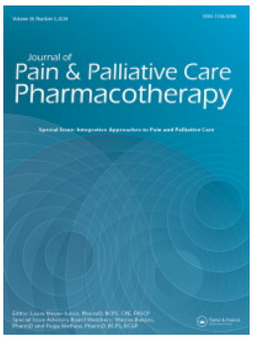

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ARTICLE

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ABSTRACT

This cohort study aims to assess the outcomes of fibromyalgia patients enrolled in the UK Medical Cannabis Registry prescribed a homogenous selection of cannabis-based medicinal products (CBMPs). A cohort study of fibromyalgia patients treated with oils (Adven®, Curaleaf International, UK), dried flower (Adven®, Curaleaf International, UK) or both CBMPs was performed. Primary outcomes were changes from baseline at 1, 3, 6 and 12 months in validated patient-reported outcome measures. Secondary outcomes included descriptive analysis of adverse events. One hundred and forty-eight participants were treated with oils ($n=77$; 52.03%), dried flower ($n=14$; 9.46%) or both ($n=57$; 38.51%). Improvements in the generalized anxiety disorder-7 questionnaire, single-item sleep quality scale, fibromyalgia symptom severity score and EQ-5D-5L Index values were observed at each follow up period compared to baseline ($p<0.050$). Thirty-six (24.32%) patients experienced 648 adverse events. Improvements were observed across all primary outcomes with no differences observed across different formulations of CBMPs. Adverse events were reported by one-quarter of participants and were more likely to reported by cannabis naïve patients. This present work through focusing on a homogeneous group of CBMPs can help inform randomized controlled trials after observing signals of improvement associated with a specific cultivar of CBMPs.

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Fibromyalgia; chronic pain; cannabidiol; tetrahydrocannabinol; medical cannabis

Background

Fibromyalgia is a chronic illness characterized by widespread pain, muscle stiffness, difficulty sleeping, fatigue, headaches, and increased incidence of mental health comorbidities, affecting approximately 2.7% of the global population, with a higher prevalence in women (1–4). Although the etiology of Fibromyalgia is unknown, current hypotheses classify it as a central sensitization disorder, in which the central nervous system amplifies peripheral sensory inputs leading to chronic widespread pain, in addition to greater sensitivity to other sensory inputs (5). Fibromyalgia significantly impacts patients' quality of life, often necessitating changes in daily activities, and is associated with a ten-fold increased risk of suicide (6, 7).

Management of fibromyalgia requires a multidisciplinary approach, given its heterogenous nature and diverse symptoms. Non-pharmacological therapies, including exercise training and cognitive behavioral therapy, are supported by evidence, but their effects are modest (8–12). Moreover, the PACFiND study has previously highlighted challenges in accessing non-pharmacological therapies for fibromyalgia in the UK (13). First-line pharmacological treatments include serotonin-norepinephrine reuptake inhibitors, gabapentinoids, and tricyclic antidepressants, but high-quality data supporting their effectiveness are lacking, especially concerning pain and

Surya Sridharan, BSc (Hons) and Simon Erridge, MBBS BSc (Hons), Medical Cannabis Research Group, Imperial College London, London, UK. Simon Erridge, MBBS BSc (Hons), Carl Holvey, MPharm MRPharmS DipCLinPharm IPresc MBA and Ross Coomber, MBBS BSc (Hons) FRCS Eng (Tr & Orth) PGcert Med Ed, Curaleaf Clinic, London, UK. Ross Coomber, MBBS BSc (Hons) FRCS Eng (Tr & Orth) PGcert Med Ed, St. George's Hospital NHS Trust, London, UK. Wendy Holden, MBBS MSc FRCP DO and James J. Rucker, MBBS MRCPsych PhD, Curaleaf Clinic, London, UK. James J. Rucker, MBBS MRCPsych PhD, Department of Psychological Medicine, Kings College London, London, UK. James J. Rucker, MBBS MRCPsych PhD, South London & Maudsley NHS Foundation Trust, London, UK. Michael Platt, MA MBBS FRCA FFPM RCA, Curaleaf Clinic, London, UK. Mikael H. Sodergren, MBChB DIC PhD FRCS, Medical Cannabis Research Group, Imperial College London, London, UK. Mikael H. Sodergren, MBChB DIC PhD FRCS, Curaleaf Clinic, London, UK.
CONTACT Mikael H. Sodergren m.sodergren@imperial.ac.uk Department of Surgery & Cancer, Academic Surgical Unit, Imperial College London, 10th Floor QEQM, St Mary's Hospital, South Wharf Road, London, W2 1NY, UK.
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other core fibromyalgia symptoms, underlining the need to identify additional therapies for this common condition (14–21).

Cannabis-based medicinal products (CBMPs) offer promise for managing fibromyalgia. The two main active constituents in CBMPs are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). These interact with the endocannabinoid system, most notably cannabinoid receptors type 1 (CB1R) and type 2 (CB2R) primarily located in the central nervous system, and immune system and peripheral tissues respectively (22). Pre-clinical studies have evidenced the role of these receptors in modulating pain signaling, sleep regulation and anxiety, suggesting CBMPs may provide therapeutic benefit to fibromyalgia patients (23–31).

With respect to clinical evidence of the effects of CBMPs, there is a paucity of high-quality evidence, particularly within the setting of fibromyalgia. In 2021, Wang et al. published a meta-analysis of outcomes for people prescribed cannabinoids or CBMPs for chronic pain, which modeled a 10% risk difference of non-inhaled medical cannabis products providing a clinically significant improvement in pain when compared to placebo (32). However, this meta-analysis only considered one study where the participants had fibromyalgia, with other studies being deemed of either poor quality or investigating other outcomes (33). Beyond chronic pain, there is similarly an absence of high-quality data informing the effects of medical cannabis on other core symptoms of fibromyalgia. With respect to fatigue there are limited evaluations of its effects, however self-reported observational data suggests there may be associated benefits in this domain in individuals who consumed dried cannabis flower (34).

