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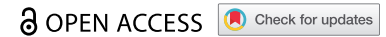


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ORIGINAL RESEARCH



UK medical cannabis registry: assessment of clinical outcomes in patients with headache disorders

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ABSTRACT

Objectives: Headache disorders are a common cause of disability and reduced health-related quality of life globally. Growing evidence supports the use of cannabis-based medicinal products (CBMPs) for chronic pain; however, a paucity of research specifically focuses on CBMPs' efficacy and safety in headache disorders. This study aims to assess changes in validated patient-reported outcome measures (PROMs) in patients with headaches prescribed CBMPs and investigate the clinical safety in this population.

Methods: A case series of the UK Medical Cannabis Registry was conducted. Primary outcomes were changes from baseline in PROMs (Headache Impact Test-6 (HIT-6), Migraine Disability Assessment (MIDAS), EQ-5D-5L, Generalized Anxiety Disorder-7 (GAD-7) questionnaire and Single-Item Sleep Quality Scale (SQS)) at 1-, 3-, and 6-months follow-up. P-values <0.050 were deemed statistically significant.

Results: Ninety-seven patients were identified for inclusion. Improvements in HIT-6, MIDAS, EQ-5D-5L and SQS were observed at 1-, 3-, and 6-months ($p < 0.005$) follow-up. GAD-7 improved at 1- and 3-months ($p < 0.050$). Seventeen (17.5%) patients experienced a total of 113 (116.5%) adverse events.

Conclusion: Improvements in headache/migraine-specific PROMs and general health-related quality of life were associated with the initiation of CBMPs in patients with headache disorders. Cautious interpretation of results is necessary, and randomized control trials are required to ascertain causality.

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1. Introduction

Headache disorders, such as migraine, tension-type headache, and cluster headache, are a common cause of disability and reduced quality of life globally [1,2]. Migraine is the 2nd most common neurological condition, affecting 15% of the United Kingdom (UK) population [3], with females being more commonly affected [4,5]. The International Classification of Headache Disorders defines migraines as attacks lasting 4–72 hours which typically manifest as unilateral, pulsating, and severe headache pain often associated with nausea, vomiting, photophobia, and phonophobia [6]. Symptoms of headache disorders can render patients physically, socially, and psychologically incapacitated [7] and the World Health Organization ranks headaches in the top 10 global causes of disability [8]. Additionally, headaches have a considerable burden on health services globally [9,10] and are responsible for high economic impact [11].

Current migraine management includes a combination of acute and preventative pharmacological therapies [12,13].

Acute therapies include non-steroidal anti-inflammatory drugs, paracetamol and, for more severe attacks, triptans [12]. Patients suffering from frequent migraine attacks may require additional preventative therapies, including repurposed medications such as beta-blockers, tricyclic antidepressants, and anticonvulsants [12]. However, these regimes are associated with unpredictable effectiveness, with only one in three patients reporting symptom improvement [14]. Moreover, side effects like fatigue, rashes, dizziness, weight gain, and constipation lend to their poor tolerability [15]. Furthermore, due to frequent requirement for analgesia, patients may subsequently suffer from medication overuse headache (MOH) in the attempt to alleviate their migraine, resulting in a vicious circle of headache symptoms [16,17]. In recent years, new therapies have been introduced for migraine, including onabotulinumtoxin A injections, and monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or its receptor [12]; whilst effective for many patients, these treatments are expensive, and access to them remains limited [12]. Therefore, a clear demand remains to develop novel therapeutics.

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The endocannabinoid system (ECS) influences a variety of physiological processes including pain signaling pathways and has been identified as a target for novel therapeutics for primary headache disorders [18–20]. The main receptors of the ECS are cannabinoid receptor type 1 (CB₁), a G-protein coupled receptor principally located in the brainstem, prefrontal cortex, cingulate cortex and amygdala, and cannabinoid receptor type 2 (CB₂), a G-protein coupled receptor principally located in peripheral immune cells [20]. Anandamide and 2-arachidonoylglycerol (2-AG) are two key endocannabinoids that act as retrograde or local neurotransmitters through interactions with CB receptors [21]. Anandamide is a CB₁ partial agonist and is degraded by fatty acid amide hydrolase (FAAH), whilst 2-AG is a CB₁ and CB₂ full agonist and is degraded by monoacylglycerol lipase [18]. The binding of these endocannabinoids regulates γ -aminobutyric acid (GABA) and glutamate release in nociceptive pathways [22]. Translational research findings suggest that modulation of the ECS may affect clinical outcomes in headache disorders [23–25].

Cannabis-based medicinal products (CBMPs) contain over 100 phytocannabinoids which act as ligands for CB_{1/2} receptors [21,26]. (–)-trans- Δ 9-tetrahydrocannabinol (Δ 9-THC) and cannabidiol (CBD) are the two most abundant phytocannabinoids within the cannabis plant [26]. Δ 9-THC is a partial agonist of CB_{1/2} receptors [21]. Comparatively, CBD's primary mechanism of action is to inhibit the breakdown of anandamide at synapses, therefore keeping anandamide constitutively active [21].

There is growing evidence of the role of CBMPs in the setting of chronic pain, including headache disorders [27]. Real-world evidence which has assessed pharmaceutical-grade and other preparations of cannabis, supports a potential benefit of using cannabis-based products for headache disorders [28–30]. In 2012, the first single-centered, crossover trial demonstrated that 30 patients with MOH experienced reduced headache pain duration and consumed less daily analgesia during an 8-week trial of nabilone, a synthetic Δ 9-THC mimic, compared to ibuprofen [31]. These findings are mechanistically corroborated by pre-clinical studies [32–36]. Additionally, CBMPs have been deemed clinically safe, with few or no reports of severe and life-threatening adverse events (AEs) [29,30,37]. Already, CBMPs are being utilized in an off-label manner for the treatment of severe psychiatric disorders such as post-traumatic stress disorder [38]. Notably, unlike tightly controlled CBMPs, illicit cannabis, in particular high potency skunk, has been associated with negative effects on existing psychiatric disorders [39–41].

Existing studies investigating the use of CBMPs in headaches are primarily observational, small-scale, and retrospective [42]. They frequently analyze outcomes from individuals who consume recreational cannabis which lack the regulations, and therefore consistency, of CBMPs [28]. Furthermore, their outcomes have been inconclusive, owing to small sample sizes [31] and significant heterogeneity due to variations in formulation, routes of administration and concentrations of constitute cannabinoids [30]. Additionally, a paucity of research exists on the use of CBMPs in headache disorders specifically; instead, their use has been studied under the

umbrella of chronic pain disorders [27]. Lastly, studies often focus on headache-specific measures such as the number of days acute medications were required [29,30], which may not reflect the most valuable outcomes to patients, such as health-related quality of life (HRQoL) [43].

