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ORIGINAL RESEARCH

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Clinical outcome data of chronic pain patients treated with cannabis-based oils and dried flower from the UK Medical Cannabis Registry

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ABSTRACT

Background: The following study evaluated the clinical outcomes of patients enrolled in the UK Medical Cannabis Registry, who were treated with inhaled dried flower (Adven® EMT2, Curaleaf International, Guernsey), and sublingual/oral medium-chain triglyceride-based oils (Adven, Curaleaf International, Guernsey) for chronic pain.

Methods: In this cohort study, the primary outcomes were changes in validated patient reported outcome measures (PROMs) at 1, 3, and 6 months compared to baseline, and adverse event analysis. Statistical significance was defined as $p < 0.050$.

Results: Three hundred and forty-eight (45.7%), 36 (4.7%), and 377 (49.5%) patients were treated with oils, dried flower, or both, respectively. Patients treated with oils or combination therapy recorded improvements within health-related quality of life, pain, and sleep-specific PROMs at 1, 3, and 6 months ($p < 0.050$). Patients treated with combination therapy recorded improvements in anxiety-specific PROMs at 1, 3, and 6 months ($p < 0.050$). 1,273 (167.3%) adverse events were recorded, with previously cannabis naïve users, ex-cannabis users, and females more likely to experience adverse events ($p < 0.050$).

Conclusions: This study observed an association between initiation of CBMP treatment and improved outcomes for chronic pain patients. Prior cannabis use and gender were associated with adverse event incidence. Placebo-controlled trials are still necessary to establish the efficacy and safety of CBMPs for chronic pain.

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1. Introduction

Chronic pain is a condition characterized by physical pain persisting for longer than 3 months, as defined by the International Association for the Study of Pain [1]. In the UK, chronic pain is estimated to affect between one-third to one-half of the adult population over the course of their lives [2]. Existing treatments include non-steroidal anti-inflammatory drugs, opioids, and gabapentinoids [1]. However, due to increasing evidence of the associated risk of long-term use and variable evidence of their efficacy across all causes of chronic pain, these medications are not suitable for every individual [3,4].

The endocannabinoid system, in particular cannabinoid type 1 (CB1R) and type 2 receptors (CB2R), has been implicated in pain sensation and perception pathways. CB1R, found most commonly within the nervous system, inhibits ascending nociceptive transmission from the dorsal horn in the spinal column, as well as stimulates descending analgesic pathways [5,6]. In contrast, CB2R predominantly modulates the release of inflammatory ligands and endogenous opioids in peripheral immune cells and keratinocytes [7]. CB2R is also present in the central nervous system within glial cells, endothelial cells, and neurons, where they have been found to play a neuroprotective role in neurological disorders and mediate neuronal sensitization in chronic pain conditions [6].

The (-)-trans-Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) compounds found within the cannabis plant are known to influence the endocannabinoid system [8]. THC is a CB1R and CB2R partial agonist [7]. CBD inhibits fatty acid–binding ligands responsible for transporting endocannabinoids intracellularly to be broken down by the enzyme fatty acid amino hydrolase [7]. Thus, CBD primarily produces

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a reduction in pain by increasing the concentration of endocannabinoids present at synaptic junctions. CBD also acts as an agonist in serotonin 1A (5-HT_{1A}) receptors and transient receptor potential subfamily V member 1 (TRPV1) cation channels, as well as inhibiting serotonin 3A (5-HT_{3A}) receptors [8]. THC, alternatively, produces a dose-dependent blockade of TRP cation channels [8,9]. Cannabis-based medicinal products (CBMPs) containing THC and CBD, have therefore been postulated as promising therapeutics for chronic pain considering their multifactorial role in reducing nociceptive signals in both the peripheral and central nervous system, as well as modulating the pathways in the primary somatosensory cortex and limbic system involved in the emotional and cognitive manifestations of pain via these receptors [6].

Despite growing evidence implicating CBMPs as a viable chronic pain treatment, the results have been heterogenous, differing based on the type of CBMP administered, chronic pain type assessed, and study duration [10,11]. Additionally, there remains a paucity of evidence regarding the long-term safety of CBMPs [10]. This was reflected in a recent systematic review, which investigated patient preferences and concerns regarding the use of CBMPs for chronic pain, finding that adverse effects were identified as a common concern, alongside medication composition, legal status, and cost [12]. Moreover, factors such as route of administration, age, body mass index (BMI), and prior cannabis exposure influence CBMP safety have not been adequately investigated [13].

As further clinical trials addressing these unknowns are awaited, patient registries can assist by collecting prospective data from patients prescribed CBMPs in a real-world setting [14]. The UK Medical Cannabis Registry (UKMCR) records longitudinal, long-term data collected from patients prescribed CBMPs to better assess the therapeutic benefits for different conditions. This study aimed to evaluate changes in general health-related quality of life (HRQoL), chronic pain-specific outcomes, and adverse events in patients treated exclusively with CBMPs. Changes in opioid prescriptions following CBMP treatment were also investigated.

2. Methods

2.1. Data collection

A prospective cohort study of patients from the UKMCR treated with an inhaled dried flower (Adven® EMT2, Curaleaf International, Guernsey, UK), sublingual/oral medium-chain triglyceride-based oil (Adven®, Curaleaf International, Guernsey, UK), or a combination of both for chronic pain was conducted. The UK Medical Cannabis Registry has received ethical approval from the South West – Central Bristol Research Ethics Committee (reference 22/SW/0145). All patients completed formal, written consent prior to enrollment. The study was reported in line with the STROBE statement for reporting observational studies [15].