Current evidence regarding the clinical benefits of CBMPs on addressing sleep disturbance includes a randomized, double-blind, active-control, equivalency crossover trial comparing nabilone, a THC analogue, to amitriptyline before bedtime in fibromyalgia patients with chronic insomnia. Both treatments resulted in better sleep quality, however those receiving nabilone showed greater improvement (35). Addressing the psychological symptoms associated with fibromyalgia, a recent systematic review assessed 49 studies to determine the potential of CBD as a treatment for anxiety disorders (36). Blessing et al. concluded that human experimental findings support preclinical findings, which conclusively demonstrate CBD's efficacy in managing anxiety behaviors relevant to disorders including post-traumatic stress disorder, generalized anxiety disorder and obsessive-compulsive disorder (36). However, the quality of clinical evidence is largely of low quality and there is a paucity of evidence assessing the effectiveness of long-term effects of CBMPs, with most studies utilizing short follow up periods (36). Additionally, much of clinical CBMP research lacks applicability due to heterogeneity of CBMPs prescribed.

Due to the lack of both randomized and observational data on the outcomes of patients prescribed CBMPs for fibromyalgia, this study therefore seeks to analyze the outcomes of patients receiving a homogeneous selection of CBMPs. The primary aims of this analysis are to analyze changes in general health-related quality of life (HRQoL) and fibromyalgia symptom severity assessed by patient reported outcome measures (PROMs). Secondary aims are to report the incidence of adverse events associated with this unlicensed therapy.

Methods

Study design

A prospective observational cohort study to assess the outcomes of individuals prescribed Adven® CBMPs (Curaleaf International, UK) for fibromyalgia was performed. The data was collected by the UK Medical Cannabis Registry in accordance with research and ethics committee approval (Ref: 22/SW/0145). Participants were recruited consecutively following the provision of informed consent. This study has been outlined and the results reported according to the STROBE guidelines for observational cohort studies (37).

Settings and participants

The UK Medical Cannabis Registry, which is privately owned and managed by Curaleaf Clinic, is the largest patient registry on CBMP prescribing

in the UK. The registry has recruited patients from the UK and Channel Islands since December 2019. Data is collected from patients from an electronic reporting portal, with additional information on demographics, comorbidities, medications, and adverse events supplemented by clinicians. The registry has previously undergone a patient and public evaluation which found the process through which it collects data to be easy to use (38). This research also highlighted how assessment of the effects of CBMPs on health-related quality of life was the highest research priority for patients (39).

CBMPs were prescribed in accordance with national guidance (40). All CBMPs were manufactured in line with Good Manufacturing Practice (41).

Inclusion criteria for the present study were as follows: enrolled in the UK Medical Cannabis Registry for a minimum of 12 months prior to data extraction (January 9, 2023) and to have fibromyalgia listed as the primary indication for treatment with CBMPs. Participants were excluded if they had not completed baseline PROMs or if they were prescribed any CBMPs except for Adven® (Curaleaf International, UK).

The decision to restrict to Adven® products (Curaleaf International, UK) was made as at the time this was the most prescribed brand of CBMPs on the UK Medical Cannabis Registry. This, along with restricting to those enrolled for 12 months of longer, ensured the longest follow up period whilst maintaining homogeneity and ensuring a sufficient sample size for analysis.

Data collection

Demographic data was collected at baseline, including age, gender, body mass index (BMI). Occupation was documented and classified according to the International Standard Classification of Occupations (42). Relevant co-morbidities were recorded, and a Charlson comorbidity index (CCI) score was calculated for each patient, a validated tool often used in patient registries that offers prognostic utility and the ability to adjust for co-morbidities (39, 43).

Data on tobacco, alcohol and cannabis consumption was collected. Tobacco and alcohol use was quantified as pack years and units per week respectively. Cannabis use frequency and grams per day were documented and "cannabis gram years" (average consumption (g) per day × years of usage) were calculated to quantify prior cannabis use (44).

Information on CBMPs was mapped to prescription data, with information available on the specific product prescribed. Information on major cannabinoid and terpene profile was available from the manufacture. Dominant terpenes were classified as having a concentration ≥200 parts per million (ppm). Significant terpenes were classified as having a concentration between 100–200 ppm.

The primary outcome of the study was to compare PROMs at baseline with scores at follow up periods of 1, 3, 6, and 12 months following intervention with CBMP treatment, consisting of: the generalized anxiety disorder–7 (GAD-7) questionnaire (45–47), single-item sleep quality scale (SQS) (48), EQ-5D-5L (49, 50), fibromyalgia symptom severity score (FSS) (51) and patient global impression of change (PGIC) (52, 53), shown in Table 1 below.

Secondary outcomes included analysis of adverse events graded according to the common terminology criteria for adverse events (CTCAE) version 4.0 (54). These were reported as incidence (%) calculated in proportion to the number of participants.

Changes in medications, including dose were recorded throughout the study period. Opioid doses were transformed into oral morphine equivalent doses to enable longitudinal comparison of prescribed opioids (55, 56).

Missing data

Inclusion criteria required completed PROMs at baseline, however some patients were lost to follow up leading to missing data. Sixty-nine (46.62%) participants had complete data sets and 79 (53.38%) incomplete. Regarding all data points, recorded values were present for 6,366 (72.90%) of data points, with 2,366 (27.10%) missing. To account for missing values a baseline-observation carried forward (BOCF) method was utilized, whereby missing data was replaced by baseline values. This method was used in accordance with

Table 1. Showing the PROMs used as predictors of patient wellbeing.

