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ORIGINAL RESEARCH

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UK medical cannabis registry: an updated clinical outcomes analysis of patients with post-traumatic stress disorder

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ABSTRACT

Background: Cannabis-based medicinal products (CBMPs) are a potential treatment for post-traumatic stress disorder (PTSD), but their long-term efficacy and safety need further investigation. This study assessed the changes in health-related quality of life (HRQoL) and adverse events in PTSD patients prescribed CBMPs.

Research design and methods: This observational cohort study included PTSD patients enrolled on the UK Medical Cannabis Registry for 18 months or longer. Changes in PTSD-specific symptoms (IES-R), anxiety (GAD-7), sleep quality (SQS), and general HRQoL (EQ-5D-5 L) were assessed at 1, 3, 6, 12, and 18 months.

Results: In 269 patients, significant improvements in PTSD symptoms, anxiety, sleep quality, and HRQoL were observed at all follow-up points ($p < 0.001$). On multivariate logistic regression, male gender (OR = 0.51; 95% CI:0.28–0.94; $p = 0.034$) was associated with a reduced chance of reporting improvements in IES-R. Adverse events were reported by 70 (26.02%) patients, with insomnia ($n = 42$, 15.61%) and fatigue ($n = 40$, 14.87%) being the most common.

Conclusions: CBMPs were associated with improvements in PTSD symptoms, anxiety, sleep, and HRQoL at up to 18 months. Although the study's observational nature limits causal conclusions, these findings support further assessment of medical cannabis.

Trial registration: This is an observational study and is not registered as a clinical trial.

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Cannabis; post-traumatic stress disorder; anxiety; sleep; psychiatry

1. Introduction

Post-traumatic stress disorder (PTSD) is a mental health condition that develops after experiencing or witnessing a traumatic event. It is characterized by persistent symptoms including flashbacks, nightmares, avoidance of reminders, and hyperarousal [1]. The prevalence within the UK is estimated to be between 5–10% of the population [2]. Coexisting psychiatric conditions, such as anxiety and depression, which can arise after trauma, often worsen PTSD severity [3]. Furthermore, people with PTSD are more likely to develop medical comorbidities. These include chronic pain, dementia, and cardiometabolic disorders [4]. PTSD therefore results in significant personal and societal burden [5]. As PTSD is more prevalent in socio-economically deprived populations, effective treatment is essential to address healthcare inequalities [6].

Psychotherapy is the gold-standard treatment for PTSD, including trauma-focused cognitive behavioral therapy and eye movement desensitization and reprocessing [7]. Although pharmacological treatments such as selective serotonin reuptake inhibitors (SSRIs) and nonselective monoamine oxidase inhibitors are also effective therapies, there are limitations to their widespread use [8]. Up to one-third of individuals with PTSD do not respond to currently available treatments. For psychotherapies and first-line SSRIs, the non-response rate may be as high as 50% and 40%, respectively [9]. Consequently, further research into therapies for PTSD is crucial [10].

Cannabis-based medicinal products (CBMPs) have emerged as novel treatments for PTSD. The two main phytocannabinoids found in CBMPs are (–)-*trans*-Δ^9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) [11]. The primary mechanism of action of Δ9-THC is at the G-protein coupled cannabinoid receptor type 1 and 2 (CB_1R/CB_2R) [12]. CB_1R is densely localized in areas of the central nervous system such as the amygdala, hippocampus, and ventromedial prefrontal cortex, which are involved in the modulation of fear [13,14]. Agonism of CB_1R in these areas prevents presynaptic neurotransmitter release, leading to neuronal plasticity and resultant psychotropic effects, such as mood alteration and reduction in anxiety [15].

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While Δ9-THC primarily acts as a partial agonist for CB_1R and CB_2R, CBD has a more complex pharmacological profile [16]. Although CBD has a low affinity for both CB_1R and CB_2R, some studies suggest that it acts as a negative allosteric modulator of CB_1R [17], thereby decreasing the activation of CB_1R receptors by both endogenous and exogenous agonists, including Δ9-THC [18]. While these mechanisms are of interest, the clinical relevance remains uncertain, and further research is needed to fully elucidate their impact. In the context of PTSD, preclinical studies in animal models have shown promising results, demonstrating the potential therapeutic efficacy of cannabinoids. In rodents, for example, CBD has shown reduction in fear expression through CB_1R mediated signaling [19].

Beyond CB_1R and CB_2R, cannabinoids can also induce effects through activation of other targets, such as 5-hydroxytryptamine$_{1A}$ (5-HT_{1A}) receptors, transient receptor potential vanilloid type 1 (TRPV1) channels, and peroxisome proliferator-activated receptors [15]. The 5-HT_{1A} receptor is expressed on serotonergic neurons in the median raphe nucleus and is an established anxiolytic target [20]. *In vivo* studies have suggested that low-doses of CBD may facilitate 5-HT_{1A} signaling, reducing stress and enhancing fear extinction in individuals [21].