In the UK, individuals with headache disorders may only be prescribed unlicensed CBMPs by consultant neurologists, if they have undertaken a satisfactory trial of previously licensed therapies and have failed to achieve sufficient clinical benefit [44]. Each individual's case must be reviewed by a multidisciplinary team to ensure that a prescription is suitable according to all physical and mental health requirements. Finally, all CBMPs must be manufactured to Good Manufacturing Practice criteria to ensure they meet the safety requirements outlined in the British Pharmacopeia [44]. The UK Medical Cannabis Registry (UKMCR) was established in December 2019 and is privately owned by Sapphire Medical Clinics. The registry longitudinally captures data and outcomes of patients from the UK and the Channel Islands being treated with CBMPs for several medical conditions, including headache disorders.

This study aims to fill an evidence gap by examining real-world evidence from the largest prospectively enrolled case series of UK patients prescribed CBMPs for headache disorders. The primary aims of this study were to assess changes in validated patient-reported outcome measures (PROMs). Supplementary aims included analysis of AE frequency and dosage regimes.

2. Methods

2.1. Study design

This study reports a case series of patients diagnosed with a primary headache disorder, enrolled in the UKMCR. Participants were consecutively enrolled into the registry after they provided fully informed, written consent. Patients completed electronically administered questionnaires at baseline, 1-month, 3-months, and 6-months to record PROMs and AEs.

This study conforms to the STROBE statement for reporting observational studies [45]. In line with NHS Health Research Authority and Research Ethics Committee's guidance, this study was considered to not require formal ethical approval.

2.2. Settings and participants

The UKMCR was established in December 2019 and is a patient registry owned by Sapphire Medical Clinics which longitudinally captures pseudonymized data of patients prescribed CBMPs in the UK and the Channel Islands. The registry collates data on indication for CBMP treatment, patient demographics, PROMs, and AEs.

CBMPs in accordance with Good Manufacturing Practice were prescribed by specialists ensuring quality, consistency, and compliance with standards set by the Medicines and Healthcare products Regulatory Agency (MHRA) [46]. It is unlikely patients were using medical grade cannabis/CBMP products prior to enrollment.

Patients were included if they were ≥ 18 years old and had been commenced on CBMP therapy with the intention to treat a headache disorder. Patients were excluded if they had not completed a baseline PROMs assessment or had been enrolled in the UKMCR < 1 -month prior to data extraction. No other reasons for exclusion were used. Patients who were consuming non-prescribed cannabis at baseline were additionally counseled to cease doing so. Data were extracted on 15 February 2022.

2.3. Outcomes of interest

Patient demographic details, including age, gender, and occupation were recorded. Additionally, patient body mass index (BMI) was calculated. The incidence of relevant co-morbidities was recorded, including anxiety/depression, arthritis, endocrine dysfunction, epilepsy, hypertension, and venous thromboembolic disease. Moreover, a Charlson comorbidity index score, a widely used prognostic scoring tool to measure health status in population studies [47], was calculated for each patient.

Drug and alcohol data was captured and analyzed, including smoking status, smoking pack years, alcohol consumption,

cannabis status and cannabis gram years. Gram years is a metric to assess lifetime cannabis consumption developed by our group. It is calculated as the average cannabis consumption per 24 hours, multiplied by years of use [48].

Patients' medication data was recorded, including drug names, drug dosages per 24 hours, and prescriptions' start/end dates. Medication names were mapped to SNOMED CT codes to ensure consistent terminology [49]. Opioid medications were converted to oral morphine equivalents (OMEs) using conversion factors from the British National Formulary [50].

Primary, secondary, and tertiary indications for which CBMPs had been prescribed were recorded by the treating physician. Patient records were linked with prescription data, including manufacturing company, formulation, route of administration and dose of $\Delta 9$ -THC and CBD. Dose of each cannabinoid was calculated as the concentration of cannabinoid (mg/g) multiplied by the prescribed dose of dried flower per 24 hours.

2.3.1. Patient-reported outcome measures

Table 1 depicts and describes the PROMs which were measured at baseline, and at 1-, 3-, and 6-months follow-up,

Table 1. Displays and describes the patient-reported outcome measures (PROMs) measured at baseline, and at 1-, 3-, and 6-months follow-up.

PROM	Description	Patient Response	Scoring
HIT-6	The 6-item headache impact test (HIT-6) is a brief tool to assess the impact of headaches, including, pain severity, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.	Patients respond with 'never' (=6), 'rarely' (=8), 'sometimes' (=10), 'very often' (=11), or 'always' (=13) to a set of questions.	Scores are added together to a total ranging from 36–78, with a higher score being associated with a greater headache burden. A > 2.5 -point reduction of HIT-6 scores is associated with a minimal clinically significant change.
MIDAS	The migraine disability assessment (MIDAS) questionnaire is designed to determine the level of pain and disability caused by a headache disorder. Five questions are used to assess the impact of a patient's headaches during the past 3 months.	Patients are required to quantify the number of days the headaches prevented their involvement of usual activities, the total number of days headaches occurred and state pain intensity level during attacks.	Scores are added together to a total MIDAS score with scores of 0–5, 6–10, 11–20, and 21+ corresponding to little, mild, moderate, and severe disability, respectively. A > 5.0 -point reduction of HIT-6 scores is associated with a minimal clinically significant change.
EQ-5D-5L	The EQ-5D-5L is NICE's preferred standardized assessment tool for measuring HRQoL. Respondents describe their health considering 5 domains: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression.	Each domain is scored with a 5-level scale of severity: 'no problem' (=1), 'slight problem' (=2), 'moderate problem' (=3), 'severe problem' (=4) to 'unable to' (=5).	These scores are combined into a 5-digit code corresponding to an overall health state. This health state is mapped into a single EQ-5D-5L index value specific for a UK population. An index value of 1 represents perfect HRQoL and an index value < 0 is equivalent to a health state worse than death.
GAD-7	The GAD-7 is a 7-question screening tool designed to measure the severity of generalized anxiety disorder (GAD). It encompasses 7 indicative symptoms of GAD, including feelings of worry, irritability, impending doom, and inability to relax.	Patients respond with "not at all" (=0), 'several days' (=1), 'more than half the days' (=2) and 'nearly every day' (=3) over the last 2 weeks.	Scores are added together generating a score ranging from 0–21 with ≥ 5 , ≥ 10 , and ≥ 15 signifying mild, moderate, and severe anxiety symptoms, respectively.
SQS	The single-item sleep quality scale (SQS) assesses the overall quality of sleep for most nights in the past 7 days.	'0' represents terrible sleep quality, whilst '10' denotes excellent sleep quality. Respondents are prompted to consider all components of sleep quality including hours slept, sleep onset latency, and night-time waking.	Scored 0–10
PGIC-1	The Patients' Global Impression of Change (PGIC-1) scale assesses how the patient would describe the change in their clinical status since starting treatment. Patients are asked to consider activity limitations, symptoms, emotions, and overall quality of life. PGIC-2 is an additional question where respondents are asked to signify the degree of change since beginning care at the clinic.	This is rated on a scale of 1–7, 1 = 'no change (or the condition has got worse)' and 7 = 'a great deal better and a considerable improvement that has made all the difference.' 0 = 'much better.' 5 = 'no change' and 10 = 'much worse.'	Scored 1–7
PGIC-2			Scored 1–10