PROM	Description	Response system	Scoring system
GAD − 7	A 7-item anxiety scale, used to identify and assess the severity of generalized anxiety disorder (GAD). The items consist of symptoms indicative of GAD, including feeling nervous, difficulty relaxing, and restlessness.	Patients are asked to rate the frequency of symptoms from the last 2 weeks on a 4-point Likert scale from "not at all" (0), "several days" (1), "more than half the days" (2) and "nearly every day" (3).	A final score between 0 and 21 is calculated. These scores correspond to the severity of the participant's anxiety: ≥5 – mild, ≥10 – moderate and ≥15 – severe. Clinically significant improvements are considered in those with a reduction in GAD-7 ≥ 4.
SQS	A single-item questionnaire consisting of a numeric rating scale from 1 to 10 to determine the overall quality of sleep.	Patients are asked to consider: "how many hours of sleep they had, how easily they fell asleep, how often they woke up during the night (except to go to the bathroom), how often they woke up earlier than they had to in the morning, and how refreshing their sleep was" and rate the quality of their sleep from 0 (terrible) to 10 (excellent).	Increasing scores reflect a better quality of sleep. 0 – Terrible/1–3 – Poor/4-6 – Fair/7–9 – Good/10–Excellent
EQ-5D-5L	A questionnaire used to measure health-related quality of life, consisting of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.	Each dimension is scored via a 5 level Likert scale in respect to its severity on the day of answering, with no problem" (1), "slight problem" (2), "moderate problem" (3), "severe problem" (4) to "unable to" (5).	An index value is calculated with higher values corresponding to better health (1 – ideal quality of life) with an index value <0 representing a state worse than death. These are calculated in accordance with crosswalk values provided by Van Hout et al.
FSS	A score consisting of the widespread pain index (WPI) and symptom severity score (SSS) summated, used to aid the diagnosis of and assess the severity of fibromyalgia in patients.	WPI: Patients are asked to identify which of 19 areas of their body they experience pain in. Scoring 0–19. SSS: Patients are asked to rate the severity of fibromyalgia symptoms, and state whether other symptoms have been present, giving a score between 0 and 12.	One point is added for: each area experiencing pain in the WPI, and each symptom present in the SSS. For fibromyalgia to be present: patients must have a WPI of ≥7 and an SSS of >5 OR a WPI of 4-6 and an SSS of ≥9. With a total FSS score ranging from 0 to 31, with increasing scores representing an increasing severity of disease.
PGIC	A single scale used to assess how the patient perceives the change in their quality of life since beginning treatment. Patients are asked to take into account, activity limitations, symptoms, emotions and overall quality of life.	Their response is rated on a scale of 1–7. With 1 representing "no change (or condition has got worse)", and 7 representing a "great deal better, and a considerable improvement that has made all the difference".	The scores represent the state of the disease: with: (0–3) disease deterioration, (4) stable disease and (5–7) disease improvement. With a score of ≥5 representing clinically significant change, in keeping with the IMMPACT recommendations.

Generalized anxiety disorder assessment (GAD-7) (45–47), single-item sleep quality scale (SQS) (48), EQ-5D-5L (49, 50), fibromyalgia symptom severity score (FSS) (51), patient global impression of change (PGIC) (52, 53).

guidance from the European Medicines Agency whereby when participants withdraw from trials assessing chronic pain outcomes it should be assumed that individuals return to baseline health state rather than experiencing any long-term benefit (57).

Statistical analysis

Analysis was performed using IBM SPSS (v. 29.0.0.0 (241)). Significance was defined as a p-value < 0.050.

Demographic and adverse events data were analyzed using descriptive statistics with parametric data being reported as mean values (± standard deviation) and non-parametric as median (interquartile range) and frequencies as n (%).

In accordance with the central limit theorem, PROM data was analyzed using a repeated measures analysis of variance (ANOVA) test with a Greenhouse-Geisser correction irrespective of normality to assess for significant differences between PROM scores at baseline and 12 months post CBMP treatment. A post-hoc pairwise comparison with Bonferroni correction was used to assess for statistically significant differences between specific timepoints for variables with a p-value < 0.050. To compare different treatment groups, a one-way ANOVA was performed of the mean difference in FSS score at 1, 3, 6, and 12 months compared to baseline between those treated with oils only, dried flower only, or both formulations of CBMP. A Tukey's honest significant difference test was planned to be performed for pairwise analysis if any values were statistically significant.

Univariate logistic regression analyses were performed to assess the associated odds ratios (ORs) and their respective confidence intervals (95% CI) of experiencing a clinically significant

improvement in GAD-7 score (≥4) at 12 months and an adverse event at any point (47). To account for intrinsic biases and confounding factors subsequent multivariate logistic regression models incorporating each independent variable studied within the univariate model were performed for each respective outcome. An analysis could not be performed using the FSS as there is no validated minimal clinically important difference value for this PROM.

Results

Data was extracted on January 9, 2023, with 9,464 patients being present on the registry. From this data set 9,316 patients were excluded due to being enrolled in the registry for <12 months ($n = 6{,}406$), not having a primary diagnosis of fibromyalgia ($n = 2{,}417$), having not completed initial PROMs at baseline ($n = 364$), and not being prescribed Adven® CBMPs ($n = 129$) only. Resulting in a final participant number of 148.

Baseline demographics

Table 2 displays the baseline demographic, tobacco, alcohol, and cannabis consumption details for the study cohort. The cohort consisted of 119 female participants (80.41%) and 29 male (19.59%), with a mean age of 47.20 (±13.54) years and mean BMI of 29.90 (±8.39) kg/m^2. The median Charlson Comorbidity Index was 2.93 (IQR 0.00-6.00). All patients included had a primary indication for CBMPs of fibromyalgia, see Supplementary Appendix A for the prevalence of specific secondary and tertiary indications.

Also detailed are the tobacco, alcohol, and cannabis consumption of participants. There were 36 (24.32%) current and 60 (40.54%) ex-smokers. Current smokers had a median pack year history of 10.50 (3.00–20.00) and ex-smokers of 8.00 (3.00–16.50). Median alcohol consumption was 0.00 (0.00–3.00) units per week. Upon initiation of treatment 53 (35.81%) patients were current users of cannabis, 23 (15.54%) were ex-users and 72 (48.65%) were cannabis naïve. Among current users, 48 (90.57%) consumed cannabis daily with a median usage of 1.00 (0.75–1.50) grams per day. Lifetime cannabis consumption was 5.00 (1.00–12.00) gram years in current users and 2.00 (1.00–8.00) gram years in ex-users.

Table 2. Details of baseline demographics, smoking, alcohol and cannabis consumption of participants included in the study, $n = 148$.