The UKMCR is a patient registry, set up in December 2019 to collect prospective, clinical data from patients prescribed CBMPs outside of the NHS. It is privately owned and managed by Sapphire Medical Clinics.

Patient demographics, medications, comorbidities, occupations, and drug and alcohol history were collected by clinicians. Clinicians recorded indications for CBMP therapy using primary, secondary, and tertiary diagnoses (Supplementary Table S1). Participants updated their concomitant medications using an online platform, or informed clinicians of any changes during follow-up appointments. Opioid medications were converted to oral morphine equivalents using conversion factors quoted by the British National Formulary and GP notebook [16]. The Charlson comorbidity index, a model of underlying health status, was calculated for each patient in line with other longitudinal health-care registries [17]. THC and CBD dosages (mg/24 h) were recorded for each CBMP prescription.

Occupations were classified according to the International Standard Classification of Occupations [18]. Patients provided their cannabis history prior to receiving a CBMP prescription. Cannabis naïve users had never used cannabis before, ex-users had previously used cannabis but were not using it at the time of starting a CBMP prescription, and current users were using illicit cannabis up until the time of prescription. For ex- and current users, a novel metric, cannabis gram-years, was used to quantify cannabis use as previously described [14]. Smoking status, smoking pack-years, and weekly alcohol consumption were also recorded. Patients were sent patient reported outcome measures (PROMs) and adverse event questionnaires electronically at baseline, 1, 3, and 6 months after CBMP treatment commenced.

2.2. Patient and public engagement

To develop the methodology of the present study, a concurrent patient evaluation of 600 patients enrolled on the UKMCR was performed [19]. The majority found the electronic data collection platform easy to use when reporting PROMs (91.6%), adverse events (73.1%), and medication changes (90.4%). Over 90% of the patients agreed or strongly agreed that contribution to the UKMCR would impact the care of future patients [19]. Finally, the highest priorities for future research were identified as 'assessing the impact of medical cannabis on quality of life,' 'assessing the impact of medical cannabis on condition-specific outcomes,' 'collecting information about the side effects of medical cannabis,' and 'assessing the impact of medical cannabis on other prescribed medications' [19].

2.3. Patient and data selection

Patient data from those prescribed Adven® CBMPs for chronic pain conditions was extracted from the UKMCR on 9 January 2022. Individuals who had a primary indication for CBMP therapy other than chronic pain, or a condition for which treatment of chronic pain symptoms is the only reason CBMPs might be prescribed, were excluded from the analysis. Cohorts were identified according to the route of administration(s) of their prescribed product(s). Patients prescribed oil-based products (including reformulated oils in lozenges or capsules), inhaled dried flowers, and both products were distinguished into three separate cohorts. Full details of oil-based and dried flower products are detailed in

Supplementary Table S2. Participants who had not completed all baseline PROMs were excluded.

2.4. PROMs

Primary outcomes of the study were changes in the following questionnaires: Pain Visual Analog Scale (P-VAS), Brief Pain Inventory Short-Form (BPI), Short-Form McGill Pain Questionnaire-2 (MPQ2), Single-Item Sleep Quality Scale (SQS), Generalized Anxiety Disorder-7 (GAD-7), EQ-5D-5L, and Patient Global Impression of Change (PGIC).

The P-VAS questionnaire asks patients to rate their pain from 0 to 10 where '0' is 'no pain at all' and '10' is 'pain as bad as it could be' on a 10 cm visual analog scale [10].

BPI is a questionnaire where patients score their worst, strongest, current, and average pain intensity. Scores are combined to create a 'pain severity score' from 0 to 10 where '0: no pain' and '10: pain as bad as you can imagine' [17]. Patients also rate the impact of their pain on daily activities, such as sleep, socializing, and work to create a 'pain interference score' from 0 to 10 with '0: no interference' and '10: completely interferes' [20].

MPQ2 assesses the character and severity of pain. Patients rate different pain descriptors and symptoms from 0 to 10 with '0: none' and '10: the worst pain possible' [21]. Questions are organized into four subscales: continuous pain, intermittent pain, neuropathic pain, and affective descriptors [18]. An average from 0 to 10 is then calculated for each subscale and total score, with greater numbers indicating higher pain severity.

The SQS is a single validated efficacy measure whereby patients rate their sleep quality over the previous week from 0 to 10 with '0: terrible' and '10: excellent' [22].

GAD-7 asks patients for the frequency of symptoms of generalized anxiety disorder over the past 2 weeks, generating a score from 0 to 21 [20]. The score is classified according to severity, whereby mild, moderate, and severe anxiety are determined by scores of ≥5, ≥10, and ≥15, respectively [23].

EQ-5D-5L is a global metric of HRQoL consisting of questions with 5 levels of severity across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [24,25]. Respondents assign scores from 1 to 5 for each domain, where '1: no problems,' '2: slight problems,' '3: moderate problems,' '4: severe problems' and '5: extreme problems' [24,25]. Collectively, these scores generate one of the 3125 health states, with each health state mapped to a UK-specific index value in line with the preferred methodology outlined by the National Institute of Health and Care Excellence [25,26]. An index value of '1' represents 'full health.' An index value <0 represents a HRQoL 'worse than death.'

PGIC uses a 7-point scale to determine if there has been an improvement or decline in a patient's quality of life since treatment commenced. Scores range from '1: no change' to '7: a great deal better' [27].