PROM: patient-reported outcome measure; HRQoL: Health-related quality of life; HIT-6: headache-impact test-6⁽⁵¹⁾; MIDAS: migraine disability assessment score⁽⁵²⁾; GAD-7: generalized anxiety disorder-7 questionnaire⁽⁵³⁾; NICE – National Institute for Health and Care Excellence; SQS: single-item sleep-quality scale⁽⁵⁵⁾; PGIC: patient's global impression of change⁽⁵⁶⁾.

including the 6-item headache impact test (HIT-6) [51], migraine disability assessment score (MIDAS) [52], EQ-5D-5L [53], generalized anxiety disorder-7 questionnaire (GAD) [54] and single-item sleep quality scale (SQS) [55]. Additionally, Table 1 defines the patients' global impression of change (PGIC-1/2) [56].

2.3.2. Adverse events

AEs were self-reported by patients at follow-up assessments or inputted following a clinical encounter. They were reported and analyzed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[57].

2.4. Outcome measures

Primary outcomes were changes from baseline in PROMs (HIT-6, MIDAS, EQ-5D-5L, GAD-7 questionnaire and SQS) at 1-, 3-, and 6-months compared to baseline. Sub-group analyses were also conducted according to prior cannabis exposure for these outcome measures. Median PGIC-1/2 scores at 1-, 3-, and 6-months were also analyzed. Secondary outcomes included analysis of the incidence and severity of reported AEs.

2.5. Statistical methods

Demographic variables, drug and alcohol use, medication data and AEs were analyzed using descriptive statistics. Data from PROMs were independently analyzed by comparing measurements recorded at 1-, 3-, and 6-months to the baseline independently to minimize the effects of missing data values during follow-up. Normality was assessed using the Shapiro-Wilk test. Thereafter, parametric data were presented as mean (\pm standard deviation (SD)), whilst non-parametric data were presented as median (interquartile range (IQR)). Statistical analysis was performed with a paired Student's t-test or Wilcoxon rank-sum test for parametric and non-parametric data, respectively. Data were analyzed using SPSS (version: 28.0.0.0 SPSS Inc., [New York, IL], USA), and figures were created using GraphPad Prisma (version: 9.3.1(350) for macOS, GraphPad Software Inc., [San Diego, CA], USA). P-values <0.050 were deemed statistically significant.

3. Results

Preliminary data extraction from the UKMCR yielded 3546 patients. After exclusion of patients who had not completed a baseline PROM, not received CBMPs for >1-month or did not have a primary diagnosis of headache disorder, 97 patients remained for final analysis. Of these, PROMs had been recorded for 81 patients at 1-month, 63 patients at 3-months and 35 patients at 6-months.

3.1. Patient data

The mean age of patients was 37.9 (\pm 11.1) years, and the female-to-male ratio was 1:1.3. The mean BMI of patients was 28.0 (\pm 7.0) kg/m². The most common occupation was 'professional' (n = 14; 14.4%), but more patients were unemployed (n = 23; 23.7%) (Table 2).

Table 2. Patient baseline demographic data (n = 97).

Demographic Detail	n (%) / mean \pm SD
Age	37.9 \pm 11.1
Sex	
Female	42 (43.3)
Male	55 (56.7)
BMI	28.0 \pm 7.0
Occupation	
Clerical support workers	1 (1.0)
Craft and related trades	2 (2.1)
Elementary occupation	7 (7.2)
Managers	6 (6.2)
Plant and machine operator and assemblers	1 (1.0)
Professional	14 (14.4)
Service and sales worker	2 (2.1)
Technician and associate professional	8 (8.2)
Other occupation	8 (8.2)
Unemployed	23 (23.7)
Unreported	25 (25.8)

BMI: Body Mass Index kg/m²; SD: standard deviation

Baseline drug and alcohol data analysis revealed that 36.1% (n = 35), 41.2% (n = 40), and 22.7% (n = 22) of patients had never smoked, were ex-smokers, and were current smokers, respectively. The median smoking pack years was 6.0 (2.0–14.0). At the time of enrollment, most patients were current cannabis consumers (n = 54; 55.7%), nearly half of these patients consumed cannabis every day (n = 42; 43.3%). Fewer patients were ex-consumers of cannabis (n = 17; 17.5%) or were cannabis naïve (never consumed cannabis in the past) (n = 26; 26.8%). The cohort's median cannabis gram years was 5.0 (1.0–20.0), with a median consumption of 1.0 (0.3–1.5) grams per day. The median alcohol consumption was 0.0 (0.0–3.0) units per week, and 88.5% (n = 86) of patients consumed \leq 5 units per week.

Most patients had a primary indication of migraine (n = 82; 84.5%), followed by cluster headache (n = 9; 9.3%), and tension-type headache (n = 6; 6.2%). Anxiety was the most common secondary indication (n = 16; 16.5%), followed by insomnia and chronic pain (n = 7; 7.2%), and depression (n = 4; 4.1%) (Table 3).

The median Charlson comorbidity index was 0.0 (0.0–0.0), with 79.4% (n = 77) of patients scoring 0.0% and 8.3% (n = 8) of patients scoring >3.0. Arthritis was the most common comorbidity recorded (n = 7; 7.2%), followed by hypertension (n = 4; 4.1%), and uncomplicated diabetes (n = 4; 4.1%).