Baseline demographic details	*n* (%)/Mean (± S.D)/Median (IQR)
Sex	
Male	29 (19.59%)
Female	119 (80.41%)
Age (years)	47.20 (± 13.54)
BMI (kg/m^2)	29.90 (± 8.39)
Employment status	
Employed	76 (51.35%)
Unemployed	60 (40.54%)
Missing data	12 (8.11%)
Charlson Comorbidity Index	2.93 (0.00-6.00)
Smoking, alcohol and cannabis status at baseline	**n (%) / Mean (± S.D) / Median (IQR)**
Smoking status	
Current smoker	36 (24.32%)
Pack years	10.50 (3.00-20.00)
Ex - smoker	60 (40.54%)
Pack years	8.00 (3.00 – 16.50)
Never smoked	52 (35.14%)
Alcohol consumption per week (units)	0.00 (0.00-3.00)
Cannabis status	
Never used	72 (48.65%)
Ex - user	23 (15.54%)
Lifetime quantity of grams of cannabis consumed (gram years)	2.00 (1.00-8.00)
Current user	53 (35.81%)
Grams used per day (g/day)	1.00 (0.75-1.50)
Lifetime quantity of grams of cannabis consumed (gram years)	5.00 (1.00-12.00)
Frequency of use for current users $n = 53$	
Everyday	48 (90.6%)
Every other day	3 (5.7%)
More than once a month	1 (1.9%)
Less than once a month	1 (1.9%)

Results are reported as mean ± standard deviation (±SD), median and interquartile range (IQR) or frequency and percentage *n*(%) of the total cohort $n = 148$.

Table 3. Details of administration route, content, and dosage of CBMP prescriptions.

CBMP usage details	*n* (%)/Median (IQR)
Method of administration	
Oils only	77 (52.03%)
Dried flower only	14 (9.46%)
Combination therapy (dried flower & oils)	57 (38.51%)
CBMP content	
Patients prescribed THC only	5 (3.38%)
Patients prescribed CBD only	2 (1.35%)
Patients prescribed a combination of THC & CBD	141 (95.27%)
CBMP dosage	
Median (IQR) dosage of CBD (mg/day)	20.00 (20.00-40.00)
Median (IQR) dosage of THC (mg/day)	25.00 (10.00-115.00)

Results reported as mean ± standard deviation (±SD), median and interquartile range (IQR) or frequency and percentage *n* (%) of the total cohort $n = 148$.

Prescription data is detailed in Table 3. Seventy-seven (52.03%) participants were prescribed oils only, 14 (9.46%) dried flower only, and 57

(38.51%) both oils and dried flower. Primarily participants were prescribed CBMPs containing a combination of THC & CBD ($n=141$; 95.27%). However, 5 (3.38%) participants were prescribed THC only and 2 (1.35%) were prescribed CBD only. The median dose for CBD and THC across the cohort was 20.00 (20.00–40.00) mg/day and 25.00 (10.00–115.00) mg/day respectively. The most prescribed CBD-dominant sublingual oil was Adven® 50 mg/ml CBD <4 mg/ml THC (Curaleaf International, UK). The dominant terpene of this product was β-carryophyllene and the significant terpenes were α-bisabolol, α-humulene, and linalool. The most prescribed THC-dominant sublingual oil was Adven® 20 mg/ml THC (Curaleaf International, UK). The significant terpenes of this product were guaiol and α-bisabolol. Adven® EMT1 dried flower (Curaleaf International, UK) was the most prescribed dried flower for vaporization. The significant terpenes of this product were α-pinene, β-pinene, and myrcene.

Primary outcomes: Patient-reported outcome measures

Table 4 displays the results of the repeated measures one-way ANOVA analysis comparing baseline PROM scores to future timepoints of 1, 3, 6, and 12 months as well as PGIC scores at each follow up. Improvements were observed in all PROMs ($p<0.050$), except the anxiety and depression domain of the EQ-5D-5L ($p=0.124$). PGIC scores were 5.00 (4.00–6.00) at 1 month and 5.00 (5.00–6.00) at 3, 6, and 12 months.

A *post-hoc* pairwise analysis of the results of the repeated measures one-way ANOVA are reported in Table 5 to determine significance of individual comparisons between baseline and all future timepoints, with a Bonferroni correction. Improvements were observed across all comparisons to baseline in the GAD − 7, SQS, EQ-5D-5L Index value, symptom severity score and fibromyalgia symptom severity score. Significant differences were also observed at comparing baseline to widespread pain index scores at 1, 3 and 12 months, ($p<0.050$).

Figure 1 demonstrates the outcomes of PGIC at 1, 3, 6, and 12 months following initiation of treatment. At 3, 6, and 12 months follow up ≥ 75% of participants experienced reported a score of 5 or greater, representing subjective therapeutic benefit.

Table 4. Patient reported outcome measures of participants ($n=148$) at baseline and 1, 3, 6 and 12 months.