Currently, the clinical evidence supporting the use of cannabinoids for PTSD is scarce, yet promising. Black *et al*. conducted a systematic review which found that pharmaceutical preparations of Δ9-THC/CBD demonstrated an advantage over placebo in improving day-to-day functioning and nightmare frequency in PTSD patients [13]. A prior analysis of the UK Medical Cannabis Registry (UKMCR) by our group has also shown that patients with treatment-resistant PTSD report improvements in PTSD-specific, sleep, and anxiety symptoms after 6 months of CBMP treatment [22].

Nevertheless, the current body of research in this area has significant limitations. There remains a paucity of high-quality evidence due to a lack of randomized control trials, small sample sizes, and heterogeneity across studies [13]. Furthermore, current research has mostly investigated the effects of cannabinoids over a short time period, which may not provide insight into long-term effectiveness and adverse event incidence. Given that chronic cannabis exposure is associated with a reduction in CB_1R activity, there is a need to investigate whether this causes long-term side-effects or tolerance to short-term anxiolytic effects [23].

This study's primary aim was to assess the changes in PTSD-specific and general patient-reported outcomes measures (PROMs) over 18 months for PTSD patients treated with CBMPs. The secondary aim was to assess the incidence of adverse events within this cohort to evaluate the long-term safety of using CBMPs for the management of PTSD.

2. Patients and methods

2.1. Study design

This prospective cohort study examined longitudinal clinical data from the UKMCR to investigate the effects of CBMPs in PTSD patients. Written and informed consent was obtained from participants prior to their data being collected. Consenting patients completed online questionnaires remotely at 1, 3, 6, 12, and 18 months after initial baseline assessment to evaluate PROMs and adverse events. The UKMCR was given ethical approval from the Central Bristol Ethics Committee (Reference: 22/SW/0145). Hereafter, this study adheres to the STROBE guidelines for strengthening the reporting of observational studies [24].

2.2. Setting and participants

Since 2019, the UKMCR has prospectively collected sequential, pseudonymized clinical data from patients in the UK and Crown Dependencies who are prescribed CBMPs for any approved clinical indication. The inclusion criteria for this study were patients aged 18 years and older who have initiated CBMP treatment for a primary diagnosis of PTSD. Participants were excluded from the study if they had not completed baseline PROMs, if they were not enrolled in the UKMCR 18 months prior to data extraction, or if the primary indication for receiving treatment with CBMPs was not for PTSD.

2.3. Data collection

At baseline assessment, clinicians recorded demographic details including age, gender, occupation, body mass index (BMI), alcohol consumption, smoking status, and cannabis exposure. The term 'cannabis gram-years' represents a novel metric which was used to quantify an individual's lifetime cannabis consumption, regardless of their current status [25]. These individuals were counseled to stop all external sources of cannabis upon commencement of CBMPs.

For patients with a primary diagnosis of PTSD, the incidence of relevant comorbidities was documented. Additionally, the Charlson Comorbidity Index, an assessment tool designed to predict long-term mortality risk associated with comorbidities, was calculated for each patient [26].

Throughout the duration of treatment, pertinent details of CBMPs were recorded, including strain, dosing, and route of administration. Prescriptions were available as oil-based formulations, inhaled dried flower, or a combination of the two. All prescribed CBMPs complied with Good Manufacturing Practice standards [27]. These were used to calculate the daily dose of prescribed THC and CBD.

2.4. Patient-reported outcome measures

The main outcome measured in this study was the change in PROMs from baseline to follow-up points at 1, 3, 6, 12, and 18 months. The following assessment tools were employed to evaluate symptom improvement in PTSD patients: the impact of event scale – revised (IES-R), EQ-5D-5L, generalized anxiety disorder-7 (GAD-7), single-item sleep quality scale (SQS), and patient global impression of change (PGIC) [28–32].

The IES-R is a self-reported questionnaire consisting of 22 items designed to measure the subjective distress associated with traumatic experiences [28]. It is mapped to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for PTSD. Respondents evaluate each item using a 5-point scale, where 0 indicates 'not at all' and 4 signifies 'extremely.' The total score can range from 0 to 88, and additional subscale

scores can be derived for its symptomatic dimensions of intrusions, avoidance, and hyperarousal.

The EQ-5D-5L is a standardized measure used to assess health-related quality of life. It consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension, respondents rate their health state on a 5-point scale ranging from 'no problems' to 'extreme problems' [29]. In addition to the individual dimension scores, a summary index score is generated, which can be used to quantify the overall health status of an individual, with higher scores indicating better health.