3.2. CBMP dosing and mode of administration

The median dose of CBD and THC per 24 hours was 20.0 (5.0–40.0) mg and 120.0 (53.6–204.1) mg, respectively. Twenty-five (25.8%) patients were prescribed vaporized flower (flos) only, 19 (19.6%) patients were prescribed oral/sublingual administration (oils) only and 51 (52.6%) patients were prescribed

Table 3. Primary, secondary, and tertiary indication for patients included in the analysis (n = 97).

Indication for treatment	Primary n (%)	Secondary n (%)	Tertiary n (%)
Migraine	82 (84.5)	3 (3.1)	0 (0.0)
Tension-type headache	6 (6.2)	1 (1.0)	1 (1.0)
Cluster headache	9 (9.3)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	16 (16.5)	4 (4.1)
Attention deficit hyperactivity disorder	0 (0.0)	1 (1.0)	0 (1.0)
Chronic pain	0 (0.0)	7 (7.2)	4 (4.1)
Depression	0 (0.0)	4 (4.1)	3 (3.1)
Insomnia	0 (0.0)	7 (7.2)	3 (3.1)
Obsessive compulsive disorder	0 (0.0)	1 (1.0)	0 (0.0)
Tourette's syndrome	0 (0.0)	1 (1.0)	0 (0.0)
Post-traumatic stress disorder	0 (0.0)	1 (1.0)	0 (0.0)
Autistic spectrum disorder	0 (0.0)	0 (0.0)	1 (1.0)
Complex regional pain syndrome	0 (0.0)	0 (0.0)	1 (1.0)
Depression	0 (0.0)	0 (0.0)	3 (3.1)
Epilepsy (adult)	0 (0.0)	0 (0.0)	1 (1.0)
Fibromyalgia	0 (0.0)	0 (0.0)	1 (1.0)

both. Two (2.1%) patients had missing CBMP data. In patients prescribed both oils and flos, the median CBD and THC dose of oils were 20.0 (4.5–30.0) mg and 20.0 (10.0–20.0) mg, respectively and for flos were 5.0 (0.0–5.0) mg and 100.0 (100.0–195.0) mg, respectively. The most common CBMP therapies were Adven® 20 THC oil, Adven® 50 CBD oil, Adven® EMT1 19% THC flower (Curaleaf International, Guernsey, UK).

3.3. PROMs analysis

Median HIT-6 scores decreased at 1- [n = 75; 66.0 (62.0–71.0) vs 62.0 (57.0–67.0); p < 0.001], 3- [n = 60; 66.5 (62.0–71.0) vs 59.5 (52.0–68.0); p < 0.001], and 6-months [n = 33; 66.0 (62.0–71.0) vs 59.0 (52.0–66.0); p < 0.001] follow-up, respectively (Figure 1a). Median MIDAS scores decreased at 1- [n = 75; 44.0 (12.0–118.0) vs 26.0 (6.0–102.0); p < 0.001], 3- [n = 60; 47.5 (14.3–121.0) vs 20.0 (4.0–70.0); p < 0.001], and 6-months [n = 33; 46.0 (9.0–146.0) vs 21.0 (3.5–69.5); p = 0.004] follow-up also (Figure 1b).

The proportion of patients' reporting >2.5-point reduction in HIT-6 scores was 61.3% (n = 46/75), 71.7% (n = 43/60), and 66.7% (n = 22/33) at 1-, 3-, and 6-months, respectively. The proportion of patients' who had >5.0-point reduction in MIDAS scores was 57.3% (n = 43/75), 66.7% (n = 40/60), and 63.6% (n = 21/33) at 1-, 3-, and 6-months, respectively.

Sub-group analysis according to prior cannabis exposure demonstrated that there were significant reductions in HIT-6 scores at 1- and 3-months follow-up for all sub-groups (p < 0.05), but only the sub-group of current cannabis consumers had a significant reduction in HIT-6 at 6-months follow-up (p < 0.001). There were significant reductions in MIDAS scores at 1-month for the cannabis naïve and current cannabis consumer sub-groups (p < 0.05), but only the sub-group of current cannabis consumers had a significant reduction in MIDAS at 3-months (p < 0.01). There was no significant change in MIDAS for ex-cannabis consumers at any follow-up point (p > 0.05). Full details of the sub-analysis are displayed in *Supplementary Table 1*.

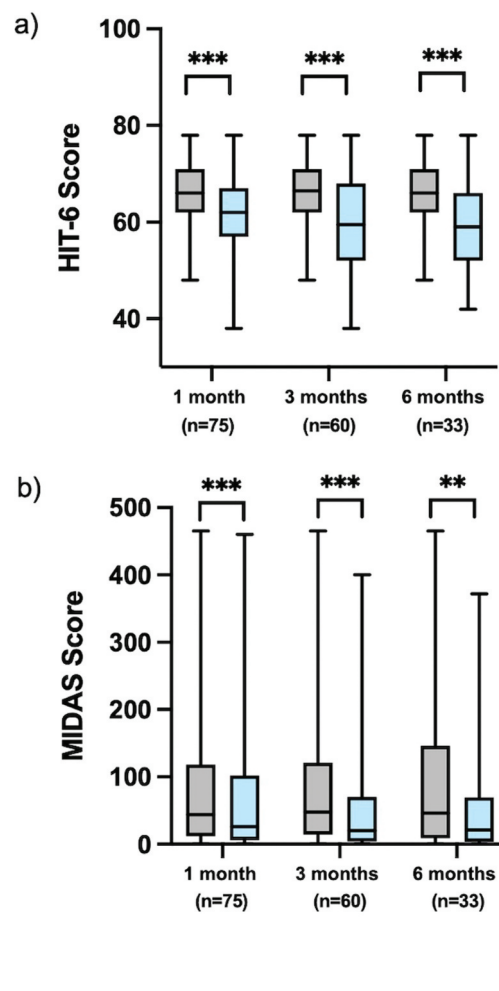


Figure 1. A) HIT-6 and b) MIDAS scores at baseline and follow-up measures at 1-, 3-, and 6-months in patients with headache disorders prescribed cannabis-based medicinal products. * < 0.050; ** < 0.010; *** < 0.001; HIT-6: 6-item headache impact test; MIDAS: migraine disability assessment score.

Table 4 depicts paired baseline and follow-up scores at 1-, 3-, and 6-months for EQ-5D-5L index values and EQ-5D-5L domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Median EQ-5D-5L index values increased at 1- [n = 79; 0.70 (0.34–0.80) vs 0.77 (0.57–0.84); p < 0.001], 3- [n = 62; 0.70 (0.34–0.80) vs 0.74

Table 4. Paired baseline and follow-up scores for EQ-5D-5L measures at 1-, 3-, and 6-months in patients with headache disorders prescribed cannabis-based medicinal products.