Patient reported outcome measure	Follow up period (months)	Score at baseline ± S.D	Score at follow up ± S.D	*p*-Value (Bonferroni corrected)
GAD-7	1	9.41 ± 6.70	8.13 ± 6.28	0.007
	3		8.38 ± 6.42	0.048
	6		8.28 ± 6.30	0.023
	12		8.05 ± 6.30	<0.001
SQS	1	3.69 ± 2.41	4.79 ± 2.54	<0.001
	3		4.74 ± 0.74	<0.001
	6		4.63 ± 2.60	<0.001
	12		4.40 ± 2.57	<0.001
EQ-5D-5L mobility	1	2.99 ± 0.98	2.83 ± 1.04	0.216
	3		2.91 ± 1.04	1.000
	6		2.80 ± 1.05	0.019
	12		2.89 ± 1.04	0.505
EQ-5D-5L self-care	1	2.45 ± 0.98	2.32 ± 1.06	0.632
	3		2.43 ± 1.07	1.000
	6		2.33 ± 1.05	0.290
	12		2.28 ± 1.01	0.002
EQ-5D-5L usual activities	1	3.26 ± 0.963	2.93 ± 0.997	<0.001
	3		3.01 ± 1.082	0.075
	6		2.95 ± 1.105	<0.001
	12		3.07 ± 1.024	0.120
EQ-5D-5L pain and discomfort	1	3.79 ± 0.859	3.43 ± 0.956	<0.001
	3		3.43 ± 0.941	<0.001
	6		3.45 ± 0.906	<0.001
	12		3.53 ± 0.951	<0.001
EQ-5D-5L index value	1	0.277 ± 0.3022	0.370 ± 0.3070	<0.001
	3		0.349 ± 0.3240	0.032
	6		0.369 ± 0.3097	<0.001
	12		0.348 ± 0.3148	<0.001
Symptom severity score	1	9.26 ± 2.207	8.24 ± 2.576	<0.001
	3		8.45 ± 2.650	<0.001
	6		8.43 ± 2.596	<0.001
	12		8.64 ± 5.499	<0.001
Widespread pain index	1	13.90 ± 4.037	12.52 ± 4.453	<0.001
	3		12.53 ± 4.476	<0.001
	6		12.97 ± 4.695	0.530
	12		12.88 ± 4.567	0.001
FSS	1	23.16 ± 5.567	20.76 ± 6.164	<0.001
	3		20.98 ± 6.335	<0.001
	6		21.40 ± 6.577	0.001
	12		21.52 ± 6.432	<0.001

Data are presented as either mean ± standard deviation or median (interquartile range). The *p*-values represent the outcomes of a repeated measures one-way ANOVA and have undergone a Greenhouse-Geisser correction. The results of a repeated measures one-way ANOVA. $n=148$.

Sub-group analysis

The mean reported change in FSS at 1, 3, 6, and 12 months compared to baseline are displayed in Table 6. No significant differences in the magnitude of improvement were observed between methods of administration ($p>0.050$).

Prognostic factors for improvement in anxiety

Supplementary Tables (Appendix C and D) outline all variables assessed to identify any association

Table 5. Patient reported outcome measures of participants ($n = 148$) at baseline and 1, 3, 6 and 12 months.

Patient reported outcome measure	Baseline	1 Month	3 Months	6 Months	12 Months	p – Value(Greenhouse-Geisser corrected)
GAD – 7	9.41 ± 6.70	8.13 ± 6.28	8.38 ± 6.42	8.28 ± 6.30	8.05 ± 6.30	< 0.001
SQS	3.69 ± 2.41	4.79 ± 2.54	4.74 ± 2.74	4.63 ± 2.59	4.40 ± 2.57	< 0.001
EQ-5D-5L mobility	2.99 ± 0.98	2.83 ± 1.04	2.91 ± 1.04	2.80 ± 1.05	2.89 ± 1.04	0.039
EQ-5D-5L self-care	2.45 ± 0.98	2.32 ± 1.06	2.43 ± 1.07	2.33 ± 1.05	2.28 ± 1.01	0.048
EQ-5D-5L usual activities	3.26 ± 0.96	2.93 ± 1.00	3.01 ± 1.08	2.95 ± 1.11	3.07 ± 1.02	< 0.001
EQ-5D-5L pain and discomfort	3.79 ± 0.86	3.43 ± 0.96	3.43 ± 0.94	3.45 ± 0.91	3.53 ± 0.95	< 0.001
EQ-5D-5L anxiety and depression	2.76 ± 1.22	2.64 ± 1.14	2.63 ± 1.21	2.57 ± 1.17	2.56 ± 1.16	0.124
EQ-5D-5L index value	0.277 ± 0.30	0.370 ± 0.31	0.349 ± 0.32	0.369 ± 0.31	0.348 ± 0.32	< 0.001
Symptom severity score	9.26 ± 2.21	8.24 ± 2.58	8.45 ± 2.65	8.43 ± 2.60	8.64 ± 5.50	< 0.001
Widespread pain index	13.90 ± 4.04	12.52 ± 4.45	12.53 ± 4.48	12.97 ± 4.70	12.88 ± 4.57	< 0.001
FSS	23.16 ± 5.57	20.76 ± 6.16	20.98 ± 6.34	21.40 ± 6.58	21.52 ± 6.43	< 0.001
PGIC		5.00 (4.00-6.00)	5.00 (5.00-6.00)	5.00 (5.00-6.00)	5.00 (5.00-6.00)	

Data are presented as either mean ± standard deviation or median (interquartile range). The p-values represent the outcomes of a pairwise analysis and have undergone a Bonferroni correction. The results of a pairwise analysis. $n = 148$.

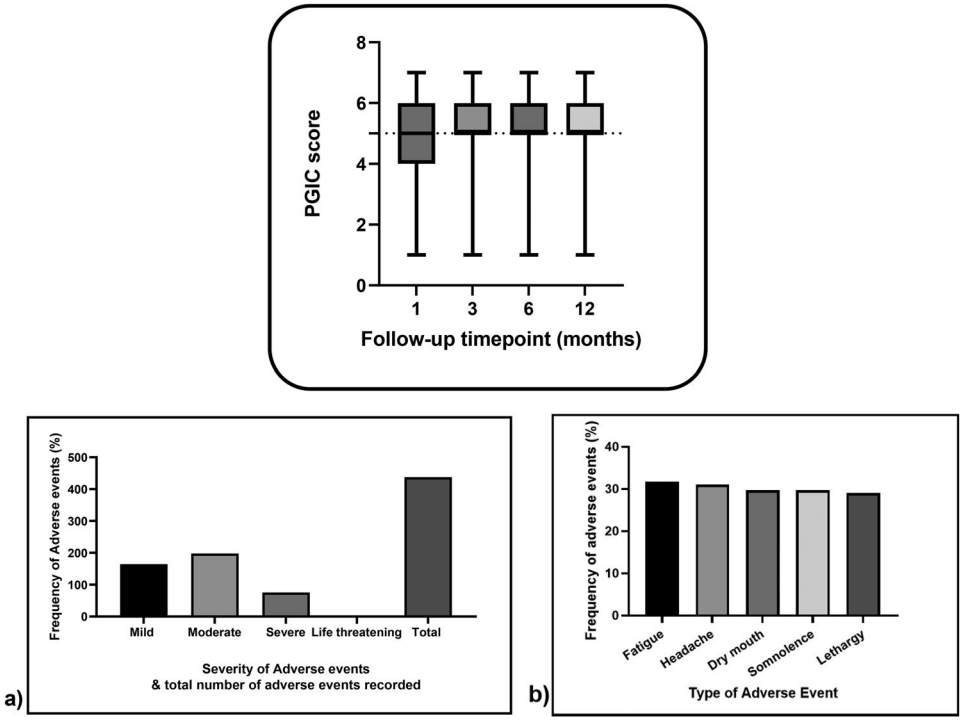

Figure 1. Boxplot showing PGIC scores, with a horizontal line at 5 representing any change above this line signifying a clinically significant change, in keeping with IMMPACT recommendations (52).

