


A cohort study comparing the effects of medical cannabis for anxiety patients with and without comorbid sleep disturbance

Matthew Murphy¹  | Simon Erridge^{1,2} | Carl Holvey² | Ross Coomber^{2,3} |
James J. Rucker^{4,5} | Mikael H. Sodergren^{1,2}

¹Medical Cannabis Research Group,
Department of Surgery and Cancer,
Imperial College London, London, UK

²Sapphire Medical Clinics, London, UK

³St. George's Hospital NHS Trust, London,
UK

⁴Department of Psychological Medicine,
Kings College London, London, UK

⁵South London & Maudsley NHS
Foundation Trust, London, UK

Correspondence

Mikael H Sodergren, Department of
Surgery & Cancer, Imperial College
London, Academic Surgical Unit, 10th
Floor QEQM, St Mary's Hospital, South
Wharf Road, London W2 1NY, UK.
Email: m.sodergren@imperial.ac.uk

Abstract

Background: Research on cannabis-based medicinal products (CBMPs) in anxiety remains inconclusive due to a paucity of high-quality evidence. Studies indicate a bidirectional relationship between generalized anxiety disorder (GAD) and sleep disruption, but it is unclear how this affects CBMP treatment outcomes. This study aims to compare the patient-reported outcome measures (PROMs) of patients prescribed CBMPs for GAD, with and without impaired sleep.

Methods: Changes in PROMs were recorded from baseline to 1, 3, 6, and 12 months between those with impaired or unimpaired sleep. Multivariate logistic regression was applied to compare factors associated with a clinically significant improvement in GAD-7 at 12 months. Secondary outcomes included adverse event incidence and frequency.

Results: Of the 302 patients that fit the inclusion criteria, mean GAD-7, single-item sleep quality, and EQ-5D-5L index values improved at all time points ($p < 0.001$). A relationship between sleep impairment and clinically significant changes in GAD-7 at 1 and 3 months was identified ($p \leq 0.01$). On multivariate regression, only baseline GAD severity was associated with an increased likelihood of observing a clinically significant improvement in anxiety ($p < 0.001$). Seven hundred and seven (234%) adverse events were reported by 55 (18.21%) participants.

Conclusions: This study observed an association between CBMP treatment and improvements in anxiety in patients with GAD. While patients with comorbid sleep disruption had greater improvements in anxiety, the differences were not maintained in a multivariate analysis. Baseline anxiety severity may be a predictor for CBMP treatment outcomes.

KEYWORDS

anxiety, cannabidiol, cannabis, sleep, tetrahydrocannabinol

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2023 The Authors. *Neuropsychopharmacology Reports* published by John Wiley & Sons Australia, Ltd on behalf of The Japanese Society of Neuropsychopharmacology.

1 | INTRODUCTION

Anxiety, a neuropsychiatric disorder, affects more than 8 million people in the United Kingdom.¹ The most common, generalized anxiety disorder (GAD), is a chronic condition defined as excessive and uncontrolled anxiety causing significant distress over a minimum of 6 months, characterized by symptoms of restlessness, difficulty concentrating, and sleep disturbances.^{2,3} A diagnosis of GAD is often comorbid with other psychiatric conditions.⁴ Individuals with GAD are more likely to experience a diminished quality of life, unemployment, and suicidality which places a greater socioeconomic burden on society.^{1,4-8}

GAD is associated with and maintained by a wide array of precipitating and perpetuating factors.⁹⁻¹⁴ Avoidance, substance abuse, and rumination are typical maladaptive coping mechanisms that maintain and heighten the severity of GAD.¹⁵⁻¹⁷ Insomnia, difficulty getting to sleep, or staying asleep for long enough, is correlated with the development and reinforcement of anxiety disorders.¹⁸⁻²⁰ The coexistence of insomnia and GAD has been shown to decrease responsiveness to treatment and exacerbate anxiety symptoms, worsening social and mental well-being.^{21,22}

GAD is also associated with neurobiological changes. The hypothalamic-pituitary-adrenal (HPA) axis is dysregulated by excessive stress, leading to a diminished capacity to inhibit conditioned fear.^{23,24} The circuitry between the reticular formation and the amygdala is also affected, contributing to sleep disruption, emotional imbalance, and cognitive deficits.¹⁹ The complex origin of GAD, its comorbidity with other psychiatric conditions, and its impact on brain circuitry make a best-fit treatment difficult to identify.

Pharmacotherapy and psychotherapy are the primary treatments for GAD.²⁵⁻²⁷ The most common pharmacological treatments, monoamine reuptake inhibitors, act by increasing the synaptic concentration of the monoaminergic neurotransmitters.^{25,28} Crucial to mood regulation, these neurotransmitter systems are often disrupted in individuals with anxiety disorders and current pharmacotherapy is centered around this concept.²⁹ With current treatment options, fewer than 85% of patients experience a 50% improvement, half of which achieve clinical recovery.³⁰ There is therefore scope to improve present management of GAD, especially when also considering the adverse effect (AE) profile of currently available therapies and the rate of recurrence.^{25,31-33}

Cannabis-based medicinal products (CBMPs) present a novel pharmacotherapeutic approach to GAD. CBMPs containing cannabis plant derivatives, including Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD), primarily interact with the body's endocannabinoid system (ECS).³⁴ The ECS is a complex signaling network of receptors, enzymes, and ligands, notably the cannabinoid receptors type 1 and 2 (CB1/CB2).³⁵ CB1 is concentrated within brain regions associated with emotion, memory, and higher order processing-particularly the hippocampus, amygdala, and neocortex.³⁵ Activation of CB1 in these areas leads to the inhibition of glutamate and gamma-aminobutyric acid release.³⁶ Δ^9 -THC is a partial

agonist of both CB1 and CB2, whereas CBD has a low affinity for both receptors, acting as a noncompetitive agonist for CB1 and an inverse agonist at high concentrations.^{37,38} CBD also inhibits anandamide (AEA) uptake and degradation, increasing the concentration of this endogenous cannabinoid receptor agonist.³⁹ Hippocampal neurogenesis and synaptic plasticity are crucial to reconsolidation and fear extinction, impairment of which are associated with anxiety pathogenesis.²³ The association of CBD with hippocampal neurogenesis and long-term potentiation provides justification for CBMP use in treating neuropsychiatric disorders.⁴⁰

Studies also indicate CBD is an agonist of the serotonin_{1A} (5-HT_{1A}) receptor and transient receptor potential vanilloid type 1 (TRPV1) channels.^{39,41-43} Located within the HPA axis, 5-HT_{1A} heteroreceptor activation is associated with increased fear extinction, while TRPV1-mediated glutamate release induces synaptic plasticity, contributing to fear conditioning.^{40,44,45} CBD and AEA have synergistic effects across both receptors, desensitizing TRPV1 and activating 5-HT_{1A}, putative mechanisms for reducing learned fear and facilitating fear extinction.^{42,45} Furthermore, via increasing AEA, CBD also increases monoaminergic activity, contributing to a reduction in stress-related behaviors and fear conditioning.^{38,42}

Δ^9 -THC has sedative effects, decreasing arousal, and sleep onset latency, potentially through CB1 and subsequent cholinergic neuron activation in the pons.^{46,47} Additionally, high concentrations of CBD are correlated with increased total sleep time, a process thought to be mediated by increased AEA accumulation.⁴⁶

Presently, the evidence for cannabinoid use in psychiatric disorders is minimal but promising. A 2019 systematic review indicated cannabinoid treatment significantly reduced anxiety symptoms compared to placebo.⁴⁸ Analysis of the UK Medical Cannabis Registry (UKMCR) has demonstrated similar improvements in anxiety symptoms and sleep quality scores.⁴⁹⁻⁵³ There have only been two randomized clinical trials (RCT) investigating CBD against a placebo for social anxiety disorder^{54,55}; positive effects were identified but results were not statistically significant. A recent RCT comparing cannabinoid treatment to placebo for chronic insomnia was limited by the small sample size and poor maintenance of blinding.⁵⁶ However, the results did indicate improvements in insomnia symptoms and across some self-reported measures.