The GAD-7 assesses the severity of symptoms associated with generalized anxiety disorder. It is a questionnaire consisting of seven items, each reflecting common anxiety-related symptoms such as excessive worry, restlessness, and tension. Respondents rate each item on a 4-point Likert scale (0 = 'not at all' to 3 = 'nearly every day'), with total scores ranging from 0 to 21. Scores of 5, 10 and 15 are used as cutoff points to classify the severity of anxiety symptoms into mild, moderate, and severe, respectively [30]. A change of ≥ 4 on the GAD-7 was considered a clinically significant improvement, as this value represents the minimally clinically important difference (MCID) [33].

The SQS is a self-administered, single-item measure used to assess a patient's sleep quality over a 7-day recall period [31]. Scores range from 0 ('terrible') to 10 ('excellent'). The MCID for a clinically significant improvement in the SQS was a change of ≥ 2.6 [31].

The PGIC is a brief self-report scale used to assess a patient's overall perception of their improvement or worsening over a specified time period. It consists of a single item where patients rate their change in condition on a 7-point scale, ranging from 'no change, or condition has got worse' to 'a considerable improvement' [32].

2.5. Missing values

The method used to address missing PROMs data at follow-up intervals was baseline observation carried forward (BOCF). In the BOCF approach, if a subject lacks a post-baseline measurement at the study endpoint, their baseline value is used to replace the missing data for that variable [34]. This method is particularly recommended in clinical studies where there is a high likelihood of dropout, as it provides a conservative estimate of the treatment effect [35].

2.6. Adverse events

Adverse events (AE) were either reported by patients through remote self-reporting or noted by healthcare providers during scheduled appointments. These events were then categorized in line with the Common Terminology Criteria for Adverse Events, version 4.0 [36].

2.7. Statistical analysis

Descriptive statistics were used to summarize the key findings relating to baseline demographics, comorbidities, substance use history, CBMP prescriptions, and AE incidence. Data that follows a parametric distribution is presented as the mean ± standard deviation (SD), whereas nonparametric data is displayed as the median with interquartile range (IQR).

To investigate changes in PROMs, a repeated measures analysis of variance (ANOVA) was performed. Following this, significant results were further analyzed using post-hoc pairwise comparisons, with a Bonferroni correction applied to control for multiple comparisons. This approach was adopted to reduce the risk of Type I error [37].

A univariate logistic regression analysis was performed to determine whether any individual variables were associated with the likelihood of reporting an improvement in the IES-R Total Score at 18 months. Following this, a multivariate logistic regression analysis was conducted, which considered the combined influence of multiple variables on the likelihood of improvement. This approach allows for a more comprehensive analysis, as it adjusts for potential confounding factors and highlights the independent effect of each variable in the context of others [38]. All values from the univariate analysis were taken forward into the multivariate analysis due to the known relationship between variables such as prior cannabis use, gender, type of CBMP prescribed and dose of CBD and THC for example. This is to help control for known confounders present within the dataset.

A p-value of < 0.050 was considered indicative of statistical significance. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) (IBM Statistics version 29 SPSS Inc [New York, IL], USA).

3. Results

3.1. Baseline demographics and cannabis status

At the time of data extraction (13 December 2023), a total of 19,763 patients were registered in the UKMCR. From this cohort, 1,105 patients (5.59%) were excluded for not completing any baseline PROMs 13,684 patients (69.24%) for not being enrolled with the UKMCR at least 18 months prior to data extraction, and 4,704 patients (23.80%) for having a primary indication for CBMP treatment other than PTSD. Therefore, a total of 269 patients (1.36%) met the inclusion criteria and were included in the analysis. Analysis for PROMs completion was performed at 1 month (n = 244; 90.71%), 3 months (n = 224; 83.27%), 6 months (n = 189; 70.26%), 12 months (n = 155; 57.62%), and 18 months (n = 116; 43.12%).

The majority of patients were male (n = 164; 60.97%). The mean age was 38.74 (±10.05) years, and the mean body mass index (BMI) was 27.40 (±7.31) kg/m^2 (Table 1). A significant portion of the cohort was unemployed (n = 133; 49.44%) and over half had a concurrent diagnosis of anxiety or depression at baseline (n = 170; 63.20%). Most participants were active cannabis consumers at baseline (n = 198; 73.61%), with a median lifetime exposure of 10.00 (4.00–20.00) gram years across the cohort (Table 2).

3.2. Cannabis-based medicinal product dosing and prescription

At baseline, the prescribed median daily CBD dose was 5.00 [0.00–11.00] mg/day. This increased to 20.00 [10.00–65.00] mg/day at 18-months (Table 3). For Δ9-THC, the prescribed median

Table 1. Demographic details of study participants at baseline assessment (n = 269).