	Month	n	Baseline	Follow-up	P-value	Sig.
EQ-5D-5L Index Value	1-month	79	0.7 (0.3–0.8)	0.8 (0.6–0.8)	<0.001	***
	3-months	62	0.7 (0.3–0.8)	0.7 (0.5–0.8)	0.016	*
	6-months	34	0.7 (0.5–0.8)	0.8 (0.7–0.9)	0.009	***
EQ-5D-5L Mobility	1-month	79	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.544	ns
	3-months	62	1.0 (1.0–3.0)	1.0 (1.0–3.0)	0.830	ns
	6-months	34	1.0 (1.0–3.0)	1.0 (1.0–2.0)	0.201	ns
EQ-5D-5L Self-Care	1-month	79	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.302	ns
	3-months	62	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.825	ns
	6-months	34	1.0 (1.0–2.0)	1.0 (1.0–1.3)	0.366	ns
EQ-5D-5L Usual Activity	1-month	79	2.0 (1.0–3.0)	2.0 (1.0–2.0)	0.013	*
	3-months	62	1.5 (1.0–3.0)	2.0 (1.0–2.3)	0.180	ns
	6-months	34	1.5 (1.0–3.0)	1.0 (1.0–3.0)	0.227	ns
EQ-5D-5L Pain and Discomfort	1-month	79	3.0 (2.0–4.0)	2.0 (2.0–3.0)	<0.001	***
	3-months	62	3.0 (2.0–4.0)	2.0 (2.0–3.0)	<0.001	***
	6-months	34	3.0 (2.0–4.0)	2.0 (1.8–3.0)	0.006	**
EQ-5D-5L Anxiety and Depression	1-month	79	2.0 (1.0–3.0)	2.0 (1.0–3.0)	<0.001	***
	3-months	62	2.0 (1.0–3.0)	2.0 (1.0–2.0)	0.089	ns
	6-months	34	1.0 (1.0–3.0)	2.0 (1.0–2.0)	0.983	ns

ns: no statistically significant difference; * <0.050 ; ** <0.010 ; *** <0.001

(0.53–0.84); $p = 0.016$], and 6-months [$n = 34$; 0.70 (0.48–0.82) vs 0.75 (0.65–0.85); $p = 0.009$] follow-up. Median EQ-5D-5L pain/discomfort domain scores decreased at 1- [$n = 79$; 3.0 (2.0–4.0) vs 2.0 (2.0–3.0); $p < 0.001$], 3- [$n = 62$; 3.0 (2.0–4.0) vs 2.0 (2.0–3.0); $p < 0.001$], and 6-months [$n = 34$; 3.0 (2.0–4.0) vs 2.0 (1.8–3.0); $p = 0.006$] follow-up. Additionally, statistically significant improvements were observed in the usual activity domain [$n = 79$; 2.0 (1.0–3.0) vs 2.0 (1.0–2.0); $p = 0.013$] and the anxiety/depression domain [$n = 79$; 2.0 (1.0–3.0) vs 2.0 (1.0–3.0); $p < 0.001$] at 1-month compared to baseline. scores decreased at 1- [$n = 79$; 3.0 (2.0–4.0) vs 2.0 (2.0–3.0); $p < 0.001$], 3- [$n = 62$; 3.0 (2.0–4.0) vs 2.0 (2.0–3.0); $p < 0.001$], and 6-months [$n = 34$; 3.0 (2.0–4.0) vs 2.0 (1.8–3.0); $p = 0.006$] follow-up. Additionally, statistically significant improvements were observed in the usual activity domain [$n = 79$; 2.0 (1.0–3.0) vs 2.0 (1.0–2.0); $p = 0.013$] and the anxiety/depression domain [$n = 79$; 2.0 (1.0–3.0) vs 2.0 (1.0–3.0); $p < 0.001$] at 1-month compared to baseline.

Sub-group analysis according to prior cannabis exposure demonstrated that there were significant improvements in EQ-5D-5L index value at 1-month follow-up for the cannabis naïve and current consumer of cannabis sub-groups ($p < 0.01$) and at 6-months for the current consumer of cannabis sub-group ($p < 0.01$). There were no other significant changes in the EQ-5D-5L index value according to prior cannabis use sub-groups ($p > 0.05$). Full details of the sub-analysis are displayed in *Supplementary Table 1*.

Median GAD-7 scores significantly improved at 1- [$n = 81$; 5.0 (2.0–10.5) vs 4.0 (1.0–7.0); $p < 0.001$] and 3-months [$n = 63$; 5.0 (2.0–9.0) vs 4.0 (1.0–6.0); $p < 0.001$] follow-up. At 6-months there was no change in GAD-7 score [$n = 35$; 4.0 (1.0–10.0) vs 4.0 (2.0–8.0); $p = 0.239$] (*Figure 2a*). Median SQS scores improved at 1- [$n = 78$; 4.0 (3.0–7.0) vs 7.0 (4.0–8.0); $p < 0.001$], 3- [$n = 61$; 4.0 (3.0–7.0) vs 7.0 (6.0–9.0); $p < 0.001$], and 6-months [$n = 33$; 4.0 (3.0–7.0) vs 6.0 (4.0–8.0); $p = 0.002$] follow-up (*Figure 2b*).