Table 6. Sub-group analysis results of a One-way ANOVA comparing the mean changes in FSS score between baseline and follow-up periods: 1, 3, 6 and 12 months, across method of administration of CBMPs to assess for significant differences across groups. ($p < 0.05$).

	Oil only (mean change between baseline and follow-up period ± S.D)	Dried flower only (mean change between baseline and follow-up period ± S.D)	Combination of oils and dried flower (mean change between baseline and follow-up period ± S.D)	p – Value
1 Month	−2.389 ± 4.802	−2.571 ± 3.777	−2.351 ± 4.241	0.987
3 Months	−1.753 ± 4.311	−2.929 ± 3.751	−2.561 ± 5.898	0.541
6 Months	−1.312 ± 4.908	−2.214 ± 4.594	−2.246 ± 6.211	0.584
12 Months	−1.156 ± 3.204	−1.857 ± 4.204	−2.228 ± 5.565	0.365

with the likelihood of achieving a clinically significant improvement in generalized anxiety at 12 months, as measured using the GAD-7 (47). On univariate analysis, participants within BMI category 30–34.99 kg/m^2 had a reduced likelihood of achieving clinically significant GAD-7 changes (OR = 0.07; 95% CI: 0.01–0.58; $p = 0.014$). Conversely, participants classified with severe anxiety at baseline (OR = 2.46; 95% CI: 1.04–5.82; $p = 0.040$), on combined oil & flower CBMP therapy (OR = 2.95; 95% CI: 1.19*7.28; $p = 0.019$) and with THC doses above the median dosage

Table 7. Oral morphine equivalent of opioid analgesic doses of participants ($n = 148$) at baseline and 1, 3, 6 and 12 months.

	Baseline	1 Month	3 Months	6 Months	12 Months	p – Value (Greenhouse-Geisser corrected)
Oral morphine equivalent	36.03 ± 84.36	35.27 ± 84.53	35.14 ± 84.58	35.06 ± 84.61	32.44 ± 84.75	0.009

Data are presented as either mean ± standard deviation. The p-values represent the outcomes of a repeated measures one-way ANOVA and have undergone a Greenhouse-Geisser correction. The results of a repeated measures one-way ANOVA. $n = 148$.

(OR = 3.55; 95% CI: 1.40–8.97; $p = 0.07$) were more likely to achieve clinically significant GAD-7 changes. On multivariate analysis, participants with more severe anxiety at baseline (OR = 3.38; 95% CI: 1.07–10.70; $p = 0.039$) and participants prescribed THC doses above the median (OR = 21.70; 95% CI: 1.33–355.60; $p = 0.031$) both continued to be more likely to report clinically significant GAD-7 changes at 12 months. Additionally, BMI categories 30–35kg/m^2 (OR = 0.08; 95% CI: 0.01 – 0.81; $p = 0.032$) and ≥40kg/m^2 (OR = 0.07; 95% CI: 0.01 – 0.91; $p = 0.042$) were less likely to experience clinically significant reductions in generalized anxiety symptoms.

Changes in prescribing of opioids (using oral morphine equivalents)

Table 7 displays the results of a repeated measures one-way ANOVA analysis comparing quantity of opioid analgesic dosing, quantified as oral morphine equivalents (OMEs) at baseline to future timepoints of 1, 3, 6 and 12 months. A statistically significant improvement of reduction in OMEs was observed.

Further pairwise analysis was conducted to determine significance of individual comparisons between baseline and future timepoints, with a Bonferroni correction, with no statistically significant improvements observed, results displayed in Table 8.

Adverse events

Thirty-six (24.32%) participants experienced a total of 648 adverse events of which 243 were mild, 293 were moderate and 112 were severe (Figure 2(a)). No life-threatening adverse events were reported. The most frequent adverse events were fatigue ($n = 47$; 31.76%), headache ($n = 46$; 31.08%), dry mouth ($n = 44$; 29.72%), somnolence ($n = 44$; 29.72%) and lethargy ($n = 43$; 29.05%) (Figure 2(b)). For a full summary of adverse events see Supplementary Appendix D.

Table 8. Oral morphine equivalent of opioid analgesic doses of participants ($n = 148$) at baseline and 1, 3, 6 and 12 months.

	Follow up period (months)	Score at baseline ± S.D	Score at follow up ± S.D	p-Value (Bonferroni corrected)
Oral morphine equivalent	1	36.03 ± 84.36	35.27 ± 84.53	1.000
	3		35.14 ± 84.58	1.000
	6		35.06 ± 84.61	1.000
	12		32.44 ± 84.75	0.061

Data are presented as either mean ± standard deviation. The p-values represent the outcomes of a pairwise analysis and have undergone a Bonferroni correction. The results of a pairwise analysis. $n = 148$.