Baseline characteristics	No. (%)/Mean ± SD/Median [IQR]
Gender	
Female	105 (39.03%)
Male	164 (60.97%)
Age (Years)	38.74 ± 10.05
Body mass index (kg/m^2)	27.40 ± 7.31
Occupation	
Unemployed	133 (49.44%)
Professional	23 (8.55%)
Elementary occupations	13 (4.83%)
Service and sales workers	11 (4.09%)
Technicians and associate professionals	11 (4.09%)
Craft and related trades workers	7 (2.60%)
Armed forces occupations	5 (1.86%)
Managers	5 (1.86%)
Clerical support workers	3 (1.12%)
Skilled agricultural, forestry and fishery workers	3 (1.12%)
Plant and machine operators, and assemblers	1 (0.37%)
Retired	1 (0.37%)
Other occupations	42 (15.61%)
Unknown	11 (4.09%)
Charlson Comorbidity Index	0.00 [0.00–0.00]
AIDS	0 (0.00%)
Anxiety/depression	170 (63.20%)
Arthritis	23 (8.55%)
Cerebrovascular accident or transient ischemic attack	3 (1.12%)
Chronic obstructive pulmonary disease	5 (1.86%)
Congestive heart failure	1 (0.37%)
Connective tissue disease	4 (1.49%)
Dementia	0 (0.00%)
Diabetes (uncomplicated or end-organ damage)	13 (4.83%)
Endocrine thyroid dysfunction	10 (3.72%)
Epilepsy	3 (1.12%)
Hemiplegia	0 (0.00%)
Hypertension	10 (3.72%)
Leukaemia	1 (0.37%)
Liver disease	5 (1.86%)
Lymphoma	0 (0.00%)
Moderate to severe chronic kidney disease	1 (0.37%)
Myocardial infarction	1 (0.37%)
Peptic ulcer disease	2 (0.74%)
Peripheral vascular disease	1 (0.37%)
Solid tumor	7 (2.60%)
Venous thromboembolism	0 (0.00%)

Parametric data are presented as mean ± standard deviation and non-parametric data are presented as median [interquartile range].
Abbreviations: SD, standard deviation; IQR, interquartile range; AIDS, acquired immunodeficiency syndrome.

daily dose at baseline was 20.00 [8.15–22.00] mg/day. It increased to 195.00 [105.00–260.00] mg/day at 18-months. The most common prescription at baseline was dried flower only (n = 142; 52.79%), and this continued to be the most common regimen throughout all follow-up periods. Adven EMC1 50/<4 mg/ml CBD/THC (Curaleaf International, United Kingdom) and Adven EMT 20 mg/ml THC (Curaleaf International, United Kingdom) were the most frequently prescribed CBD- and THC-dominant oils. The most commonly prescribed dried flower was Adven EMT2 16%/<1% THC/CBD (Curaleaf International, United Kingdom).

3.3. Patient-reported outcome measures

Table 4 shows the changes in baseline and follow-up scores at 1, 3, 6, 12, and 18 months. Additionally, Supplementary Table S1 presents the Bonferroni corrected p-values for pairwise comparisons between baseline and each follow-up period for significant findings on repeated measures ANOVA.

Global improvements in PTSD-specific symptoms, as assessed by the IES-R Total Score, were observed from baseline through all follow-up periods at 1, 3, 6, 12, and 18 months ($p < 0.001$). Furthermore, the specific subscales of avoidance, intrusions, and hyperarousal all showed improvement between baseline and all subsequent follow-up periods of the study ($p < 0.001$).

General health-related quality of life, as measured by the EQ-5D-5L Index Value, showed improvements at 1, 3, 6, 12, and 18 months compared to baseline ($p < 0.001$). This positive change in the EQ-5D-5L was observed across the domains of Usual Activities, Pain & Discomfort, and Anxiety & Depression at all time points up to 18 months ($p < 0.001$). However, for the Self-Care domain, improvement was noted only up to 1 month ($p = 0.007$), after which no further changes were observed from baseline ($p > 0.050$). At 12 (5.57 ± 1.30; $p = 0.024$) and 18 months (5.61 ± 1.28; $p < 0.001$), the mean PGIC had improved compared to 1 month follow-up (5.36 ± 1.33).

Reductions in anxiety severity and enhancements in sleep quality were noted, as indicated by the changes in GAD-7 and SQS scores. These improvements were significant between baseline and each follow-up period at 1, 3, 6, 12 and 18 months ($p < 0.001$). Furthermore, GAD-7 scores exceeding the MCID were observed in 53.53% (n = 144) at 1 month, 55.02% (n = 148) at 3 months, 44.98% (n = 121) at 6 months, 38.29% (n = 103) at 12 months, and 31.23% (n = 84) at 18 months (Supplementary Table S2). Similarly, for the SQS, clinically significant improvements were observed in 34.94% (n = 94) at 1 month, 37.92% (n = 102) at 3 months, 28.25% (n = 76) at 6 months, 24.91% (n = 67) at 12 months, and 18.22% (n = 49) at 18 months.

Table 2. Tobacco, alcohol, and cannabis exposure of study participants at baseline assessment (n = 269).