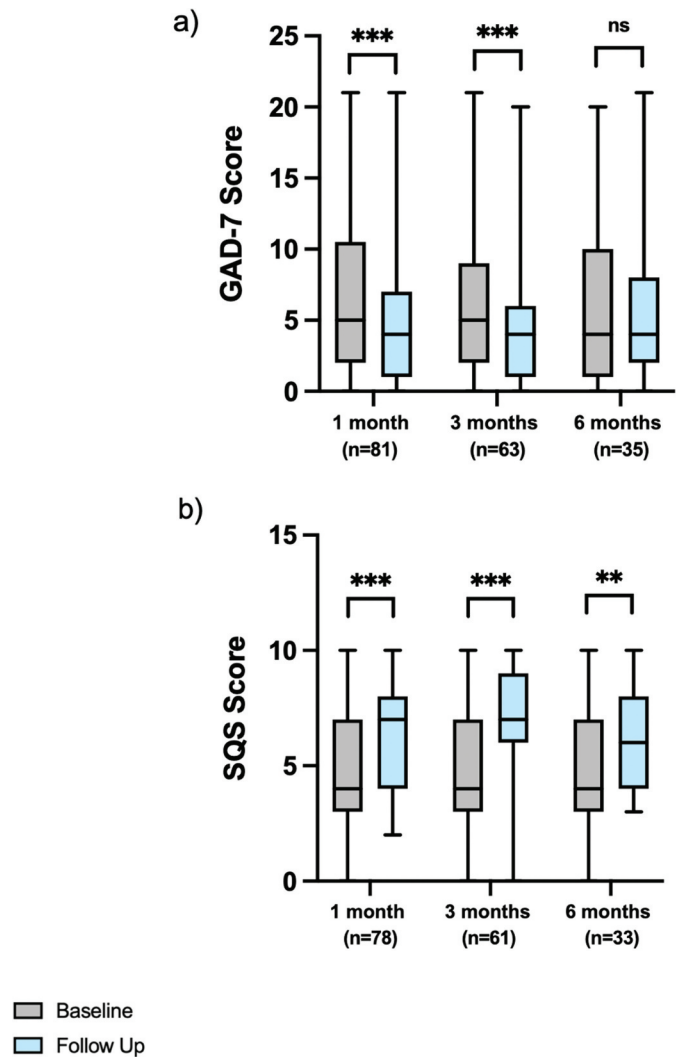


Figure 2. a) GAD-7 and b) SQS scores at baseline and follow-up measures at 1-, 3-, and 6-months in patients with headache disorders prescribed cannabis-based medicinal products. ns: no statistically significant difference; * <0.050 ; ** <0.010 ; *** <0.001 . GAD-7: generalised anxiety disorder-7 questionnaire; SQS: single-item sleep quality scale

Table 5. Paired baseline and follow-up scores for HIT-6, MIDAS, GAD-7, SQS, and EQ-5D-5L measures at 1-, 3-, and 6-months in patients with headache disorders prescribed cannabis-based medicinal products.

	Month	n	Baseline	Follow-up	T test statistic	Z score	P-value	Sig.
HIT-6	1-month	75	66.0 (62.0–71.0)	62.0 (57.0–67.0)	2305.0	–5.9	<0.001	***
	3-months	60	66.5 (62.0–71.0)	59.5 (52.0–68.0)	1418.5	–5.4	<0.001	***
	6-months	33	66.0 (62.0–71.0)	59.0 (52.0–66.0)	459.0	–4.1	<0.001	***
MIDAS	1-month	75	44.0 (12.0–118.0)	26.0 (6.0–102.0)	1795.5	–3.5	<0.001	***
	3-months	60	47.5 (14.3–121.0)	20.0 (4.0–70.0)	1273.5	–3/6	<0.001	***
	6-months	33	46.0 (9.0–146.0)	21.0 (3.5–69.5)	373.0	–2.9	0.004	**
GAD-7	1-month	81	5.0 (2.0–10.5)	4.0 (1.0–7.0)	1600.0	–3.8	p < 0.001	***
	3-months	63	5.0 (2.0–9.0)	4.0 (1.0–6.0)	1058.5	–3.4	p < 0.001	***
	6-months	35	4.0 (1.0–10.0)	4.0(2.0–8.0)	254.5	–1.2	p = 0.239	ns
SQS	1-month	78	4.0 (3.0–7.0)	7.0 (4.0–8.0)	1730.0	–5.0	p < 0.001	***
	3-months	61	4.0 (3.0–7.0)	7.0 (6.0–9.0)	1299.5	–5.2	p < 0.001	***
	6-months	33	4.0 (3.0–7.0)	6.0(4.0–8.0)	16.12	–3.1	p = 0.002	**
EQ-5D-5L	1-month	79	0.7 (0.3–0.8)	0.8 (0.6–0.8)	1896.0	–4.4	<0.001	***
	3-months	62	0.7 (0.3–0.8)	0.7 (0.5–0.8)	1168.0	–2.4	0.016	*
	6-months	34	0.7 (0.5–0.8)	0.8 (0.7–0.9)	381.5	–2.6	0.009	***

HIT-6: headache-impact test-6⁽⁵¹⁾; MIDAS: migraine disability assessment score⁽⁵²⁾; GAD-7: generalized anxiety disorder-7 questionnaire⁽⁵³⁾; SQS: single-item sleep quality scale⁽⁵⁵⁾

ns: no statistically significant difference; * < 0.050; ** < 0.010; *** < 0.001

Sub-group analysis according to prior cannabis exposure demonstrated that there were significant reductions in GAD at 1-month for the cannabis naïve and current cannabis consumer sub-groups ($p < 0.05$). Additionally, there were significant reductions in GAD at 3-months follow-up for the cannabis naïve and ex-consumer of cannabis sub-groups ($p < 0.05$). There were no other significant changes in GAD in the sub-group analysis ($p > 0.05$). There were significant reductions in SQS at 1-month for the cannabis naïve and current cannabis consumer sub-groups ($p < 0.05$), and all three sub-groups had a significant decrease in SQS at 3-months follow-up ($p < 0.05$), but only the current cannabis consumers sub-group had significant improvements at 6-months ($p < 0.01$). Full details of the sub-analysis are displayed in *Supplementary Table 1*.

Table 5 depicts the full statistical analysis of HIT-6, MIDAS, EQ-5D-5L, GAD-7, and SQS at 1-, 3-, and 6-months follow-up.

At 1-, 3- and 6-months follow-up median PGIC-1 scores were 6.0 ($n = 78$; 5.0–7.0), 6.0 ($n = 63$; 5.0–7.0), and 6.0 ($n = 35$; 6.0–7.0), respectively and PGIC-2 scores were 2.0 ($n = 78$; 1.0–3.0), 2.0 ($n = 63$; 1.0–3.0) and 2.0 ($n = 35$; 1.0–3.0), respectively. At 1- and 3-months 80.8% ($n = 63/78$) and 93.6% ($n = 59/63$) of patients rated PGIC-1 ≥ 5 , respectively.

3.4. Oral morphine equivalent (OME) analysis

Ten (10.3%) patients had records of regularly prescribed opioid-containing medications, but 2 (20.0%) of these patients were no longer prescribed these medications at the time CBMP therapy was commenced. Post CBMP treatment commencement, 1 (12.5%) patient had a reduction in OME from 24.0 mg to 6.0 mg, but all other patients ($n = 7$; 87.5%) did not have a change in OME doses. There was no change in OME doses between baseline and end of follow-up after patients were commenced on CBMP [$n = 8$; 24.0 (24.0–36.0) mg vs 24.0 (24.0–36.0) mg; $p = 0.317$].