Prognostic factors for likelihood of experiencing adverse events

Univariate analysis observed reduced odds ratios regarding experiencing adverse events in participants within age range 31–40 (OR = 0.17; 95% CI: 0.04–0.77; $p = 0.022$), ex-cannabis users (OR = 0.21; 95% CI: 0.07–0.59; $p = 0.003$) and participants on a combination of oil & flower CBMP therapy (OR = 0.38; 95% CI = 0.16–0.94; $p = 0.035$). See Supplementary Appendix E for full analyses. Results of multivariate analysis showed participants in age categories 31–40 (OR = 0.64; 95% CI: 0.01–0.49; $p = 0.008$), 41–50 (OR = 0.14; 95% CI: 0.02–0.89; $p = 0.037$) and 60+ (OR = 0.10; 95% CI: 0.01–0.69; $p = 0.019$) were less likely to experience adverse events. Additionally, patients who were ex-users (OR = 10.57; 95% CI: 1.81–61.92; $p = 0.009$) or had never used cannabis (OR = 12.06; 95% CI: 2.26–64.48; $p = 0.004$) had an increased likelihood of experiencing adverse events compared to those who are actively consuming cannabis at baseline. For full multivariate analyses see Supplementary Appendix F.

Discussion

Positive associations between initiation of CBMP therapy and decreased fibromyalgia severity were

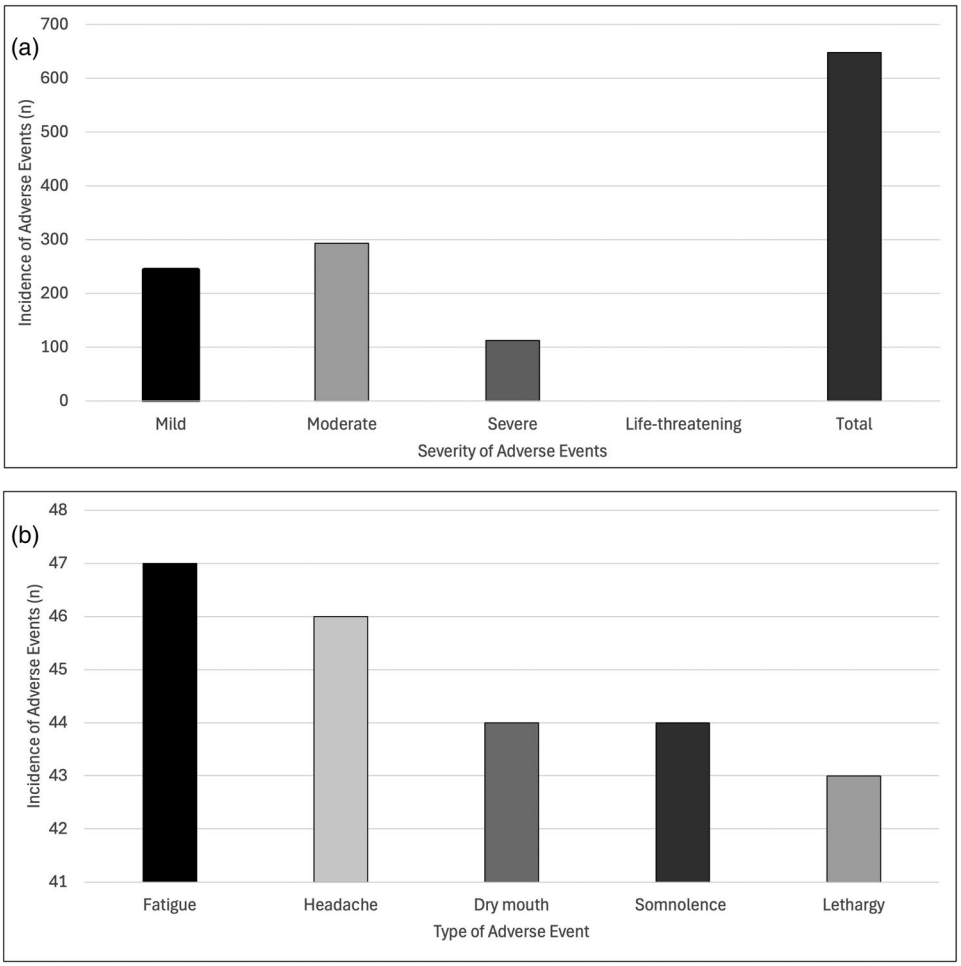

Figure 2. (a) Displaying adverse events frequency distributed by severity the total incidence (*n*). Total number of adverse events recorded is also displayed. Adverse event severity was graded in accordance with CTCAE version 4.0. (b) Displaying the five most frequent adverse events as the total incidence (*n*).

observed at all time points, in keeping with the wider literature. Giorgi et al performed a prospective cohort study assessing the viability of cannabis-based therapy in providing therapeutic benefit to 102 fibromyalgia chronic pain patients refractory to conventional analgesic management (58, 59). Although utilizing an alternative method of quantifying fibromyalgia severity, the fibromyalgia impact questionnaire (FIQR), this measure has additionally been validated and evidenced in the literature (60). Regarding fibromyalgia severity, significant improvements in FIQR score were observed in 33% of patients, furthermore concomitant analgesic medication was suspended or reduced in 47% of patients. Building on this, a study comparing fibromyalgia patients FIQR results before and after cannabis-based treatment across 2 hospitals in Israel found that 26/26 patients reported significant improvements on all aspects of the questionnaire with 50% of patients consequently terminating any other medications for managing their fibromyalgia (61). These studies help to contextualize the findings of the present study and suggest the role of CBMPs in providing a holistic therapeutic benefit to a fibromyalgia population refractory to conventional therapy.

In addressing core symptoms of fibromyalgia, participants experienced improvements in generalized anxiety symptoms at all follow-up timepoints compared to baseline. These results are corroborated by an observational cohort study by Ergisi et al, where the authors assessed the impact of CBMPs for generalized anxiety disorder (62). Their results showed significant differences between baseline GAD-7 scores and follow up at 1, 3, and 6 months, in keeping with the present study. However, the reductions observed within

the anxiety cohort were greater than this fibromyalgia cohort. Possible reasons for this could be the higher GAD-7 score at baseline. This may result in a ceiling effect, whereby those with lower initial GAD-7 scores are constrained by the range of the GAD-7 and are therefore demonstrate smaller improvements. Moreover, the present analysis utilized a BOCF approach to managing missing data. This is a conservative method of managing missing data, which was not utilized in the prior analysis. The present study results are therefore less likely to be affected by attrition bias. Regarding sleep quality, comparing baseline to 12-months follow-up, mean SQS scores increased from 3.69 (±2.41) to 4.40 (±2.57). These findings are complemented by the wider literature. A crossover double-blind placebo-controlled 6-week trial by Ried et al. assessed the impact of Entoura-10:15 CBMP oil on adults with self-reported insomnia, titrated from 2–15mg THC/3–22.5 mg CBD over 2 weeks followed by a 1-week wash-out before crossover (63). Graded according to the insomnia sleep index, a validated and sensitive measure to evaluate sleep difficulties, 79–89% of patients reported moderate to severe clinical insomnia at baseline, compared to the end of the trial, where 65% of patients were no longer classified as having clinical insomnia (64). Additionally, objective measures of assessing sleep quality were reported with improvement with midnight melatonin levels in the active group (30%) vs. a decline (20%) in the placebo group (63).