2.5. Adverse events

Adverse events were recorded in accordance with the common terminology criteria for adverse events version 4.0 [28]. Adverse events could be recorded by patients ad hoc following their occurrence, contemporaneously with PROMs, or during a clinical consultation. Dried flower users were not included in adverse event analysis due to low numbers of adverse events ($n = 1$).

2.6. Statistical analysis

Shapiro–Wilk tests were performed to determine parametric/nonparametric data. Parametric data was presented as mean ± standard deviation (SD), and nonparametric data was presented as median and interquartile range (IQR). A Wilcoxon rank-sum test was performed to compare the paired differences for PROMs for each patient at 1, 3, and 6 months compared to baseline within each treatment category, as each dataset was confirmed to be nonparametric. PGIC was not included in this analysis as the questionnaire itself establishes health changes relative to baseline. Univariate binary logistic regression models were used to individually assess the effect of age, BMI, gender, treatment type, and prior cannabis exposure on the likelihood of experiencing an adverse event, an improvement in BPI severity score, or BPI interference score, after 6 months by calculating odds ratios (ORs) and 95% confidence intervals (CI). In each analysis, variables demonstrating statistically significant associations were included in a multivariate analysis, which determines the impact of each variable on the outcome measure, after adjusting for the other included variables. A paired samples t-test was used to investigate changes in opioid prescriptions after 6 months of treatment. Statistical significance was defined as $p < 0.050$. Analyses were conducted using RStudio version 4.1.2.

3. Results

3.1. Patient demographics, clinical history, and prescriptions

The data extraction included 812 patients prescribed Adven® CBMPs for chronic pain conditions within the UKMCR. Of those, 761 (93.7%) completed baseline PROMs and were included in the analysis (Figure 1). Table 1 presents patient demographics, clinical history, and prescription information in full.

3.2. PROMs

To assess the effect of CBMP treatment on HRQoL in chronic pain patients, patients were administered HRQoL questionnaires at baseline, 1, 3, and 6 months after CBMP treatment commenced. Table 2 summarizes the paired results for pain-related PROMs. For patients only prescribed oils, statistically significant improvements in P-VAS, BPI, and MPQ2 were seen at 1, 3, and 6 months compared to the baseline ($p < 0.010$). For patients only prescribed dried flower CBMPs, statistically significant improvements were seen in P-VAS, BPI Severity Score, and MPQ2 after 1 and 3 months, respectively ($p < 0.050$). Improvements were seen after 1 month for the BPI Interference Score ($p = 0.005$). For patients prescribed both oils and dried flower CBMPs, improvements were found in P-VAS, BPI Interference Score, and MPQ2

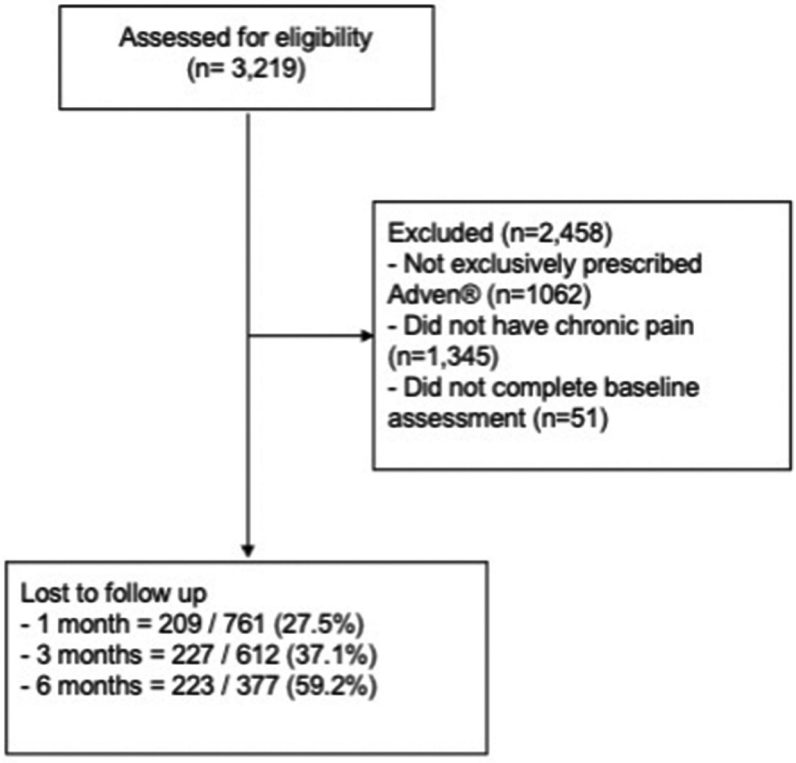

Figure 1. Flowchart of data inclusion and completeness of follow-up.

after 1, 3, and 6 months, respectively ($p < 0.010$). Additionally, improvements were seen in the BPI Severity Score after 3 and 6 months ($p < 0.01$).

To determine the impact of a patient's age, gender, BMI, prior cannabis experience, and CBMP treatment type on pain relief, a univariate binary logistic regression model was used to investigate the impact of these variables on recorded improvements in the BPI Interference and Severity scores after 6 months of treatment relative to baseline.

In univariate analysis (Supplementary Tables S3 & S4), no variables were found to be significantly associated with reduced pain severity or interference ($p > 0.050$). A multivariate analysis was conducted to confirm these findings, which similarly showed no significant difference ($p > 0.050$) (Table 3 and Supplementary Table S5).