3.5. Adverse events

Seventeen (17.5%) patients experienced a total of 113 (116.5%) AEs (**Table 6**). Of these 63 (64.9%) were classified as

mild, 39 (40.2%) as moderate and 11 (11.3%) as severe. The most common AEs were dry mouth ($n = 11$; 11.3%), headache ($n = 11$; 11.3%), fatigue ($n = 8$; 8.2%), and concentration impairment ($n = 8$; 8.2%). Two (2.1%) patients reported life-threatening/disabling AEs of fatigue ($n = 1$; 1.0%) and headache ($n = 1$; 1.0%). However, in accordance with CTCAE version 4.0[57], these AEs were downgraded to ‘severe.’

4. Discussion

This case series examined PROMs, general HRQoL metrics and AEs to evaluate the efficacy and safety of prescribed CBMPs for patients in the UK with headache disorders. Overall, results suggest that initiation of CBMP therapy was associated with improvements in validated headache- and migraine-specific PROMs and certain general HRQoL metrics, demonstrated by sustained improvements at 6-months in HIT-6, MIDAS and EQ-5D-5L index values.

There were statistically significant improvements in HIT-6 and MIDAS scores at all follow-up points compared to baseline. These results echoed previous findings by Cuttler et al.’s retrospective observational study, whereby Canadian participants with headache disorders reported a decrease in headache and migraine severity of nearly 50% after consuming inhaled medical cannabis [30]. Results in the present analysis were further corroborated in a retrospective study which investigated 121 patients with migraine across two medical cannabis specialty clinics in Colorado [29] where patients reported a decrease in migraine frequency from 10.4 to 4.6 per month at follow-up assessment. However, unlike this study, these analyses did not assess changes in clinical outcomes by using validated PROMs; therefore, it is difficult to compare the magnitude of efficacy between these cohorts. Mirroring results reported here, over half of the patient cohort in Rhyne et al.’s study were lost to follow-up, which may have contributed to an attrition bias and have led to an overestimation of the effect size in both studies [29]. However, individuals in Rhyne et al.’s study consumed medical cannabis via inconsistent routes of administration, varying product formulae, and the daily frequency of consumption was not recorded, which

Table 6. Adverse Events reported by patients prescribed cannabis-based medicinal products for headache disorders (n = 97).

	Mild N	Moderate N	Severe N	Total N (%)
Constipation	2			2 (2.1)
Somnolence		5	1	6 (6.2)
Dysgeusia	1			1 (1.0)
Blurred vision	1		1	2 (2.1)
Dry mouth	10	1		11 (11.3)
Lethargy	3		1	4 (4.1)
Urinary tract infection		2		2 (2.1)
Fatigue	3	4	1	8 (8.2)
Delirium	4			4 (4.1)
Confusion	4			4 (4.1)
Nausea	2	4		6 (5.4)
Concentration impairment	7	1		8 (8.2)
Insomnia	2	3	2	7 (6.3)
Headache	1	6	4	11 (11.3)
Pharyngitis		2		2 (2.1)
Decreased weight	2			2 (2.1)
Dizziness	2	1		3 (3.1)
Vertigo	2			2 (2.1)
Ataxia	2			2 (2.1)
Dyspepsia	2	1		3 (2.7)
Cognitive disturbance	2	1	1	4 (4.1)
Amnesia	3			3 (3.1)
Abdominal pain upper	2			2 (2.1)
Respiratory infection		2		2 (2.1)
Rash		1		1 (1.0)
Anorexia	1	1		2 (2.1)
Muscular weakness	2	2		4 (4.1)
Spasticity		1		1 (0.9)
Vomiting	1	1		2 (2.1)
Fall	1			1 (1.0)
Bloating	1			1 (1.0)
Total %	63 (64.9)	39 (40.2)	11 (11.3)	113 (116.5)

potentially confounded the results [29]. In contrast, in this study, healthcare and CBMP prescriptions were delivered in compliance with standards set by MHRA and other regulatory bodies [46].

More recently, Baraldi et al. conducted a retrospective study of 32 Italian patients with chronic migraine where three oral cannabinoid preparations (Bediol, Bedrocan, and FM2) were prescribed [42]. They reported a reduction of headache pain intensity at 3- and 6-months follow-up compared to baseline; however, the number of migraines per month did not decrease. From the present study, it is unclear if the improvements in HIT-6 and MIDAS were uniquely a result of a decreased pain intensity or is attributed to a reduced migraine frequency. Regardless, headache-specific PROMs are a gold-standard measure of headache/migraine burden, which encompass many different components; thus, this study builds on previous studies by providing a more holistic and validated summary of CBMPs' effect on HRQoL [58].

The associated changes in headache- and migraine-specific PROMs reached clinically important thresholds. At all follow-up points, PGIC-1 scores reflected 'a definite improvement' that had made a 'real and worthwhile difference' and PGIC-2 scores indicated a 'good' degree of change since beginning care at the clinic. Furthermore, the minimal clinically important changes in HIT-6 and MIDAS are -2.5 [59] and -5.0 [60] points, respectively. At 3-months follow-up, 71.7% and 66.7% of patients had exceeded the minimally clinically important decrease in HIT-6 and MIDAS, respectively. This proportion was higher than a study which previously reported that 53% of

patients receiving lasmiditan for migraines had a minimally clinically important decrease in MIDAS at 3-months follow-up [61]. Furthermore, a recent study reported that only 58.1% of the patient cohort would continue taking triptans for acute relief of their migraines, with the leading reason for patient dissatisfaction being that patients did not consider the regimes to be working well [62]. In this study, a higher proportion of clinical response and patient satisfaction is notable, especially considering that CBMPs may only be prescribed in the UK for patients refractory to first-line therapies, such as triptans. These encouraging results mandate further evaluation with randomized controlled trials to assess if CBMPs are the causative agent for the associated change rather than regression to the mean.

Previous studies have reported that many patients with headache disorders are already self-treating with cannabis products [63,64]. A similar trend was identified in the baseline demographic data from the present study where, in comparison to the general population [65], a larger number of patients were current and daily cannabis consumers. Sub-group analysis according to prior cannabis exposure demonstrated that there were differences in reported PROMs at 1-, 3-, and 6-months follow-up between sub-groups compared to baseline. However, these differences were inconsistent, and no specific trend was identified. Importantly, the present study demonstrated that even when patients had consumed cannabis regularly, they still benefited from switching to or addition of CBMP therapy. This implies that access to consistent, safe CBMPs under the supervision of medical care may

provide additional benefits. However, in the present study, the large proportion of participants who were consuming cannabis at the time of enrollment potentially confounded results due to influences such as tolerance [30]. Moreover, the cohort is self-selected introducing a selection bias because patients may have anticipated the same beneficial experience of illicit cannabis with CBMP therapy, thus, improvements have perhaps been overstated. This theoretical limitation is supported by the results as cannabis naïve patients had less pronounced reductions in headache/migraine-specific PROMs.