The existing research in this field shares some notable limitations. Anxiety and sleep quality are often evaluated as secondary outcomes in the context of other conditions, reducing the translation of results to patients with GAD and insomnia, respectively.⁴⁸ Heterogeneity in the formulation, route of administration, and study length is witnessed across the literature.⁵⁷ Most participants are studied over a short period, which greatly limits the understanding of long-term AEs. Especially in the context of psychiatric disorders, the psychotropic effects of Δ^9 -THC must be investigated over a longer duration.^{48,58}

While the effects on anxiogenic and sleep-wake pathways may suggest the role for CBMPs in treating GAD and comorbid impaired sleep, there is no research investigating this outcome. Therefore, the aim of this study was to compare the patient-reported outcome



measures (PROMs) of patients prescribed CBMPs for GAD, with and without impaired sleep. The secondary aim of this study was to investigate the safety profile of CBMPs over a 12-month period and to assess the impact of age, body habitus, prior cannabis use, treatment type, cannabinoid dosage, anxiety severity, and sleep quality on the likelihood of experiencing an adverse event.

2 | METHODS

2.1 | Study design and participants

This study is a prospective cohort study of patients from the UKMCR that are receiving CBMP treatment for a primary condition of GAD. Since December 1, 2019, the UKMCR has recorded longitudinal pseudonymized data from patients prescribed CBMPs outside the NHS for any clinical indication. The UKMCR has received ethical approval from the Central Bristol Research Ethics Committee (Reference: 22/SW/0145). This study was reported in line with STROBE statement.⁵⁹ Written and informed consent was provided by all patients upon registration, before baseline data collection, after which participants were enrolled consecutively.

Therapy with CBMPs was initiated in line with UK regulations.⁶⁰ The decision to prescribe was made following an appointment with a consultant psychiatrist, supported by a multidisciplinary team. Patients must demonstrate insufficient benefit or have experienced intolerable AEs from licensed therapies.⁶¹ All medications adhere to Good Manufacturing Practice.^{60,61}

2.2 | Data collection

This analysis utilizes UKMCR participant data from December 1, 2019. The inclusion criteria for this study were patients with a primary indication of GAD. Participants enrolled in the UKMCR for less than 12 months prior to the extraction of data (January 9, 2023) were excluded. Those with incomplete baseline PROMs were excluded due to the lack of a reliable baseline to compare changes outcomes.

During enrolment, the primary indication for CBMP treatment was recorded. Clinicians also collected demographic characteristics including age, gender, occupation, and body mass index. Relevant comorbidities were recorded and the Charlson comorbidity index was calculated for each patient.⁶² Data on tobacco, alcohol and cannabis use including smoking status, smoking pack years, weekly alcohol consumption (units), cannabis smoking status, and cannabis gram years were recorded. Gram years is a novel metric, described by our group, to quantitatively measure an individual's previous cannabis use.⁵¹ Patients were prompted to complete electronic questionnaires for PROMs and AEs at baseline, and 1, 3, 6, and 12 months. A patient evaluation of the UKMCR reported that this process was found to be easy to complete by over 95% of respondents.⁶³

Details regarding CBMP treatment were recorded throughout the course of treatment including the formulation, cannabis strains,

route of administration, and THC and CBD doses per 24h (mg). Treatment options were administered via sublingual or oral preparations, or vaporized dried flower.

2.3 | Patient-reported outcome measures

The primary outcomes of this study were changes from baseline at 1, 3, 6, and 12 months, which were self-reported using the following PROMs: Generalized Anxiety and Depression-7 (GAD-7), Single-Item Sleep Quality Scale (SQS), and EQ-5D-5L. Values for Patient Global Impression of Change (PGIC) were also collected at each follow-up session.

The GAD-7 is designed to screen, measure, and interpret the severity of GAD. It poses seven questions, assigning a score to the frequency of core GAD symptoms experienced (0 = "not at all" to 3 = "nearly every day").⁶⁴ With a maximum total of 21 points, the severity is classified into mild, moderate, and severe anxiety, determined by scores of ≥ 5 , ≥ 10 , and ≥ 15 , respectively. Based on Toussaint et al.'s sensitivity to change analysis, a minimally clinically important difference (MCID) of at least a 4-point change was deemed clinically meaningful.^{65,66}

The SQS scale is a rapid self-reported assessment of sleep quality.⁶⁷ Patients rate their sleep quality over the last 7 days using a numerical value between 0 ("terrible") and 10 ("excellent"). In keeping with Snyder et al.'s evaluation of the SQS, an MCID of at least a 2.6-point change conferred "somewhat improved" while a ≥ 4.9 -point change was "greatly improved"—both changes are viewed as clinically significant.⁶⁷

The EQ-5D-5L is a measure of a patient's Health-Related Quality of Life (HRQoL), recommended by the National Institute for Health and Care Excellence.^{68,69} Covering five domains that constitute quality of life (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), patients rate the level of severity in each domain from 1 to 5 (1 = none, 2 = slight, 3 = moderate, 4 = severe, and 5 = extreme). This generates a 5-digit code that is mapped to a country-specific EQ-5D-5L index value.⁶⁹ An index value of 1 is the highest possible score, while < 0 represents an HRQoL worse than death.

The PGIC assesses the patient's perceived improvement in symptoms since commencing the therapy.⁷⁰ The patient is asked to rate their improvements in activity limitations, symptoms, emotions, and overall quality of life on a scale from 1 to 7 (1 = "no change at all" to 7 = "a great deal better").

2.4 | Prescribed medication

Details regarding prescribed medications were collected at baseline and updated by patients and clinicians throughout the course of the treatment. Prescribed medications were separated into three categories: antidepressants, benzodiazepines, and gabapentinoids. Antidepressants included amitriptyline, baclofen,

bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, pramipexole, sertraline, trazadone, and vortioxetine.

2.5 | Adverse events

Patients were provided with a list of AEs and the option to report using free text. Data were self-reported from patients simultaneously with PROMs or at the time of the event. AEs could also be recorded during follow-up appointments with clinicians. AEs were recorded in accordance with the common terminology criteria for adverse events version 4.0.⁷¹

2.6 | Missing data

Baseline observation carried forward was the method employed for addressing missing PROMs data, whereby a patient's missing data would be replaced by the baseline value recorded, regardless of whether post-baseline PROMs are recorded.⁷² This method was selected as it is more conservative than last observation carried forward, whereby a patient's missing data is replaced by their more recently recorded value.