Table 4 summarizes the paired results for non-pain-specific HRQoL questionnaires. For patients prescribed oils, statistically significant improvements were seen in SQS and the EQ-5D-5L index, usual activities, and pain and discomfort subscales after 1, 3, and 6 months ($p < 0.050$). Improvements in GAD-7 and the EQ-5D-5 L anxiety and depression subscales were found at 1 and 3 months compared to baseline ($p < 0.001$). For PGIC, the median remained constant at 5.00.

For dried flower users, improvements were seen after 1 and 3 months for SQS, and the EQ-5D-5L index, as well as the pain and discomfort subscale ($p < 0.050$). Improvements were also seen after 1 month for the EQ-5D-5L usual activities domain ($p = 0.032$).

For patients prescribed both oils and dried flower CBMPs, statistically significant improvements were found in SQS, GAD-7, as well as the EQ-5D-5L index, mobility, usual activities and pain and discomfort subscales after 1, 3, and 6 months, respectively ($p < 0.050$). Additionally, improvements were seen in the EQ-5D-5 L self-care and anxiety and depression subscales after 1 and 3 months ($p < 0.050$). The median PGIC increased from 5.00 at 1 month to 6.00 after 3 and 6 months.

3.3. Change in opioid medications

To investigate the impact of CBMP treatment on opioid prescriptions, a paired samples t-test was used to determine changes in patient opioid usage after 6 months of treatment relative to baseline. There was a reduction in opioid prescriptions after 6 months (40.7 mg/24 h ± 57.6 mg/24 h) compared to baseline (42.1 mg/24 h ± 58.3 mg/24 h; $p = 0.018$). This represents a 3.28% reduction in mean opioid dose.

3.4. Adverse events

Patients also reported adverse events to assess the safety profile of each CBMP treatment, as well as identify if prior cannabis exposure affected adverse event incidence.

For patients prescribed oils, 857 total adverse events were recorded, with 91 patients (26.1%) experiencing at least 1 adverse event. There were 387 (111.2%) mild, 360 (103.4%) moderate, 109 (31.3%) severe and 1 (0.3%) life-threatening adverse events recorded, respectively. For patients prescribed both oils and dried flowers, 415 total adverse events were recorded, with 56 (14.9%) patients experiencing at least 1

Table 1. Patient demographics, clinical history, and prescriptions.

Baseline Characteristics	No. (%)/Mean ± SD/Median [IQR]
Prescription information	
Oils	348 (45.7)
CBD, mg/24 h	20.0 [20.0–30.0]
THC, mg/24 h	10.0 [10.0–20.0]
Dried flower	36 (4.7)
CBD, mg/24 h	2.5 [0.0–5.0]
THC, mg/24 h	125.0 [100.0–196.3]
Oils and dried flower	377 (49.5)
CBD, mg/24 h	20.0 [20.0–25.0]
THC, mg/24 h	120.0 [110.0–205.0]
Gender	
Female	401 (52.7)
Male	360 (47.3)
Age, years	46.8 ± 15.4
Body mass index*, kg/m2	27.7 ± 7.0
Occupation	
Unemployed	273 (35.9)
Undisclosed	211 (27.7)
Professional	73 (9.6)
Managers	46 (6.0)
Other occupations	45 (5.9)
Elementary occupations	32 (4.2)
Technicians and associate professionals	31 (4.1)
Craft and related trades workers	16 (2.1)
Service and sales workers	15 (2.0)
Clerical support workers	13 (1.7)
Plant and machine operators and assemblers	3 (0.4)
Armed forces	2 (0.3)
Skilled agricultural, forestry and fishery workers	1 (0.1)
Cannabis status	
Current user	326 (42.8)
Cannabis naïve	313 (41.1)
Ex-user	122 (16.0)
Cannabis use, gram years	6.0 [1.9–20.0]
Smoking status	
Ex-smoker	310 (40.1)
Nonsmoker	255 (33.5)
Current smoker	196 (25.8)
Smoking pack years	10 [5.0–20.0]
Weekly alcohol consumption, units	0 [0.0–5.0]
Charlson Comorbidity Index	1.0 [0.0–6.0]

Data on patients prescribed cannabis-based medicinal products (CBMP) for chronic pain was recorded by clinicians. Cannabis naïve users had never used cannabis before,©and ex-users had previously used cannabis but were not using it at the time of their prescription. Current users were using nonprescription cannabis at the time of their prescription. Median cannabis use in gram years for ex- and current users was calculated as previously described38. *n = 615. CBD = cannabidiol, THC = (-)-trans-Δ9-tetrahydrocannabinol. SD = standard deviation, IQR = interquartile range.

adverse event. There were 178 (47.2%) mild, 167 (44.3%) moderate, and 70 (18.6%) severe adverse events recorded. Supplementary Table S6 details the quantity and severity of adverse events in full for each treatment group, as well as patients' prior cannabis exposure status. The most common recorded adverse events were fatigue ($n = 114$; 14.0%), somnolence ($n = 88$; 10.8%), and dry mouth ($n = 84$; 10.3%) (Supplementary Table S7).

On univariate analysis (Supplementary Table S8), the following were found to be associated with a higher incidence of adverse events; age between 71 and 80 years (OR = 2.294; 95% CI: 1.069–4.919; $p = 0.033$), ex-users of cannabis (OR = 2.316; 95% CI: 1.296–4.137; $p = 0.005$), and naïve cannabis users (OR = 3.697; 95% CI: 2.359–5.794; $p < 0.001$). Male patients (OR = 0.320; 95% CI: 0.213–0.481; $p < 0.001$) and those prescribed oils and dried flower (OR = 0.493; 95% CI: 0.340–0.714; $p < 0.001$) were less likely to experience and adverse events.