Almost one-quarter of participants experienced an adverse event and reported a total of 648 adverse events during the 12-month study period, resulting in an incidence rate of 4.38 events/person-year, comparable to 4.61 events/person-year observed in the COMPASS study, a controlled prospective cohort study assessing the safety profile of CBMPs in a chronic pain cohort (65). Additionally, most adverse events experienced in the present cohort were mild-to-moderate in severity, further supported by the COMPASS study, where no significant difference in the likelihood of developing serious adverse events in participants receiving CBMPs compared to the control group was observed. However, the COMPASS study did report an increased risk of mild-to-moderate adverse events (RR= 1.73, 95% CI = 1.41–2.13) (65). The logistic regression analysis of the present study highlighted that individuals who were cannabis naïve were more likely to experience adverse events. As fewer than half of patients included in the analysis were cannabis naïve at baseline, it is important to recognize that this may lead to an underreporting of adverse events as they may apply to the broader fibromyalgia population. For example, Workman et al highlighted that individuals prescribed CBMPs, may be at increased risk of falls, which was not highlighted in this present analysis (66). Additionally, when considering adverse events, it is important to contextualize our findings by comparing our adverse event incidence against current pharmacological therapies used for fibromyalgia. In a meta-analysis of TCAs, collating data from 12 studies, an increased risk ratio of 2.35 (95% CI, 1.59–3.46) for withdrawing from the study was observed due to adverse events (67). Additionally, a systematic review assessing gabapentinoids observed increased risk of experiencing co-ordination and cognitive adverse effects such as, incoordination (RR 7.21; 95% CI 1.36, 38.25), abnormal gait (RR 6.71; 95% CI 1.57, 28.71), and dizziness (RR 3.33; 95% CI 2.39, 4.65). Moreover, Perucca et al. found that adverse events relating to these domains were those that most impair HRQoL for patients (68, 69). Given this context there may be potential for CBMPs to be a viable alternative. These findings further emphasize the need for randomized controlled trials of sufficient quality.

To assess the applicability of these results it is important to place them in context of the of limitations of this study. The most important limitation is that this is an observational study without appropriate placebo control, randomization, or blinding. Consequently, causality cannot be inferred and the associated improvements in HRQoL cannot be confirmed as being secondary to CBMPs, rather than other phenomena, such as regression to the mean. In addition, the participants are subject to selection bias. Unlicensed CBMPs are predominantly prescribed in private healthcare settings introducing selection bias. A meta-analysis conducted by Finegan and colleagues previously demonstrated that socioeconomic deprivation is associated with poorer

treatment outcomes regarding the same intervention (70). Given that the UKMCR consists of patients accessing CBMPs on private prescription this adds a cost limiting factor to the study cohort potentially skewing baseline demographics to higher socioeconomic status. Moreover, most patients were currently consuming cannabis at baseline or had previously consumed cannabis, which introduces further selection bias. The high prevalence of previous cannabis consumers and having to pay privately for treatment may introduce an expectancy bias, leading to inflated outcomes. Ideally, collecting data for these factors as well as other potentially confounding variables such as lifestyle factors, prior fibromyalgia treatments and ongoing medical conditions would better help to better contextualize the present analysis.

To control for the external effects of additional variables a multivariate analysis was conducted. Additionally, events per variable was maintained as ≥10 in accordance with literature to avoid inappropriate skewing of data, resulting in inaccurate odds ratios (71). However, there are challenges when conducting multivariate analyses which fail to account for all potential confounders. For example, the determination of whether to include the median value in CBD dose in either the high or low dose of CBD could result in a change of 47 participants between each group. Such large variances could potentially skew results adversely. Furthermore, these analyses are not able to control for all possible external factors. Therefore, these outcomes must be interpreted with caution, which further emphasizes the need for controlled trials to assess the efficacy of CBMPs isolated from the influence of these variables.

Patient registry data of any kind is subject to loss of follow up and attrition bias consequently limiting the accuracy of the findings. The completion rate of the present study at 12 months follow-up was 47.3%, with a 2019 study on compliance regarding PROM suggesting that to ensure the reliability of PROM analysis, study completion rate should aim to reach 60% (72). To control for this a BOCF method was used to account for missing data. This is a more conservative measure to account for missing data, which biases the results toward the null. Subsequently, statistically significant results are more likely to represent true findings. Furthermore, fibromyalgia is a chronic condition for which patients can be on lifelong treatment; in order to more accurately assess the long-term efficacy and safety profile of CBMP treatment, follow-up studies of greater duration are required.

Conclusion

To conclude, in a cohort of 148 fibromyalgia patients receiving CBMP treatment, a potential association between initiation of CBMPs and positive therapeutic benefit for fibromyalgia patients measured by HRQoL changes and subjective impressions of disease burden was observed, with an appropriate adverse event profile. This study aimed to provide further clinical data of CBMP therapy outcomes as alternative pharmacological management for fibromyalgia patients, needed given the lack of efficacy of current treatments. This study provides signals of improvement for these patients, which support further evaluation of Adven® CBMPs (Curaleaf International, UK) with randomized controlled trials for fibromyalgia. However, given the limitations of the study and the lack of ability to infer any causal relationships it is not possible to definitively conclude the effect of CBMPs on fibromyalgia.

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