2.7 | Statistical analysis

Descriptive analysis was performed on patient demographics, drug and alcohol data, prescription changes, and reported AEs. The distribution of the data were determined by a Shapiro–Wilk test. Parametric data was presented as mean \pm standard deviation (SD), nonparametric data was presented as median and interquartile range (IQR), except where parametric tests were applied to large sample sizes in accordance with the central limit theorem.^{73,74}

A repeated measures one-way analysis of variance (ANOVA) was used to compare the mean difference between patients for each PROM at each time point. A post hoc Bonferroni correction was then applied to correct for multiple comparisons.

Participants were also stratified according to SQS scores: a score of 0–4 was “impaired sleep” while scores ≥ 5 meant “unimpaired sleep.” An independent samples t-test was performed to compare the mean changes in PROMs from baseline between the two sleep quality groups. These subgroups were subject to further analysis and the PROM values were separated into “clinically significant improvement” or “not clinically significant improvement.” EQ-5D-5L was excluded from this aspect of the analysis due to inconsistencies of the MCID in literature. A Chi-squared test was used to identify a relationship between sleep quality and clinically meaningful improvements in PROMs.

A univariate binary logistic regression model was applied to assess the individual effect of age, BMI, gender, prior cannabis exposure, treatment type, current THC and CBD dosage, baseline sleep

quality, and baseline anxiety on the likelihood of achieving a clinically significant improvement in GAD-7 at 12 months. All variables were then included in a multivariate regression model, which adjusts according to the other included variables and determines the impact of each independent variable on the dependent variable. Data from the regression models were presented as the odds ratio (OR) and 95% confidence interval (CI).

A further univariate binary logistic regression model was then applied to assess the effects of the same independent variables on the likelihood of experiencing an adverse event after 12 months of CBMP treatment. All variables were taken forward to a multivariate regression model.

Patients were then stratified by treatment type and a one-way ANOVA was used to compare the mean difference between patients for each PROM and treatment type, at each time point.

A further ANOVA was used to compare the mean differences between patients treated with oils, dried flowers, or a combination for each PROM and treatment type at every time point. A post hoc Bonferroni correction was then applied to correct for multiple comparisons.

Statistical significance was defined as $p < 0.05$. All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) (IBM Statistics version 29 SPSS Inc [New York, IL], USA).

3 | RESULTS

3.1 | Baseline characteristics and cannabis exposure

At the point of data extraction (January 9, 2023), 9464 patients were enrolled on the UKMCR. After applying inclusion criteria, 302 patients were included. Half of all participants had a complete set of PROMs ($n = 151$; 50.00%). Most patients were male ($n = 210$; 69.50%) and over half of the cohort had impaired sleep quality at baseline ($n = 156$, 51.66%) (Table 1). The mean age of participants and body mass index (BMI) were 38.06 (± 11.70) and 26.85 (± 7.30) kg/m², respectively. The comorbidities and indications for treatment were also analyzed (Table 1; Tables S1 and S2). Secondary and tertiary indications with the highest frequency were depression ($n = 85$, 27.61%) and insomnia ($n = 23$, 7.61%). Most participants were current users of cannabis at baseline ($n = 193$, 63.91%) and the median lifetime exposure was 5.00 (2.00–18.00) gram years (Table 1). The majority of the cohort (76.75%) were either current or ex-smokers with a median lifetime exposure to tobacco of 8.50 (3.00–20.00) pack years (Table 1).

3.2 | CBMP prescription and dosage

Most patients were only prescribed dried flower preparations throughout the period of analysis ($n = 167$, 55.30%) (Table 2). The

TABLE 1 Demographic details at baseline.

Demographic details	n (%) / mean \pm SD / median [IQR]
Sex	
Male	210 (69.50%)
Female	92 (30.50%)
Age (years)	38.06 \pm 11.70
Body mass index, kg/m ²	26.85 \pm 7.30
Occupation	
Clerical support workers	14 (4.63%)
Craft and related trades workers	16 (5.30%)
Elementary occupations	19 (6.29%)
Managers	16 (5.30%)
Other occupations	38 (12.58%)
Plant and machine operators, and assemblers	1 (0.33%)
Professional	51 (16.89%)
Service and sales workers	18 (5.96%)
Skilled agricultural, forestry, and fishery workers	2 (0.66%)
Technicians and associate professionals	15 (4.97%)
Undisclosed	24 (7.95%)
Unemployed	88 (29.14%)
Charlson comorbidity score	0 [0.00–0.00]
Smoking status	
Ex-smoker	119 (39.40%)
Current smoker	114 (37.75%)
Never smoked	69 (22.85%)
Smoking pack years	8.50 [3.00–20.00]
Weekly alcohol consumption, units	0.00 [0.00–6.00]
Cannabis status	
Ex-user	70 (23.18%)
Current user	193 (63.91%)
Cannabis naïve	39 (12.91%)
Cannabis usage, gram years	5.00 [2.00–18.00]

Note: Data for patients prescribed any formulation of cannabis-based medicinal products (CBMPs) for a primary indication of anxiety was recorded by clinicians. Information on patient smoking, alcohol, and cannabis history was also collected by clinicians at baseline. Cannabis-naïve patients had never used cannabis before their prescription, ex-users had previously used cannabis, and current users were currently using nonprescription cannabis. Data are presented as either *n* (%), mean \pm SD, or median [IQR]. *n* = 302.

Abbreviations: IQR, interquartile range; SD, standard deviation.

median CBD and Δ 9-THC doses were 10.00 (5.00–20.00) and 200.00 (125.00–300.00) mg/24 h, respectively. Individuals only prescribed oils (*n* = 43, 14.24%) had median CBD and Δ 9-THC doses of 55.00 (20.00–55.00) and 5.00 (5.00–10.00) mg/24 h, respectively. Those prescribed a combination of these formulations (*n* = 92, 30.46%) had a median CBD and Δ 9-THC dose of 55.00 (15.00–69.38) and 206.25.00 (110.00–280.09) mg/24 h,

TABLE 2 Cannabis-based medicinal product prescription and dosage.

Prescription information	n (%) / median [IQR]
Oils	43 (14.24%)
CBD, mg/24h	55.00 [20.00–55.00]
Δ 9-THC, mg/24h	5.00 [5.00–10.00]
Dried flower	167 (55.30%)
CBD, mg/24h	10.00 [5.00–20.00]
Δ 9-THC, mg/24h	200.00 [125.00–300.00]
Oils and dried flowers (combination)	92 (30.46%)
CBD, mg/24h	55.00 [15.00–69.38]
Δ 9-THC, mg/24h	206.25.00 [110.00–280.09]

Note: Patients were treated with either oils, dried flower, or a combination of both. The dose of CBD and Δ 9-THC is calculated as mg/24 h and presented as median [IQR]. *n* = 302.