Tobacco, alcohol, and cannabis status	No. (%)/Median [IQR]
Cannabis status	
Cannabis naïve	30 (11.15%)
Ex-user	41 (15.24%)
Current user	198 (73.61%)
Cannabis consumption, gram years	10.00 [3.00–25.00]
Tobacco status	
Non-smoker	57 (21.19%)
Ex-smoker	111 (41.26%)
Current smoker	101 (37.55%)
Tobacco pack years	10.00 [4.00–20.00]
Weekly alcohol consumption, units	0.00 [0.00–1.00]

Parametric data are presented as mean ± standard deviation (SD) and non-parametric data are presented as median [interquartile range (IQR)]. 'Gram-years' is a novel metric used to quantify and standardize lifetime cannabis use in ex and current smokers.
Abbreviations: IQR, interquartile range.

3.4. Univariate and multivariate analysis

A univariate analysis was conducted to assess the individual variables that were associated with improvement in the IES-R Total Score at the 18-month follow-up (Supplementary Table S3). This revealed that current cannabis users at baseline (OR = 2.73; 95% CI: 1.06–7.01; $p = 0.037$), patients prescribed dried flower only preparations (OR = 4.39; 95% CI: 1.24–15.54;

Table 3. CMBP dosing and route of administration for study participants at baseline, 1 month, 3 months, 6 months, 12 months, and 18 months follow-up.

	Baseline	1 month	3 months	6 months	12 months	18 months
CBD Dose (mg/day)	5.00 [0.00–11.00]	20.00 [0.00–60.00]	20.00 [0.00–62.50]	20.00 [0.00–65.00]	22.00 [10.00–70.00]	20.00 [10.00–65.00]
THC Dose (mg/day)	20.00 [8.15–22.00]	102.50 [80.00–150.00]	110.00 [100.00–200.00]	150.00 [100.00–212.50]	195.00 [105.00–246.95]	195.00 [105.00–260.00]
Oils only	60 (22.30%)	51 (18.96%)	29 (10.78%)	31 (11.52%)	25 (9.29%)	23 (8.55%)
Dried flower only	142 (52.79%)	139 (51.67%)	135 (50.19%)	132 (49.07%)	140 (52.04%)	141 (52.42%)
Both	67 (24.91%)	79 (29.37%)	103 (38.29%)	99 (36.80%)	100 (37.17%)	103 (38.29%)

Dosage is displayed as median [interquartile range] mg/day, whilst route of administration is displayed as n (%).
Abbreviations: CBD, cannabidiol; THC, (–) -trans-Δ9-tetrahydrocannabinol.

Table 4. Results of repeated measures ANOVA for changes in patient-reported outcome measures.

PROMs	Baseline	1 month	3 months	6 months	12 months	18 months	p-value
IES-R							
Avoidance	18.93 ± 6.61	15.68 ± 6.58	14.39 ± 7.59	15.05 ± 7.52	15.44 ± 7.82	16.01 ± 8.13	<0.001***
Intrusions	22.38 ± 7.00	16.39 ± 7.71	15.80 ± 8.21	16.38 ± 8.59	17.57 ± 8.62	18.43 ± 8.73	<0.001***
Hyperarousal	17.10 ± 5.38	12.41 ± 5.90	11.91 ± 6.46	12.95 ± 6.46	13.45 ± 6.70	14.03 ± 6.72	<0.001***
Total Score	58.41 ± 17.00	44.48 ± 18.32	42.09 ± 20.60	44.38 ± 20.99	46.46 ± 21.80	48.47 ± 22.01	<0.001***
EQ-5D-5L							
Index Value	0.39 ± 0.29	0.55 ± 0.26	0.56 ± 0.28	0.52 ± 0.28	0.51 ± 0.30	0.48 ± 0.30	<0.001***
Mobility	1.81 ± 0.99	1.73 ± 0.99	1.72 ± 0.99	1.81 ± 0.98	1.81 ± 0.98	1.82 ± 0.97	0.081
Self-Care	1.99 ± 1.03	1.83 ± 0.95	1.88 ± 0.99	1.88 ± 0.98	1.94 ± 1.02	1.92 ± 1.00	0.011*
Usual Activities	2.86 ± 1.08	2.38 ± 0.98	2.34 ± 1.06	2.48 ± 1.06	2.45 ± 1.09	2.62 ± 1.09	<0.001***
Pain & Discomfort	2.56 ± 1.22	2.29 ± 1.10	2.25 ± 1.06	2.32 ± 1.08	2.35 ± 1.14	2.40 ± 1.17	<0.001***
Anxiety & Depression	3.71 ± 1.13	2.98 ± 1.04	2.95 ± 1.11	3.08 ± 1.10	3.11 ± 1.17	3.23 ± 1.20	<0.001***
GAD-7	14.64 ± 5.48	9.83 ± 5.82	9.45 ± 5.68	10.42 ± 5.98	11.13 ± 6.43	11.53 ± 6.30	<0.001***
SQS	3.25 ± 2.25	5.07 ± 2.52	5.04 ± 2.59	4.65 ± 2.58	4.46 ± 2.65	4.04 ± 2.65	<0.001***
PGIC		5.36 ± 1.33	5.41 ± 1.38	5.55 ± 1.28	5.57 ± 1.30	5.61 ± 1.28	0.002**

Each PROM is displayed as mean ± standard deviation. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
Abbreviations: IES-R, impact of event scale – revised; GAD-7, generalized anxiety disorder-7; SQS, sleep-quality scale; PGIC, patient global impression of change.