Statistically significant variables were taken forward to a multivariate model (Table 5). Cannabis naïve (OR = 2.515; 95% CI: 1.470–4.301) and ex-users (OR = 2.286; 95% CI: 1.246–4.195) were more likely to experience adverse events relative to current users, to a statistically significant extent. Additionally, males (OR = 0.403; 95% CI: 0.262–0.618) were less likely to experience adverse events to a statistically significant extent. No statistically significant difference in adverse event incidence was found between patients prescribed oils or both CBMPs (OR = 1.005; 95% CI: 0.639–1.581), or between age groups.

4. Discussion

The findings in this study demonstrate treatment with oil-based, dried flowers, or a combination of both CBMPs are

Table 2. Paired baseline and follow-up data for pain-specific patient-reported outcome measures (PROMs).

PROM	Follow-up interval	n	Baseline scores [IQR]	Scores at follow-up [IQR]	P-value
Oils					
P-VAS	1 month	242	7.00 [6.00–8.00]	7.00 [5.00–8.00]	<0.001***
	3 months	134	7.00 [6.00–8.00]	6.00 [4.00–7.00]	<0.001***
	6 months	68	7.00 [6.00–8.00]	6.00 [3.00–7.25]	<0.001***
BPI – Interference Score	1 month	247	6.57 [5.14–8.00]	5.86 [3.64–7.36]	<0.001***
	3 months	134	6.29 [4.71–7.57]	5.29 [3.43–6.82]	<0.001***
	6 months	68	5.86 [4.14–7.00]	4.71 [3.14–6.43]	<0.010**
BPI – Severity Score	1 month	247	6.00 [4.75–7.25]	5.50 [4.00–6.75]	<0.001***
	3 months	134	5.88 [4.25–7.00]	5.00 [3.75–6.19]	<0.001***
	6 months	68	5.75 [4.25–7.00]	5.00 [2.94–6.25]	<0.001***
MPQ2	1 month	243	4.13 [2.93–5.65]	3.67 [2.32–4.96]	<0.001***
	3 months	134	3.98 [2.71–5.44]	2.89 [1.79–4.81]	<0.001***
	6 months	68	3.76 [2.80–4.99]	2.66 [1.63–3.84]	<0.001***
Dried flower					
P-VAS	1 month	22	7.00 [5.25–7.75]	5.50 [3.00–6.75]	<0.010**
	3 months	17	7.00 [5.00–7.00]	5.00 [3.00–7.00]	<0.050**
	6 months	7	5.00 [3.00–7.50]	3.00 [1.50–5.00]	0.370
BPI – Interference Score	1 month	23	5.71 [4.79–7.21]	5.14 [2.21–5.93]	<0.010**
	3 months	17	5.71 [3.71–7.29]	4.14 [2.43–6.29]	0.210
	6 months	7	3.71 [1.64–4.79]	2.14 [1.50–3.64]	0.160
BPI – Severity Score	1 month	23	5.50 [3.63–6.75]	5.25 [2.88–5.63]	<0.050**
	3 months	17	6.00 [3.75–7.00]	5.00 [3.25–5.50]	<0.050**
	6 months	7	3.75 [3.25–5.38]	3.25 [1.38–4.75]	0.380
MPQ2	1 month	22	3.96 [1.77–5.45]	2.55 [1.26–3.90]	<0.010**
	3 months	17	4.69 [1.54–5.60]	2.38 [0.88–3.52]	<0.010**
	6 months	7	1.54 [1.39–1.81]	0.54 [0.35–1.44]	0.071
Oils and dried flower					
P-VAS	1 month	270	7.00 [6.00–8.00]	6.00 [5.00–7.75]	<0.001***
	3 months	183	7.00 [6.00–8.00]	6.00 [4.00–7.00]	<0.001***
	6 months	78	7.00 [5.00–8.00]	5.00 [3.00–7.00]	<0.001***
BPI – Interference Score	1 month	274	7.00 [5.57–8.43]	5.79 [3.57–7.43]	<0.010**
	3 months	183	6.57 [5.29–8.07]	5.00 [2.86–6.93]	<0.001***
	6 months	78	6.07 [4.00–7.54]	4.50 [2.64–6.64]	<0.001***
BPI – Severity Score	1 month	274	5.75 [5.00–7.00]	5.25 [3.75–6.50]	0.070
	3 months	183	5.50 [4.50–6.88]	4.75 [3.00–6.25]	<0.001***
	6 months	78	5.13 [3.75–6.00]	4.50 [3.00–5.94]	<0.010**
MPQ2	1 month	271	4.56 [3.27–6.20]	3.83 [1.98–5.37]	<0.001***
	3 months	183	4.19 [3.01–5.92]	3.33 [1.37–4.93]	<0.001***
	6 months	78	3.88 [2.59–5.65]	2.89 [1.39–4.81]	<0.001***

Chronic pain patients treated with cannabis-based medicinal products recorded pain-specific PROMs at regular follow-up intervals. Paired data©were analyzed with a Wilcoxon rank-sum test. Median and interquartile ranges (IQR) are shown. P-VAS = Pain Visual©Analog Scale, BPI = Brief Pain Inventory Short-Form, MPQ2 = McGill Pain Questionnaire-2 Short-Form. A lower score indicates reduced pain. * $p < 0.050$, ** $p < 0.010$, *** $p < 0.001$.

associated with statistically significant improvements in pain relief and sleep quality after 6 months in chronic pain patients. Additionally, patients prescribed oils or both types of CBMPs experienced reduced anxiety and an improvement in their ability to perform daily activities. Patients prescribed a combination of both CBMPs recorded improvements in their self-care and mobility abilities. Collectively, this evidence signals that initiation of CBMP treatment is associated with improved HRQoL. Improvements in pain measured by BPI scores were also independent of patient age, gender, BMI, prior cannabis experience, and CBMP treatment type. Additionally, cannabis naïve and ex-users were more likely to experience adverse events relative to current users, whereas males were less likely to experience adverse events.