Abbreviation: IQR, interquartile range.

respectively. The most commonly prescribed dried flower was Adven® EMT1 (Curaleaf International, United Kingdom), while the most commonly prescribed medium chain triglyceride oils were Adven® 50 mg/mL CBD (Curaleaf International, United Kingdom) and Adven® 20 mg/mL THC (Curaleaf International, United Kingdom).

3.3 | Patient-reported outcome measures

To assess the effect of CBMP treatment on anxiety, sleep, and HRQoL in patients with GAD, the PROMs were analyzed using a repeated measures one-way ANOVA (Table 3). At each time point, there was a statistically significant improvement, from baseline, in GAD-7, SQS, and most domains of the EQ-5D-5L (*p* < 0.001). The mean PGIC was 5.45 (\pm 1.41) at 1 month and this increased to 5.72 (\pm 1.32) at 12 months.

To further analyze the effect of CBMP treatment, the cohort was separated into three groups depending on their prescription type. A repeated measures ANOVA was then used as displayed in Table S3. Statistically significant improvements were identified in GAD-7, SQS, and the EQ-5D-5L index value for each treatment type (*p* < 0.001). For patients prescribed oils, the only other statistically significant improvements were in usual activities, pain/discomfort, and anxiety/depression domains of the EQ-5D-5L (*p* < 0.05). Patients prescribed dried flower reported improvements in usual activities, pain/discomfort, and anxiety/depression (*p* < 0.001). For patients with the combined prescription, statistically significant improvements were identified across the same three domains and in the PGIC (*p* < 0.010). No statistically significant difference was identified for any PROM between treatment types except for the anxiety/depression domain of the EQ-5D-5L (*p* < 0.05). In summary, there were improvements in anxiety, sleep, and HRQoL PROMs throughout 12 months of treatment with CBMPs. There was no significant difference between the anxiety outcomes of patients with different prescriptions.

TABLE 3 Repeated one-way ANOVA comparing patient-reported outcome measures (PROMs) at each time point.

PROM	Baseline		1 month		3 months		6 months		12 months		F-value	p-Value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD				
GAD-7	13.25	6.02	8.52	5.77	8.42	5.79	8.90	6.36	10.21	6.48	59.42	<0.001***
SQS	4.03	2.40	5.64	2.55	5.72	2.56	5.53	2.81	5.13	2.74	42.95	<0.001***
EQ-5D-5L Index	0.53	0.28	0.65	0.25	0.65	0.27	0.64	0.27	0.61	0.28	33.34	<0.001***
EQ-5D-5L mobility	1.53	0.87	1.44	0.80	1.46	0.85	1.46	0.81	1.46	0.83	2.00	0.095
EQ-5D-5L selfcare	1.49	0.83	1.45	0.86	1.43	0.84	1.48	0.85	1.47	0.83	0.98	0.421
EQ-5D-5L usual activities	2.35	1.21	1.97	1.03	1.93	1.09	2.03	1.09	2.07	1.17	17.27	<0.001***
EQ-5D-5L pain and discomfort	2.19	1.08	1.86	0.95	1.87	0.98	1.88	0.99	1.98	1.02	16.40	<0.001***
EQ-5D-5L depression and anxiety	3.39	1.11	2.72	1.08	2.75	1.10	2.76	1.14	2.95	1.18	38.11	<0.001***
PGIC	N/A	N/A	5.45	1.41	5.71	1.19	5.68	1.29	5.72	1.32	8.52	<0.001***

Note: The one-way ANOVA analysis compared the difference in means at each follow-up period to identify improvements in PROMs over 12 months of treatment with cannabis-based medicinal products. Sample size consistent for all PROMs, $n=302$, except PGIC, $n=264$. For GAD-7, a lower score indicates decreased anxiety. For all other PROMs, a greater score indicates an improved outcome.

Abbreviations: GAD-7, generalized anxiety disorder-7; PGIC, patient global impression of change; SD, standard deviation; SQS, Single-Item Sleep Quality Scale.

*** $p < 0.001$.

3.4 | Effect of sleep quality at baseline on PROMs

To determine the influence of sleep on the outcomes of patients receiving CBMP treatment for anxiety, the cohort was divided into two groups—those with impaired sleep and those without.

An independent samples t-test was applied to investigate how the mean change in PROMs from baseline differed between the two groups (Table S4). Statistically significant differences were identified in GAD-7 at 1 month, and in SQS, at all time points ($p < 0.001$). Individuals with impaired sleep had a greater mean change in GAD-7 at 12 months (-3.70 ± 5.75) compared to those with unimpaired sleep (-2.33 ± 5.02 , $t(298.55) = -2.20$, $p = 0.028$). The mean change in the index value and the anxiety and depression domain of the EQ-5D-5L were significantly larger for individuals with impaired sleep ($p < 0.050$).

A further analysis was performed using a Chi-squared test to determine the relationship between quality of sleep at baseline and achieving a clinically meaningful improvement in PROMs. The MCID for SQS was set at ≥ 2.6 and for GAD-7 at ≥ 4 . Table 4 shows that sleep impairment at baseline was associated with clinically meaningful changes in GAD-7 at 1 month ($p < 0.01$) and 3 months ($p = 0.01$), and in SQS at all time points ($p < 0.001$). No statistically significant association was identified between sleep quality and GAD-7 at 6 and 12 months ($p > 0.05$).

In summary, there were differences between the two sleep quality groups across GAD-7, SQS, and some domains of the EQ-5D-5L. There was an association between the quality of sleep at baseline and a clinically meaningful change in anxiety and sleep-specific PROMs.

3.5 | Logistic regression—GAD-7 outcomes at 12 months

To contextualize the results from the previous analyses, a univariate logistic regression model was applied to determine how a range of independent variables affected the likelihood of achieving a

TABLE 4 Chi-squared analysis investigating relationship between sleep quality at baseline and clinically significant changes in PROMs at each follow-up period.

Prom	Impaired sleep n (%)	Unimpaired sleep n (%)	p-value
GAD-7 1 month			
<MCID	22 (14.10%)	41 (28.08%)	0.003**
\geq MCID	134 (85.90%)	105 (71.92%)	
GAD-7 3 months			
<MCID	23 (14.74%)	39 (26.71%)	0.01*
\geq MCID	124 (79.49%)	116 (79.45%)	
GAD-7 6 months			
<MCID	29 (18.59%)	41 (28.08%)	0.051
\geq MCID	127 (81.41%)	105 (71.92%)	
GAD-7 12 months			
<MCID	21 (13.46%)	32 (21.92%)	0.054
\geq MCID	135 (86.54%)	114 (78.08%)	
SQS 1 month			
<MCID	81 (51.92%)	118 (80.82%)	<0.001***
\geq MCID	75 (48.08%)	28 (19.18%)	
SQS 3 months			
<MCID	78 (50.00%)	120 (82.19%)	<0.001***
\geq MCID	78 (50.00%)	26 (17.81%)	
SQS 6 months			
<MCID	93 (59.62%)	114 (78.08%)	<0.001***
\geq MCID	63 (40.38%)	32 (21.92%)	
SQS 12 months			
<MCID	108 (69.23%)	127 (86.99%)	<0.001***
\geq MCID	48 (30.77%)	19 (13.01%)	

Note: Cohort was separated into two groups, those with impaired (SQS score ≤ 4) and unimpaired sleep (SQS score ≥ 5) at baseline. A minimally clinically important difference (MCID) in GAD-7 was a 4-point change and in SQS, ≥ 2.6 . $n=302$.