$p = 0.022$), and patients prescribed both dried flower and oil preparations (OR = 4.14; 95% CI: 1.15–14.92; $p = 0.030$) were associated with improved odds of reporting an improvement in IES-R Total Score. After subsequent multivariate analysis, the positive association of the above variables was eliminated, with now only male gender (OR = 0.51; 95% CI: 0.28–0.94; $p = 0.034$) being associated with reduced chance of reporting improvements in IES-R Total Score (Supplementary Table S4).

3.5. Adverse events

Table 5 displays the adverse events reported by participants and their severity. There were 542 adverse events (AE) reported by 70 (26.02%) patients, the majority of which were mild or moderate. The most common AEs were insomnia ($n = 42$, 15.61%) and fatigue ($n = 40$, 14.87%). There were three (0.55%) isolated life-threatening AEs reported, which were acidosis ($n = 1$; 0.18%), drug tolerance ($n = 1$; 0.18%), and pharyngitis ($n = 1$; 0.18%).

4. Discussion

This study demonstrates that treatment with CBMPs is associated with significant and sustained improvements in PTSD symptoms, anxiety, sleep quality, and overall HRQoL in a cohort of 269 patients. This builds on previous UKMCR research evaluating the clinical efficacy and safety of CBMPs for PTSD at 6 months [22]. Upon multivariate logistic regression, it was shown that males were less likely than females to demonstrate improvements in the IES-R Total Score at the 18 month follow-up. Seventy (26.02%) patients experienced adverse events, with most being mild or moderate in severity. These findings have important implications for the management of PTSD with CBMPs in individuals who have not responded to conventional therapies or who experience intolerable side effects.

In this study, patients showed statistically significant improvements in the IES-R Total Score, as well as the subscales of intrusions, avoidance, and hyperarousal, at all follow-up points compared to baseline ($p < 0.001$). These results are in line with previous observational studies in the field. A retrospective chart review by Greer *et al*. found that patients taking cannabis had an improvement of > 75% in a clinician-administered PTSD scale [39]. Pillai *et al*.'s prior UKMCR analysis, which similarly used the IES-R, also reported PTSD symptom improvement in patients taking CBMPs over a 6-month period [22]. This present study reinforces these findings whilst demonstrating that improvements in PTSD symptoms persist at 12 and 18 months. Additionally, this study features a larger sample size compared to most previous studies that have shown a positive relationship between prescribed cannabis and symptomatic improvement in PTSD [39–43]. Of note, the number of participants who reported an improvement in IES-R reduced at 12 and 18 months. The reasons for this could be related to the methods utilized to control for missing data which biases toward a null finding. Conversely, these effects could be secondary to pharmacological tolerance to the effects of CBMPs or a ceiling effect to their efficacy in PTSD. These findings will need examining further in randomized controlled trials. The findings of the present study, however, contrast with those of Johnson *et al*., who reported no reduction in PTSD symptom severity among veterans using

Table 5. Frequency and severity of adverse events.