For patients prescribed oil-based or both CBMP types, statistically significant improvements in pain-specific PROMs were recorded at all time periods. This is supported by a recent observational study, which investigated the impact of oil-based CBMPs on HRQoL in 71 chronic pain patients [29]. The study found reductions in pain impact scores after an average treatment time of 133 days. Additionally, a recent meta-analysis of randomized clinical trials found chronic pain patients treated with CBMPs experienced an average P-VAS reduction of −0.5 cm [11]. This is lower than in the present study, which reported between −1 cm and −2 cm reductions in P-VAS after 6 months of CBMP treatment. This discrepancy may have arisen from the different study durations, as the median study duration in the meta-analysis was 50 days. Further, the P-VAS reductions recorded in this study are greater than the P-VAS minimum clinically significant difference, which is a 1 cm reduction, having been previously identified as beneficial enough to warrant CBMP treatment [11].

Previous studies have not investigated the effects of age, gender, BMI, prior cannabis exposure, or CBMP treatment type on cannabis-induced analgesia. In the present study, none of the aforementioned factors were found to influence improvements in BPI scores after 6 months. This suggests that cannabis-based analgesia is independent of these factors. However, this study only considered the dichotomous outcome of whether patient's BPI scores improved and did not quantify the magnitude of improvement. As such, some factors may have correlated with a greater improvement in pain relief, which would not have been captured in the present analysis. Additionally, the impact of

Table 3. Multivariate analysis of variables affecting BPI Severity scores.

Variable	Odds Ratio [95% Confidence Interval]	P-value
Age, years		
18–30	-	Ref
31–40	1.282 [0.268–6.122]	0.756
41–50	2.025 [0.468–8.752]	0.345
51–60	0.808 [0.181–3.613]	0.780
61–70	1.419 [0.288–6.996]	0.667
71–80	1.616 [0.230–11.354]	0.629
81+	N/A	
BMI, kg/m2		
<20	0.296 [0.066–1.325]	0.111
20–25	-	Ref
25–30	0.897 [0.318–2.533]	0.838
30–35	0587 [0.187–1.844]	0.362
35+	0.869 [0.128–5.892]	0.885
Cannabis status		
Current users	-	Ref
Ex-users	1.555 [0.392–6.129]	0.532
Naïve	1.063 [0.390–2.896]	0.905
Gender		
Female	-	Ref
Male	0.609 [0.258–1.437]	0.258
Treatment type		
Oils	-	Ref
Oils and dried flower	1.359 [0.506–3.650]	0.543
Dried flower	2.115 [0.278–16.112]	0.470

A multivariate binary logistic regression model was used to assess the effect of age, body mass index (BMI), prior cannabis experience, gender, and treatment type on Brief Pain Inventory (BPI) Severity scores after 6 months relative to baseline. The BPI Severity score measures patient pain severity.

Table 4. Paired baseline and follow-up data for non-pain-specific patient-reported outcome measures (PROMs).