Abbreviations: GAD-7, generalized anxiety disorder-7; SQS, Single-Item Sleep Quality Scale.

* $p < 0.05$; ** $p < 0.010$; *** $p < 0.001$.

TABLE 5 Multivariate regression assessing the contribution of factors to a clinically meaningful change in GAD-7 at 12 months.

Variables	n	Odds ratio [95% confidence interval]	p-Value
Age (years)			
18–30	89	-	Ref
31–40	103	0.700 [0.269–1.820]	0.464
41–50	63	0.413 [0.150–1.139]	0.088
51–60	31	1.826 [0.316–10.541]	0.501
60+	15	0.640 [0.103–3.973]	0.632
BMI			
<20	38	2.077 [0.515–8.367]	0.304
20–25	96	-	Ref
25–30	85	1.131 [0.454–2.818]	0.791
30–35	34	0.905 [0.273–3.005]	0.871
>35	49	1.584 [0.489–5.129]	0.443
Gender			
Male	210	-	Ref
Female	92	1.189 [0.524–2.696]	0.679
Cannabis status			
Current	193	-	Ref
Ex-user	70	1.012 [0.417–2.458]	0.978
Naïve	39	1.371 [0.381–4.940]	0.629
Treatment type			
Oils	43	-	Ref
Dried flower	167	0.208 [0.046–0.940]	0.041*
Combination	92	0.194 [0.045–0.838]	0.028*
CBD dose			
0	22	-	Ref
Below median	129	0.896 [0.198–4.061]	0.886
Above median	151	1.053 [0.223–4.971]	0.948
Δ9-THC dose			
Below median	151	-	Ref
Above median	151	1.093 [0.523–2.283]	0.813
Sleep quality			
Impaired	156	-	Ref
Unimpaired	146	1.214 [0.559–2.634]	0.625
Baseline anxiety			
Subclinical	33	-	Ref
Mild	54	19.925 [5.807–68.370]	<0.001***
Moderate	65	26.082 [7.705–88.296]	<0.001***
Severe	149	26.268 [8.399–82.777]	<0.001***

Note: A multivariate binary regression model assessed the effect of age, BMI, gender, cannabis status, treatment type, CBD dose, Δ 9-THC dose, baseline sleep quality, and baseline anxiety severity on the likelihood of achieving a clinically significant change in GAD-7 at 12 months. Sleep quality has been previously defined. For baseline anxiety, mild, moderate, and severe anxiety are defined as scores of ≥ 5 , ≥ 10 , and ≥ 15 . $n=302$. Results are presented as the odds ratio and the 95% confidence intervals. Abbreviations: CBMP, cannabis-based medicinal products; GAD-7, generalized anxiety disorder-7, Ref, reference group.

* $p < 0.05$; *** $p < 0.001$.

clinically significant change in GAD-7 at 12 months (Table S5). The only variable deemed statistically significant was the baseline level of anxiety. Individuals with mild (OR=15.443; 95% CI: 5.207–45.796, $p < 0.001$), moderate (OR=16.387; 95% CI: 5.745–46.746, $p < 0.001$), or severe baseline anxiety (OR=20.700; 95% CI: 8.298–51.641, $p < 0.001$) were more likely to have a clinically meaningful change in GAD-7 at 12 months. There was a difference in anxiety outcomes identified between patients with impaired or unimpaired sleep at baseline, but it was not statistically significant (OR=0.554; 95% CI: 0.303–1.014, $p < 0.056$).

All factors were taken forward to a multivariate regression model (Table 5). Like the univariate model, individuals with mild (OR=19.925; 95% CI: 5.807–68.370, $p < 0.001$), moderate (OR=26.082; 95% CI: 7.705–88.296, $p < 0.001$), or severe baseline anxiety (OR=26.268; 95% CI: 8.399–82.777, $p < 0.001$) were more likely to have a clinically significant change in GAD-7 at 12 months. An association between treatment type and clinically significant anxiety outcomes at 12 months was also revealed. Individuals receiving dried flower (OR=0.208; 95% CI: 0.046–0.940, $p < 0.041$) or a combination (OR=0.194; 95% CI: 0.045–0.838, $p < 0.028$) were less likely to have a clinically significant change in GAD-7 at 12 months than those only prescribed oils. No statistically significant difference in anxiety outcomes were identified between patients with and without impaired sleep at baseline (OR=1.214; 95% CI: 0.559–2.634, $p < 0.625$).

In summary, individuals receiving oils are more likely to achieve a clinically significant anxiety outcome at 12 months and a greater than subclinical level of anxiety at baseline further increases the likelihood of this outcome.

3.6 | Adverse events

Patients also reported AEs experienced throughout their CBMP treatment (Table 6). A total of 707 (234.11%) AEs were reported by 55 (18.21%) patients—the majority of which were mild ($n=343$, 114%) or moderate ($n=285$, 94%) in severity. There were no life-threatening or disabling AEs. The AEs with the highest incidence rate were dry mouth ($n=58$, 8.20%) and concentration impairment ($n=52$, 7.36%).

3.7 | Logistic regression—Adverse events

A univariate binary logistic regression model was applied to determine how a range of variables independently affected the likelihood of experiencing an adverse event during 12 months of CBMP treatment (Table S6). Both cannabis status and baseline anxiety had a statistically significant effect on the likelihood of experiencing an adverse event. Individuals who were ex-users (OR=2.155; 95% CI: 1.082–4.294, $p < 0.029$), cannabis naïve (OR=3.360; CI: 1.529–7.383, $p < 0.003$), had moderate (OR=11.333; CI: 1.436–89.438, $p < 0.021$) or severe baseline anxiety (OR=8.000; CI: 1.051–60.923, $p < 0.045$) were more likely to experience an adverse event than current users or individuals with less than moderate baseline anxiety.

TABLE 6 Adverse event incidence and severity after 12 months of CBMP treatment.