Adverse Events	Mild	Moderate	Severe	Life-threatening	Total
Abdominal Pain	2	6	0	0	8 (2.97%)
Acidosis	0	0	0	1	1 (0.37%)
Amnesia	6	5	3	0	14 (5.20%)
Anorexia	6	15	1	0	22 (8.18%)
Anxiety	2	3	5	0	10 (3.72%)
Arthralgia	0	1	1	0	2 (0.74%)
Ataxia	4	5	0	0	9 (3.35%)
Atelectasis	2	0	0	0	2 (0.74%)
Blurred Vision	5	2	0	0	7 (2.60%)
Chills	0	1	0	0	1 (0.37%)
Cognitive Disturbance	7	5	4	0	16 (5.95%)
Concentration Impairment	16	11	4	0	31 (11.52%)
Confusion	4	7	2	0	13 (4.83%)
Constipation	5	2	0	0	7 (2.60%)
Cough	0	1	0	0	1 (0.37%)
Delirium	4	4	1	0	9 (3.35%)
Diarrhoea	1	0	2	0	3 (1.12%)
Dizziness	8	6	3	0	17 (6.32%)
Drug Tolerance	0	0	0	1	1 (0.37%)
Dry Eye	0	1	0	0	1 (0.37%)
Dry Mouth	34	2	0	0	36 (13.38%)
Dysgeusia	4	1	0	0	5 (1.86%)
Dyspepsia	13	4	1	0	18 (6.69%)
Fall	1	0	0	0	1 (0.37%)
Fatigue	11	20	9	0	40 (14.87%)
Fever	4	0	0	0	4 (1.49%)
Flank Pain	0	1	0	0	1 (0.37%)
Flashback	0	0	2	0	2 (0.74%)
Generalized Muscle Weakness	7	4	4	0	15 (5.58%)
Haemorrhoids	0	1	0	0	1 (0.37%)
Headache	15	15	4	0	34 (12.64%)
Insomnia	7	17	18	0	42 (15.61%)
Intrusive Thoughts	1	0	0	0	1 (0.37%)
Irritability	0	2	1	0	3 (1.12%)
Lethargy	14	17	0	0	31 (11.52%)
Lung Infection	0	5	0	0	5 (1.86%)
Mania	0	0	1	0	1 (0.37%)
Nausea	10	10	1	0	21 (7.81%)
Palpitations	1	0	0	0	1 (0.37%)
Paranoia	0	0	2	0	2 (0.74%)
Parasomnia	0	1	3	0	4 (1.49%)
Pharyngitis	0	12	0	1	13 (4.83%)
Rash (Non-Specific)	1	2	0	0	3 (1.12%)
Somnolence	0	24	4	0	28 (10.41%)
Spasticity	3	1	0	0	4 (1.49%)
Tremor	6	4	0	0	10 (3.72%)
Urinary Tract Infection	0	2	0	0	2 (0.74%)
Vertigo	4	6	1	0	11 (4.09%)
Vomiting	9	2	1	0	12 (4.46%)
Weight Loss	13	3	0	0	16 (5.95%)
Total	230	231	78	3	542

Adverse events are classified into mild, moderate, and severe categories, with the count for each severity level provided. The table also presents the overall percentage of adverse events for each severity category.

recreational cannabis [44]. This discrepancy is likely due to methodological differences, such as a cross-sectional study design and convenience sampling method. It has also been suggested that the motivations and usage patterns of recreational cannabis consumers differ significantly from those of medical cannabis patients [45]. Furthermore, this analysis found that males were less likely to report improvements in the IES-R Total Score at 18 months compared to females (OR = 0.51; 95% CI: 0.28–0.94; $p = 0.034$). Whilst differences in expression of cannabinoid receptors between sexes have been found in pre-clinical models, the sex-dependent effects of CBMPs in clinical settings are not well understood [46]. On univariate analysis cannabis users and those prescribed dried flower were more likely to report an improvement in IES-R. However, this was not present on multivariate analysis. This may be secondary to confounding between types of medications prescribed to those with prior cannabis exposure. This highlights the need for future research into how the effectiveness of CBMPs may vary across different populations.

The coexistence of other psychiatric disorders in PTSD is well documented, and further evidenced by 63.20% ($n = 170$) of the present series having comorbid anxiety and/or depression at baseline [47,48]. This analysis corroborates the potential anxiolytic effects of CBMPs, as patients reported improvements in both the GAD-7 and the 'Anxiety and Depression' domain of the EQ-5D-5L at all follow-up points compared to baseline ($p < 0.001$). This is supported by prior UKMCR studies which have focused on changes in the GAD-7 as a primary outcome [49,50], as well as studies investigating anxiety in PTSD specifically [22]. This suggests that CBMPs may be of benefit for PTSD patients particularly affected from anxiety symptoms or co-morbid anxiety disorders. The wide range of CBMP mediated actions within fear-related neurocircuitry likely underpins the pharmacokinetic mechanisms driving these anxiolytic outcomes [20,21,51]. Interestingly, LaFrance *et al*. note that for a significant reduction in anxiety to be achieved, high doses of cannabis are required [52]. The dose-response curve for the anxiolytic properties of CBD is complex and remains poorly understood [53]. As such, further research is required to determine the optimal therapeutic dose for maximizing the anxiolytic effects of CBMPs in patients with PTSD and anxiety-related disorders.

This analysis found that CBMPs were associated with an improvement in self-reported sleep quality ($p < 0.001$). Studies investigating sleep disturbance as a primary outcome show similar improvements, with reduced nightmare frequency and shorter sleep-onset times [54–56]. Individuals with PTSD who report sleep disturbances also tend to experience greater functional impairment compared to those without such issues [57]. Moreover, comorbid sleep problems can intensify PTSD symptoms and hinder the recovery process [58]. As such, CBMPs emerge as a potential therapeutic option to address the significant burden that sleep impairment poses in PTSD.