		Oils				Dried flower			
PROM	Follow-up interval	n	Baseline scores [IQR]	Scores at follow-up [IQR]	P-value	n	Baseline scores [IQR]	Scores at follow-up [IQR]	P-value
SQS	1 month	250	4.00 [3.00–6.00]	6.00 [4.00–7.00]	<0.001***	23	5.00 [3.00–6.00]	7.00 [3.50–8.00]	0.030*
	3 months	135	5.00 [3.00–6.00]	6.00 [4.00–8.00]	<0.001***	17	5.00 [2.00–7.00]	7.00 [6.00–8.00]	0.011*
	6 months	68	6.00 [3.00–6.00]	6.00 [4.00–8.00]	0.014*	7	7.00 [4.00–8.00]	7.00 [7.00–8.50]	0.160
GAD-7	1 month	252	6.00 [1.75–11.00]	4.00 [0.75–8.00]	<0.001***	23	4.00 [1.50–7.50]	3.00 [0.00–6.50]	0.200
	3 months	135	6.00 [2.00–10.50]	4.00 [0.00–7.00]	<0.001***	17	6.00 [1.00–8.00]	3.00 [0.00–5.00]	0.070
	6 months	68	5.00 [1.75–8.00]	4.00 [0.00–6.25]	0.088	7	1.00 [0.50–5.00]	0.00 [0.00–3.50]	0.052
EQ-5D-5L Index	1 month	250	0.33 [0.12–0.59]	0.54 [0.31–0.65]	<0.001***	23	0.55 [0.28–0.72]	0.74 [0.59–0.77]	0.034*
	3 months	135	0.43 [0.18–0.62]	0.56 [0.33–0.69]	<0.001***	17	0.58 [0.26–0.74]	0.65 [0.50–0.84]	0.010**
	6 months	68	0.48 [0.21–0.63]	0.56 [0.39–0.69]	<0.001***	7	0.74 [0.62–0.77]	0.84 [0.58–0.84]	0.240
EQ-5D-5L Mobility	1 month	250	3.00 [2.00–4.00]	3.00 [2.00–3.00]	0.003**	23	2.00 [1.00–3.00]	2.00 [1.00–2.50]	0.058
	3 months	135	3.00 [2.00–4.00]	3.00 [2.00–3.00]	0.076	17	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.240
	6 months	68	3.00 [2.00–4.00]	3.00 [2.00–4.00]	0.400	7	2.00 [1.50–2.50]	1.00 [1.00–2.00]	0.110
EQ-5D-5L Selfcare	1 month	250	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.250	23	1.00 [1.00–2.50]	1.00 [1.00–2.00]	0.370
	3 months	135	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.360	17	1.00 [1.00–3.00]	2.00 [1.00–3.00]	0.400
	6 months	68	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.400	7	1.00 [1.00–1.50]	1.00 [1.00–2.00]	0.240
EQ-5D-5L Usual activities	1 month	250	3.00 [2.00–4.00]	3.00 [2.00–3.00]	<0.001***	23	2.00 [1.00–3.00]	2.00 [1.00–2.00]	0.032*
	3 months	135	3.00 [2.00–4.00]	3.00 [2.00–3.00]	0.005**	17	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.220
	6 months	68	3.00 [2.00–4.00]	2.00 [2.00–3.00]	0.038*	7	2.00 [1.00–2.00]	1.00 [1.00–2.00]	0.400
EQ-5D-5L Pain and Discomfort	1 month	250	4.00 [3.00–4.00]	3.00 [3.00–4.00]	<0.001***	23	4.00 [3.00–4.00]	2.00 [2.00–3.00]	<0.001***
	3 months	135	4.00 [3.00–4.00]	3.00 [2.50–4.00]	<0.001***	17	3.00 [3.00–4.00]	2.00 [2.00–3.00]	0.037*
	6 months	68	4.00 [3.00–4.00]	3.00 [3.00–4.00]	0.011*	7	3.00 [2.00–3.00]	2.00 [2.00–2.00]	0.075
EQ-5D-5L Anxiety and Depression	1 month	250	2.00 [1.00–3.00]	2.00 [1.00–3.00]	<0.001***	23	2.00 [1.00–2.50]	2.00 [1.00–2.00]	0.200
	3 months	135	2.00 [1.00–3.00]	2.00 [1.00–3.00]	<0.001***	17	2.00 [1.00–3.00]	1.00 [1.00–3.00]	0.260
	6 months	68	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.370	7	1.00 [1.00–2.00]	1.00 [1.00–2.50]	0.240
PGIC	1 month	239	N/A	5.00 [3.00–6.00]	N/A	23	N/A	6.00 [5.00–6.00]	N/A
	3 months	120	N/A	5.00 [4.00–6.00]	N/A	17	N/A	6.00 [5.00–6.00]	N/A
	6 months	57	N/A	5.00 [5.00–6.00]	N/A	7	N/A	7.00 [6.50–7.00]	N/A

Median and interquartile ranges (IQR) are shown. SQS = Single-Item Sleep Quality Scale, GAD-7 = Generalized Anxiety Disorder-7, PGIC = Patient Global Impression of Change. For GAD-7, a lower score indicates reduced anxiety. For SQS,©PGIC, and EQ-5D-5 L, higher scores indicate improvement. *p < 0.050, ** p < 0.010, *** p < 0.001.

Table 5. Multivariate analysis of factors increasing the risk of adverse events from cannabis-based medicinal products.

Variable	Odds Ratio [95% Confidence Interval]	P-value
Age		
18–30	-	Ref
31–40	0.757 [0.386–1.485]	0.418
41–50	0.780 [0.407–1.495]	0.455
51–60	1.198 [0.625–2.300]	0.586
61–70	1.071 [0.520–2.206]	0.852
71–80	1.536 [0.683–3.453]	0.300
81+	1.485 [0.502–4.388]	0.475
Cannabis status		
Current users	-	Ref
Ex-users	2.286 [1.246–4.195]	0.008**
Naïve	2.515 [1.470–4.301]	<0.001***
Gender		
Female	-	Ref
Male	0.403 [0.262–0.618]	<0.001***
Treatment type		
Oils	-	Ref
Oils and dried flower	1.005 [0.639–1.581]	0.984

A multivariate binary logistic regression model was used to assess the effect of age, cannabis status, gender, and treatment type on the chances of experiencing adverse events by calculating odds ratios and 95% confidence intervals. Naïve users had never used cannabis before, ex-users had previously used cannabis but were not using it at the time of starting their prescription. Current users were using non-prescription cannabis up until the time of their prescription. Ref = reference group. *p < 0.050, **p < 0.010, ***p < 0.001.

various CBMP dosages was not considered. These represent important avenues for future research.

Patients prescribed both CBMPs reported improvements in SQS, GAD-7, and all EQ-5D-5L metrics. This is consistent with an audit of 400 patients prescribed CBD oil, which found a significant reduction in all EQ-5D-5L subscales in chronic non-cancer pain patients and patients with anxiety, depression, and insomnia after 3 weeks of treatment [30]. In contrast, this study found no difference in the EQ-5D-5L mobility or self-care subscales for those only prescribed oils. Vaporized CBMPs allow for a quicker onset of action due to bypassing first-pass metabolism and are absorbed straight into the bloodstream [31]. In contrast, oil-based CBMPs take longer to reach peak serum levels, thus the onset of action is observed later. Patients prescribed both types of CBMPs may therefore experience benefits from both administrative routes, leading to the differences observed.