Adverse events	Mild	Moderate	Severe	Total
Abdominal pain	7	2	1	10 (1.41%)
Agitation	0	1	0	1 (0.14%)
Akathisia	0	1	0	1 (0.14%)
Amnesia	9	17	6	32 (4.53%)
Anorexia	7	5	2	14 (1.98%)
Anxiety	3	7	6	16 (2.26%)
Ataxia	12	5	0	17 (2.40%)
Blurred vision	17	2	0	19 (2.69%)
Bruxism	1	0	0	1 (0.14%)
Chest pain	1	0	0	1 (0.14%)
Cognitive disturbance	12	16	4	32 (4.53%)
Concentration impairment	26	24	2	52 (7.36%)
Confusion	17	5	2	24 (3.39%)
Constipation	10	1	0	11 (1.56%)
Costochondritis	1	0	0	1 (0.14%)
Delirium	9	5	2	16 (2.26%)
Depression	1	4	15	20 (2.83%)
Diarrhea	1	1	0	2 (0.28%)
Dissociation	0	2	0	2 (0.28%)
Dizziness	14	11	4	29 (4.10%)
Dry mouth	40	18	0	58 (8.20%)
Dysgeusia	9	6	2	17 (2.40%)
Dyspepsia	7	3	3	13 (1.84%)
Fall	1	0	0	1 (0.14%)
Fatigue	18	21	3	42 (5.94%)
Fever	2	0	0	2 (0.28%)
Generalized muscle weakness	4	5	1	10 (1.41%)
Headache	19	11	3	33 (4.67%)
Hot flushes	0	0	1	1 (0.14%)
Hypertension	1	0	0	1 (0.14%)
Insomnia	9	15	10	34 (4.81%)
Lethargy	20	18	0	38 (5.37%)
Libido decreased	1	0	0	1 (0.14%)
Nausea	25	3	2	30 (4.24%)
Palpitations	0	1	0	1 (0.14%)
Paranoia	2	5	0	7 (0.99%)
Pharyngitis	0	10	0	10 (1.41%)
Postural hypotension	1	0	0	1 (0.14%)
Rash	1	4	0	5 (0.71%)
Rosacea exacerbation	1	0	0	1 (0.14%)
Seizure	0	0	2	2 (0.28%)
Sensory overload	0	0	1	1 (0.14%)
Sinus pain	1	0	0	1 (0.14%)
Sneezing	1	0	0	1 (0.14%)
Somnolence	0	37	6	43 (6.08%)

TABLE 6 (Continued)

Adverse events	Mild	Moderate	Severe	Total
Toothache	0	1	0	1 (0.14%)
Tremor	5	3	0	8 (1.13%)
Upper respiratory infection	0	3	0	3 (0.42%)
Urinary tract infection	0	5	0	5 (0.71%)
Vertigo	7	6	1	14 (1.98%)
Weight loss	14	1	0	15 (2.12%)
Total	343 (114%)	285 (94%)	79 (26%)	707 (234%)

Note: Adverse events are categorized as mild, moderate, or severe in severity. Adverse event incidence is calculated by dividing the total number of adverse events by the number of patients experiencing adverse events. $n=55$.

No significant difference in outcomes was observed across age, BMI, gender, treatment type, dosage, or sleep quality.

Despite this, all variables were taken forward to multivariable regression analysis (Table 7). Similar to the univariate model, cannabis status and baseline anxiety severity significantly affected the likelihood of experiencing an adverse event at 12 months. Naïve (OR=3.463; CI: 1.318–9.097, $p<0.012$) and ex-users (OR=2.254; CI: 1.066–4.768, $p<0.033$) were more likely to experience an adverse event than those currently using cannabis. However, moderate baseline anxiety severity was the only other factor affecting the likelihood of experiencing an adverse event (OR=13.220; CI: 1.600–109.229, $0<0.017$), increasing the chance compared to those with mild baseline anxiety.

The above results show that cannabis naïve and ex-users are more likely to experience adverse events than current users and that baseline anxiety severity can also impact the likelihood of this outcome to some extent.

3.8 | Prescription medication

A total of 154 patients were receiving antidepressants over the course of the study; 116 (74.32%) of which had no change in these medications at 12 months (Table 8). A small proportion (14.94%) stopped taking antidepressants, but eight patients had newly prescribed antidepressants by 12 months. Fewer individuals were prescribed benzodiazepines ($n=36$) but a greater proportion stopped taking the medication compared to antidepressants ($n=6$, 16.67%). Only one person began a new benzodiazepine prescription. Gabapentinoids were the least prescribed medication with only 17 people receiving them. The majority of patients continued their prescription alongside CBMP treatment (82.35%), one (5.88%) individual stopped taking the medication, and two (11.76%) started a new gabapentinoid prescription.

4 | DISCUSSION

The findings from this cohort study demonstrate that treatment with CBMPs is associated with statistically significant improvements

across anxiety-, sleep-, and HRQoL-specific PROMs after 12 months in patients with GAD. Additionally, individuals only receiving oil treatment were more likely to have a clinically significant outcome in GAD-7 at 12 months. Patients presenting with severe baseline anxiety were more likely to experience a clinically significant improvement in anxiety symptoms at 12 months. Results also indicated CBMPs were well tolerated throughout the study, with a low proportion reporting AEs (18.21%), most of which were mild or moderate in severity. Statistically significant differences in outcomes were identified between individuals with impaired and unimpaired sleep quality at baseline; a relationship between sleep quality and clinically significant anxiety and sleep outcomes was also elucidated.

Over 12 months, there was a statistically significant improvement in all PROMs except EQ-5D-5L mobility and self-care domains ($p<0.001$). This is supported by previous analyses of the UKMCR, which investigated a smaller cohort of patients with GAD.⁵³ Using similar PROMs, this study identified statistically significant improvements in GAD-7 and SQS at 1 and 3 months ($p<0.001$) and in EQ-5D-5L index value up to 6 months ($p<0.05$). The difference in results between the two studies can be attributed to the increase in sample size, study duration, and the methods applied to address missing data. In the absence of randomized controlled trial data for GAD, the results are also comparable to reported trial outcomes in social anxiety disorder.^{54,55} Although there are differences in sample size, treatment, and design, these trials identified a reduction in symptoms of anxiety. However, there was no significant difference between the placebo and treatment group in these trials.

The initial independent t-test revealed differences between individuals with impaired and unimpaired sleep across several PROMs including GAD-7, SQS, and EQ-5D-5L index value ($p<0.05$). Chi-squared analysis confirmed a relationship between baseline sleep quality and achieving clinically meaningful changes in GAD-7 and SQS at 1–3 and 1–12 months, respectively ($p\leq 0.01$). When taken forward to multivariate logistic regression, the quality of sleep at baseline was not a predictor of a clinically significant improvement in GAD-7 at 12 months. The relationship between sleep and anxiety is well documented, and poor sleep quality is correlated with anxiety onset.¹⁹ It is also a perpetuating factor, exacerbating its severity, which may explain why patients with poor sleep quality had lower GAD-7 scores at baseline. While baseline sleep quality was not associated with

TABLE 7 Multivariate regression assessing the contribution of factors to a likelihood of experiencing an adverse event.