Conversely, insomnia was the most common adverse event reported in this study, affecting 15.61% ($n = 42$) of the cohort. A study encompassing all conditions on the UK Medical Cannabis Registry, reported the prevalence of insomnia as an adverse event as 10.55% [59]. This was one of the most common adverse events, but still less than the 15.61% in this study. The reason for this could be the longer follow up time in the present study, 18 months, compared to 6 months in the prior analysis. Moreover, it is estimated that 80–90% of PTSD patients experience insomnia symptoms, while 50–70% experience nightmares [60]. Consequently, insomnia could be more commonly reported as an adverse event in studies of PTSD, particularly when they are not assessed as to whether they were caused by the therapy, such as in this pseudonymized dataset. A particular limitation of the present analysis is that adverse events were not assessed to confirm whether they were treatment-related or due to another factor. Across the study one in four participants reported an adverse event, with the majority of these being mild to moderate in

severity, indicating that CBMPs were largely well tolerated over the course of 18 months. However, it is worth noting that the average amount of THC consumed by participants at the 12- and 18-month follow-up was quite high. While this dosage was part of the individualized treatment regimen prescribed to participants, it may raise concerns regarding potential side effects or tolerance over time. Such high THC doses warrant further investigation into their long-term safety and effectiveness. Future studies could explore the impact of varying THC dose levels on therapeutic outcomes, side effect profiles, and optimal dosing strategies.

It is important to recognize the limitations of this study when interpreting findings. As an observational study, it is impossible to definitively establish causality between CBMP therapy and improvements in the IES-R, EQ-5D-5L, GAD-7, and SQS scores [61]. The lack of blinding and randomization within the study protocol also reduces the internal validity [62]. Furthermore, because this investigation lacks a control group, it is difficult to differentiate whether any observed benefits are due to the CBMP treatment or to confounding factors, such as the Hawthorne Effect [63]. Although PROMs are widely used to assess symptom burden in anxiety-related disorders, they are susceptible to recall bias [64]. Additionally, the sampling process may have been influenced by selection bias, as indicated by the disproportionate number of current and ex- cannabis users compared to cannabis-naïve patients. The limitations of BOCF to handle missing data must also be noted. This approach assumes that participants' symptoms remained stable, potentially overlooking any worsening of symptoms over time. As such, it may underestimate the true variability in symptom change and could affect the interpretation of the therapeutic effects of CBMP. Finally, the reasons for PROM incompletion and attrition were not recorded. As such, the findings of this study may not be generalizable to other cohorts.

5. Conclusion

This analysis suggests that initiation of CBMP therapy for up to 18 months is associated with improvements in PTSD-specific, HRQoL, anxiety, and sleep symptoms in PTSD patients. Moreover, CBMPs are largely well tolerated across this short-term follow-up. The findings also suggest that CBMPs may be of particular benefit to PTSD patients with comorbid anxiety or insomnia. Interestingly, multivariate logistic regression suggests that women may be more likely to report a benefit in PTSD severity after initiating CBMPs. Although causality cannot be definitively established due to the observational nature of the study, these results lay the groundwork for future randomized controlled trials. Such trials will be necessary to validate these promising findings, and to identify the patient populations most likely to benefit from this treatment.

Ethics approval

Ethical approval provided by Southwest – Central Bristol Research Ethics Committee (Reference: 22/SW/0145).

Patient consent statement

All participants completed written, informed consent prior to enrollment in the registry.

Data availability statement

Data supporting this study's findings 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.

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The authors confirm that the PI for this paper is Michael Sodergren and that he had direct clinical responsibility for patients. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Author contribution statement

All authors contributed to the study's conception and design. Material preparation and data collection were performed by A Datta, S Erridge, J Warner-Levy, E Clarke, K McLachlan, R Coomber, M Asghar, K Bexley, U Bhoskar, M Crews, A De Angelis, M Imran, F Kamal, L Korb, G Mwimba, S Sachdeva-Mohan, G Shaya, and JJ Rucker. Data analyses were performed by A Datta, S Erridge and MH Sodergren. The first draft of the manuscript was written by A Datta, S Erridge, E Clarke, K McLachlan, R Coomber, JJ Rucker, and MH Sodergren. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declaration of interest

S Erridge is Research Director at the at Curaleaf Clinic. E Clarke is the Patient Care Director at Curaleaf Clinic. K McLachlan is Chief Pharmacist at the Curaleaf Clinic. R Coomber is the Operations Director at Curaleaf Clinic. M Asghar, K Bexley, U Bhoskar, M Crews, A De Angelis, M Imran, F Kamal, L Korb, G Mwimba, S Sachdeva-Mohan, and G Shaya and are all consultant psychiatrists at the Curaleaf Clinic. JJ Rucker is a consultant psychiatrist and a former director at the Curaleaf Clinic. JJ Rucker is funded by a fellowship (CS-2017-17-007) from the National Institute for Health Research (NIHR). MH Sodergren is the Chief Medical Officer at Curaleaf International. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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