.com/). Restrictions apply to the availability of these data. Data specifications and applications are available from the corresponding author.

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