Variables	n	Odds ratio [95% confidence interval]	p-Value
Age (years)			
18–30	89	-	Ref
31–40	103	1.475 [0.649–3.352]	0.354
41–50	63	0.961 [0.376–2.454]	0.934
51–60	31	0.588 [0.148–2.346]	0.452
60+	15	1.433 [0.315–6.514]	0.641
BMI			
<20	38	0.494 [0.145–1.678]	0.258
20–25	96	-	Ref
25–30	85	0.709 [0.312–1.611]	0.412
30–35	34	0.468 [0.146–1.502]	0.202
>35	49	1.151 [0.463–2.862]	0.762
Gender			
Male	210	-	Ref
Female	92	0.683 [0.328–1.422]	0.308
Cannabis status			
Current	193	-	Ref
Ex-user	70	2.254 [1.066–4.768]	0.033*
Naïve	39	3.463 [1.318–9.097]	0.012*
Treatment type			
Oils	43	-	Ref
Dried flower	167	0.708 [0.242–2.074]	0.529
Combination	92	1.143 [0.391–3.346]	0.807
CBD dose			
0	22	-	Ref
Below median	129	0.619 [0.179–2.142]	0.449
Above median	151	0.680 [0.201–2.299]	0.535
Δ9-THC dose			
Below median	151	-	ref
Above median	151	1.599 [0.808–3.163]	0.178
Sleep quality			
Impaired	156	-	Ref
Unimpaired	146	0.988 [0.505–1.036]	0.973
Baseline anxiety			
Subclinical	33	-	Ref
Mild	54	5.420 [0.592–46.400]	0.137
Moderate	65	13.220 [1.600–109.229]	0.017*
Severe	149	7.979 [0.977–65.162]	0.053

Note: A multivariate binary regression model assessed the effect of age, BMI, gender, cannabis status, treatment type, CBD dose, Δ9-THC dose, baseline sleep quality, and anxiety on the likelihood of experiencing an adverse event after 12 months of CBMP treatment. Sleep quality has been previously defined. For baseline anxiety, mild, moderate, and severe anxiety are defined as scores of ≥ 5 , ≥ 10 , and ≥ 15 . $n = 302$. Results are presented as the odds ratio and the 95% confidence intervals.

Abbreviations: GAD-7, generalized anxiety disorder-7; Ref, reference group.

* $p < 0.05$.

clinically significant sleep improvements, this includes the supplementary effects of CBMP sleep promotion on anxiety outcomes through interrupting the bidirectional feedback loop between poor sleep and anxiety. The convergence in GAD-7 scores at 6 and 12 months could be due to either the method employed to address missing data which biases the results toward the null or a tolerance to the effects of CBMPs. Furthermore, there was a high barrier for reaching statistical significance, influenced by the BOCF method for missing data and the cutoffs for clinical significance in GAD-7.

Patients were prescribed either oils, dried flower, or a combination of both, and this study identified no difference in outcomes at 12 months between treatment groups. Multivariate analysis indicated that treatment with either dried flower (OR=0.208; 95% CI: 0.046–0.940, $p < 0.041$) or a combination (OR=0.194; 95% CI: 0.045–0.838, $p < 0.028$) was associated with a lower likelihood of achieving clinically significant change in GAD-7 at 12 months than oils alone. A previous analysis of the UKMCR investigating chronic pain patients identified no difference between the administration routes across all PROMs excluding two domains of the EQ-5D-5L and the PGIC.⁷⁵ This study had a greater proportion of patients receiving oils (45.7%); yet, this study had only 14.24%. As the cohorts had different primary indications and the desired outcomes are different, the treatment types are likely to differ. Oil-based treatment has the lowest THC:CBD ratio and, as preclinical evidence suggests, CBD has significant anxiolytic properties.^{38,40,45} Furthermore, oils have a slower onset and lower bioavailability.⁷⁶ THC can either be anxiolytic or anxiogenic depending on the concentrations; so, oils may therefore offer optimal pharmacokinetics to treat anxiety. RCTs are required to assess this, however. Recent research highlighted the anxiolytic properties of THC:CBD at 1:1 ratio, but anxiety was not the primary indication for treatment in this research.⁴⁸ As no studies to date have investigated the effects of a CBD-dominant THC:CBD treatment for anxiety, these results indicate a future area of research.

Associations between independent variables—age, gender, and cannabinoid dosage—and the likelihood of a clinically significant improvement in GAD at 12 months were also investigated, but no relationships were demonstrated. However, an association between the baseline level of anxiety and GAD-7 outcomes at 12 months was identified. Individuals with greater than subclinical anxiety were more likely to have a clinically significant change in GAD-7 at 12 months. An analysis by Probst et al. demonstrated that symptom severity was not associated with reduced treatment outcomes as 6 months.⁷⁷ They also suggested that previous studies may have shown the opposite due to bias from a floor effect. Despite the treatment and outcome measures being different, this is an important factor to consider and should be controlled in future analyses.

To date, this is the longest study of adverse events for CBMP treatment in patients with GAD. The adverse incidence in this study was 707 (234.11%) which is higher than previous UKMCR analyses, including those on a cohort of GAD patients.^{49,52,53} The difference could reflect the larger sample size, but only 55 (18.21%) patients reported AEs. As this study reports AEs over a 12-month period, there is an accumulation over the course of the treatment and, coupled

TABLE 8 Changes in concomitant prescription medication throughout treatment with cannabis-based medicinal products from baseline to follow-up at 12 months.

Medication	Total	No change	Stopped taking	Reduced dose	Increased dose	New medication
Antidepressants, <i>n</i> (%)	154	116 (74.32%)	23 (14.94%)	5 (3.25%)	1 (0.65%)	8 (5.19%)
Benzodiazepines, <i>n</i> (%)	36	28 (77.78%)	6 (16.67%)	1 (2.78%)	0 (0.00%)	1 (2.78%)
Gabapentinoids, <i>n</i> (%)	17	14 (82.35%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	2 (11.76%)

Note: Medication was separated into three categories: antidepressants, benzodiazepines, and gabapentinoids. Data are presented as *n* (%).

with an updated system for reporting AEs, this could explain the higher incidence rate. A dry mouth was the most frequent AE, which is partially explained by the administration route. Most of the cohort were prescribed dried flower in isolation or in combination with oils, leading to a greater prevalence of oromucosal AEs. Concentration impairment and fatigue were also frequently reported (Table 8). The action of cannabinoids, particularly $\Delta 9$ -THC, at CB1 receptors within the limbic and mesolimbic regions of the brain has been shown to lead to mild cognitive deficits.^{34,78,79} The median $\Delta 9$ -THC dose across prescriptions were higher compared to previous analyses and treatment doses are titrated up, possibly explaining the persisting AEs throughout treatment.^{53,80}

Upon multivariate analysis, it was revealed that neither the median $\Delta 9$ -THC nor CBD dose had any effect on the likelihood of experiencing an adverse event at 12 months. As expected, the cannabis status of the individual had a clear effect as ex-users (OR=2.254; 95% CI: 1.066–4.768, $p < 0.033$) and cannabis-naïve users (OR=3.463; 95% CI: 1.318–9.097, $p < 0.012$) were more likely to experience an adverse event than current users. This is consistent with preclinical evidence that suggests an effect of tolerance accompanying continuous cannabis usage.^{81,82} For cannabis-naïve individuals, there are a range of contextual factors that could influence the likelihood of an adverse event but pharmacologically, it can be explained by a greater density of CB1 receptors within the CNS compared to experienced users. A downregulation of CB1 receptors alongside extended experience with cannabis has been shown to reduce the cognitive impairments seen for some individuals.⁸² While this is partly subjective, it offers rationale for the differences identified between patients.

This study has some limitations. Primarily, this is an observational case series lacking a control or active comparator group meaning that no causality can be drawn. Furthermore, the lack of randomization and blinding contributes to an increased risk of confounding factors. For example, patients may be taking prescribed antidepressants concomitantly or consuming street cannabis, both of which could contribute to a complex interplay within the brain.⁸³ Additionally, the recruitment of private medical cannabis patients with a high incidence of prior or current cannabis usage at baseline introduces selection bias and is likely not representative of GAD patients on a population basis. In particular, through engagement in a legal medical system, prior cannabis consumers may be conferred additional benefits through no longer having to engage in the illicit market.