Results also indicated associated improvements in other HRQoL metrics, including sleep-quality, anxiety, and EQ-5D-5L index values. These findings are consistent with other clinical studies [37,66,67] and the longer follow-up reported in this study elucidates a sustained association with improved HRQoL. However, in this study, GAD-7 scores were ≤ 5 at baseline, signifying 'mild' anxiety symptoms, and the median GAD-7 change did not reach the estimated minimal clinically important difference of -3.3 [68] which collectively suggests changes were not meaningful. Moreover, extensive loss to follow-up reported here could disguise potential worsening anxiety and depression symptoms, which have been reported especially with high-dose cannabinoid consumption [69]. Likewise, continual consumption of cannabis products has been associated with habituation to its sleep-inducing properties and other harmful impacts on sleep [70]. Thus, it is necessary to assess the longer-term effect as well as the consequences of withdrawal from CBMPs to clarify the benefits reported here.

The present study revealed no change in OME consumption after patients commenced CBMP treatment. This contradicts findings in Baraldi et al.'s [42] retrospective study of patients with chronic migraine. However, this may be because the database did not capture data from 'pro re nata' prescriptions and so OMEs were only available for 11 patients which does not represent the true proportion of patients taking acute medications. Importantly, other studies which report significant changes in medication consumption specifically measure acute medication utilization.

AEs were experienced by 17 patients (17.5%), totaling 113 incidences (116.5%), with the majority being classified as mild. This patient proportion is marginally smaller than has been reported in a similar study [48]. It is understood that the proportions of THC, CBD, and other active pharmaceutical ingredients can influence the AEs profile of CBMPs [5] and so it is possible that these discrepancies are explained by variations in formulations and dosages between studies. Regardless, the true incidence of AEs may be overstated because they may have occurred in periods where patients' CBMP therapies were being increased to identify the optimal dose as opposed to occurring when a patient had been on a sustained dose. Thus, reported AEs may not be a true reflection of maintenance therapies. Moreover, long follow-up periods with repeated prompting to report such events during clinical assessment may have introduced a placebo effect. Notably, higher rates of headache were reported here compared to similar studies [48,66]. This may be because cannabinoids have been shown to decrease headache stress threshold in migraine patients [71]; however, it is also possible that these reports

were associated with the underlying headache pathology and not an effect of the patient's CBMP therapy. Overall, in accordance with literature [72], there were no life-threatening or disabling AEs suggesting relative clinical safety.

4.1. Limitations

Several study limitations must be noted. Crucially, a case series can only draw associations and no cause-and-effect relationship can be established. Additionally, the lack of blinding or control group, which reduces the internal validity because self-reported outcomes may have been overstated. This bias was potentially amplified because patients did not discontinue their preventative and acute medication for their headaches which may have confounded the effects of prescribed CBMPs. However, this effect may have been minimal because it has previously been demonstrated that preventative medication does not affect the outcome of changes in headache impact during CBMP therapy [42]. Moreover, PROMs are subjective scores that hold different values for each patient, reducing comparability and subject to recall bias. The follow-up period was 6-months due to insufficient data collection after this time point. This prevented the assessment of long-term efficacy and any tolerability resulting from sustained CBMP use, which may be significant because tolerability has been established both pre-clinically [73] and clinically [30]. Furthermore, loss to follow-up during these 6-months resulted in missing data which reduced statistical power and introduced an attrition bias. Similarly, the clinic involved in prescribing the CBMPs is private which not only limits external validity because results might not be generalizable to a low-middle socioeconomic group but also because patients may have been more likely to overstate clinical improvements, and the financial burden of therapies may have exacerbated loss to follow-up. However, 23.7% of patients were unemployed, implying that socioeconomic status may not have precluded access to therapy. Furthermore, in this study, males were overrepresented which is not representative of migraine patients as females have a higher incidence of migraines. However, this may be a reflection that males are more likely to access illicit cannabis and therefore transition to medical cannabis [74]. Lastly, only a small number of patients experienced cluster or tension-type headache; therefore, any conclusions may only apply to migraines and not be valid for the other headache disorders included in the analysis.

Despite these limitations, this study has many strengths. Being the largest prospective UK case series of its kind, it fills an evidence gap. Moreover, real-world data were collected from routine clinical practice without interfering with a patient's usual treatment process. Therefore, it is an inexpensive, quick, and resource-efficient method of analysis with high external validity. The study also assessed changes in PROMs which are holistic and gold-standard measures for pain conditions. Meanwhile, STROBE guidelines for observational studies were followed to minimize bias [45]. Overall, results from this study could aid in generating a hypothesis for future clinical trials.

In the future, randomized control trials (RCT) are necessary to establish causality. Importantly, trials should assess CBMP's efficacy and safety for individual primary headache disorders and should establish the place of cannabis therapy in optimal headache treatments. There is potential for linkage of the UKMCR with clinical practice data sets to create matched controls for future comparisons. Additionally, the long-term (>6-months) efficacy and safety should be assessed to determine any tolerability, and statistical adjustments should be made to ensure other medications used, such as acute medications, do not confound findings. Wearable technology, such as smart watches, could allow for more accurate prospective and contemporary recording of head pain levels, reducing recall bias and subjectivity [75]. Studies should distinguish the effects of CBMPs according to underlying clinico-pathological differences. Furthermore, full-spectrum products should be compared with isolated cannabinoids to elucidate if other compounds derived from the Cannabis plant may be contributing to an overall therapeutic effect [76].

5. Conclusion

Whilst these results provide promise with respect to the changes in health-related quality of life experienced by those with primary headache disorders, there is still a requirement for further RCTs to be conducted to understand the true efficacy of CBMPs for this indication. However, whilst these are awaited, the present study outcomes with respect to safety and efficacy provide useful insights to inform current clinical practice.

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Data Availability

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.

Ethical approval

In the UK, formal ethics approval is not required for research database analysis as detailed by the UK Health Research Authority.

Principal Investigator

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

Declaration of Interest

S Erridge, C Holvey, R Coomber, JJ Rucker, MW Weatherall & MH Sodergren are the founding clinicians of Sapphire Medical Clinics, which is the first clinic registered with the CQC to evaluate patients

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