A 3.28% reduction in daily opiate consumption was reported in the present study. A recent study determined that a 28.2% reduction was necessary for a clinically significant reduction [32]. Research on the effect of CBMPs on opioid usage remains limited as existing clinical trials investigating the use of CBMPs for chronic pain maintained opioid medications at constant doses [33]. However, pooled results from observational studies have reported a reduction of 22.5 mg/24 h oral morphine equivalents, higher than reported here [33]. There are several reasons as to why there may have under-reported the reduction in opioid usage. About 42.8% of the patients were utilizing illicit cannabis prior to enrollment. As such, these patients may have already reduced their opioid medications. Second, patient medications taken as required may have contributed to an underestimation in opioid reduction as patients may have reduced their regular opioid medications after CBMP treatment commenced, yet this change may not have been captured. Refining the data collection platform to include this consideration will be important for improving the accuracy of UKMCR medication data.

Interestingly, cannabis naïve and ex-users were more likely to experience adverse events compared to current users. This agrees with a year-long prospective cohort study of patients prescribed a 12.5% THC CBMP formulation [34]. Three hundred and sixteen adverse events were recorded from 74 cannabis naïve or ex-users, with an incidence rate ratio of 2.15 (95% CI: 1.69–2.74). In comparison, 141 current users recorded 502 adverse events (incidence rate ratio = 1.64; 95% CI: 1.35–1.99). Additionally, the present study found males were less likely to experience adverse events. A few studies have investigated the sex-dependent effects of cannabinoids [35], and further assessment in randomized controlled trial settings is required to assess if there are gender- or sex-dependent effects of CBMPs.

There are several limitations to this study. First, although follow-up scores decreased for all pain-specific PROMs, so too did the baseline scores. This may be because patients with higher pain scores may not have achieved clinical benefit and dropped out, raising the attrition bias. Second, there was a limited sample size of patients prescribed dried flowers. A similar issue occurred during a previous UKMCR study, which found improved pain relief in chronic pain patients treated with oil-based CBMPs after 1 and 3 months, but not 6 months ($n = 12$) [10]. In the current study and with increased numbers ($n = 68$), the improvements were statistically significant after 6 months of treatment. Thus, it would be beneficial to repeat this analysis as more patients are enrolled in the UKMCR and prescribed dried flower and would also provide sufficient data for adverse event analysis. Third, although this study attempted to limit heterogeneity by subgrouping patients based on route of administration, a variety of treatments remained within the oils category (Supplementary Table S2). This is an inherent drawback of observational studies, unable to control for the

diversity in prescriptions associated with clinical settings. Due to this, one could argue differences in HRQoL or adverse events may be due to different THC/CBD concentrations, not the route of administration, or patients' gender or prior cannabis use. However, whilst this compromises the internal validity of the study, it does help to elucidate outcomes in a real-world setting, outside of the stringent criteria of randomized controlled trials. Moreover, there are challenges in patients reporting the impact of symptom severity or adverse events accurately. The future incorporation of wearables would be beneficial in providing objective data. In this way, quantifiable metrics, such as step counts, sleep duration, and heart rate can be measured to accompany other outcomes. Additionally, the efficacy of CBMPs may be different according to the underlying cause of pain. Consequently, PROM responses may have been influenced by the type of chronic pain patients were treated for, which was not accounted for in this study. Future analyses with sufficient sample size should aim to perform separate analyses according to chronic pain etiology. Finally, due to the lack of an active comparator group, it is not possible to conclude that the associations observed in this study are directly caused by the CBMPs themselves. This also extends to adverse events, which were not individually assessed by clinicians as to whether they were treatment-related, which could lead to overreporting.

4.1. Conclusions

In summary, these results suggest that both oil-based and dried flower CBMPs are associated with long-term improved HRQoL in chronic pain patients, in agreement with both our hypothesis and existing literature investigating short-term outcomes. Furthermore, it details the scarcity of severe/disabling adverse events associated with long-term CBMP use and reveals increased adverse event incidence for females, cannabis naïve and ex-users. Thus, future studies and clinicians should consider the impact of gender and prior cannabis use when prescribing CBMPs. Additionally, whether these factors influence the extent of HRQoL improvements should be investigated in active comparator trials. Due to the limitations outlined, concrete conclusions regarding the efficacy and safety of individual CBMP prescriptions cannot be drawn. Hence, future analyses of the UKMCR should investigate individual CBMP products and their safety and efficacy for chronic pain treatment when controlled for confounding factors such as gender and prior cannabis use.

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Declaration of interest

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One reviewer declares that they have conducted cannabis research and have consulted for two companies regarding cannabis: Schedule 1 Therapeutics and Vectura Fertin. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Author contributions

J Tait, S Erridge, C Holvey, R Coomber, JJ Rucker and MH Sodergren declare responsibility for study conception and design. J Tait, S Erridge, C Holvey, A Usmani, M Sajad, J Hoare, S Khan, M Weatherall, JJ Rucker, M Platt acquired the data. J Tait, S Erridge, MH Sodergren are responsible for the analysis and interpretation of data while J Tait, S Erridge, MH Sodergren are responsible for drafting the manuscript. J Tait, S Erridge, C Holvey, R Coomber, A Usmani, M Sajad, J Hoare, S Khan, M Weatherall, JJ Rucker, M Platt, MH Sodergren all critically revised the manuscript, and all authors agree to be accountable for all aspects of the work.

Ethical approval

Approval from South West – Central Bristol Research Ethics Committee (reference 22/SW/0145)

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