The subjectivity of PROMs is also a core limitation of this study, as it can lead to symptom exaggeration and incorrect reporting

of AEs. Patient interviews are a potential way to counteract this; but, future application of wearable technology may be more accurate, particularly in the context of sleep since the SQS cannot inform on sleep states. Women, cannabis-naïve users, and patients prescribed oils alone are underrepresented in this study cohort, which may decrease the generalizability and external validity of this study. Previous analyses of the UKMCR suffer from patient dropout and a subsequent attrition bias. While this study applied a conservative method for tackling missing data, it makes interpretation of the data more challenging as more patients dropout. At 12 months, 49.3% of data were missing which could skew the results as discussed previously. Ultimately, it cannot be concluded whether the associations seen here are caused by just CBMP treatment. Finally, while multivariate analyses were utilized to try and control for confounding variables that may affect the likelihood of experiencing an adverse event, it is not possible to control for all confounders. Moreover, the baseline anxiety severity and the treatment administered is likely to vary according to several factors, notably whether an individual is a prior cannabis consumer. Standardized assessment within RCTs would be the most appropriate method for examining these effects further.

In summary, the results from this study suggest a relationship between baseline sleep quality and improvements in GAD-7. Individuals with worse quality sleep are more likely to have a meaningful improvement in GAD-7. However, it is not a predictor of a clinically significant outcome at 12 months when accounting for additional variables. Treatment with oils and baseline anxiety severity are associated with experiencing an improvement in GAD symptoms. The effect of anxiety severity was unexpected but will be useful for informing future studies. Despite the statistical significance of the results, the limitations must be considered, and conclusions viewed with caution. Furthermore, the evidence base in the context of anxiety is nascent and there remains a need for RCTs to determine the efficacy of CBMP treatment in GAD.

AUTHOR CONTRIBUTIONS

Study conception and design: MM, SE, CH, RC, JRR, and MHS; Acquisition of data: MM, SE, CH, RC, and JRR; Analysis and interpretation of data: MM, SE, and MHS; Drafting of article: MM, SE, and MHS; Critical revision: MM, SE, CH, RC, JRR, and MHS. All authors have contributed to and approved the final article. The authors confirm that the PI for this article is Mikael H Sodergren and that he had direct clinical responsibility for patients.



ACKNOWLEDGMENTS

The authors have nothing to report.

FUNDING INFORMATION

There was no external or commercial funding associated with this article.

CONFLICT OF INTEREST STATEMENT

Matthew Murphy is a biomedical sciences student at Imperial College London. Matthew Murphy has no shareholdings in pharmaceutical companies. Simon Erridge is a junior doctor and is the Head of Research at Sapphire Medical Clinics. Simon Erridge is an honorary clinical research fellow at Imperial College London. The views expressed are those of the author(s) and not necessarily those of the NHS. Simon Erridge has no shareholdings in pharmaceutical companies. Carl Holvey is Chief Clinical Pharmacist at Sapphire Medical Clinics. Carl Holvey has no shareholdings in pharmaceutical companies. Ross Coomber is a consultant orthopedic surgeon, Operations Director at Sapphire Medical Clinics and a consultant at St George's Hospital, London. The views expressed are those of the author(s) and not necessarily those of the NHS. Ross Coomber has no shareholdings in pharmaceutical companies. James Rucker is a consultant psychiatrist and a former director at Sapphire Medical Clinics (London). James Rucker is an honorary consultant psychiatrist at The South London and Maudsley NHS Foundation Trust, and an NIHR Clinician Scientist Fellow at the Centre for Affective Disorders at King's College London. James Rucker is funded by a fellowship (CS-2017-17-007) from the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. James Rucker has no shareholdings in pharmaceutical companies. James Rucker reviewed this article and made comments. Mikael Sodergren is a consultant hepatopancreatobiliary surgeon at Imperial College NHS Trust. He is the Chief Medical Officer at Curaleaf International. He is a senior clinical lecturer at Imperial College London. The views expressed are those of the author(s) and not necessarily those of the NHS.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the UK Medical Cannabis Registry for organizations with an appropriate data safe haven. Restrictions apply to the availability of pseudonymized data in accordance with the ethical approval provided by South West–Central Bristol Research Ethics Committee (Reference: 22/SW/0145). Data specifications and applications are available from the corresponding author.

ETHICS STATEMENT

Approval of the Research Protocol by an Institutional Reviewer Board: Ethical approval was provided by South West–Central Bristol Research Ethics Committee (Reference: 22/SW/0145).

Informed Consent: All participants completed written, informed consent prior to enrolment in the registry.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

Permission to Reproduce Material from Other Sources: N/A.

Clinical Trial Registration: N/A.

ORCID

Matthew Murphy  <https://orcid.org/0000-0002-0905-748X>

REFERENCES

1. Fineberg NA, Haddad PM, Carpenter L, Gannon B, Sharpe R, Young AH, et al. The size, burden and cost of disorders of the brain in the UK. *J Psychopharmacol*. 2013;27(9):761–70.
2. Remes O, Wainwright N, Surtees P, Lafortune L, Khaw KT, Brayne C. Generalised anxiety disorder and hospital admissions: findings from a large, population cohort study. *BMJ Open*. 2018;8(10):e018539.
3. American Psychiatric Association. Diagnostic criteria and codes: anxiety disorders. 5th ed. Washington: Diagnostic and statistical manual of mental disorders. 2013;DC2022.
4. Penninx BW, Pine DS, Holmes EA, Reif A. Anxiety disorders. *Lancet*. 2021;397(10277):914–27.
5. Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*. 2011;21(10):718–79.
6. Global Burden of Disease. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet*. 2017;390(10100):1211–59.
7. Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: a meta-analytic review. *Clin Psychol Rev*. 2007;27(5):572–81.
8. Khan A, Leventhal RM, Khan S, Brown WA. Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. *J Affect Disord*. 2002;68(2–3):183–90.
9. Martin EI, Ressler KJ, Binder E, Nemeroff CB. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. *Psychiatr Clin North Am*. 2009;32(3):549–75.
10. Kascakova N, Furstova J, Hasto J, Madarasova Geckova A, Tavel P. The unholy trinity: childhood trauma, adulthood anxiety, and long-term pain. *Int J Environ Res Public Health*. 2020;17(2):414.
11. Adshead G. Security of mind: 20 years of attachment theory and its relevance to psychiatry. *Br J Psychiatry*. 2018;213(3):511–3.
12. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry*. 2001;49(12):1023–39.
13. Munir S, Takov V. Generalized anxiety disorder. *StatPearls*. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC; 2022.
14. Pêgo JM, Sousa JC, Almeida OF, Sousa N. Stress and the neuroendocrinology of anxiety disorders. *Curr Top Behav Neurosci*. 2010;2:97–117.
15. Hofmann SG. Cognitive factors that maintain social anxiety disorder: a comprehensive model and its treatment implications. *Cogn Behav Ther*. 2007;36(4):193–209.
16. Tariq A, Quayle E, Lawrie SM, Reid C, Chan SWY. Relationship between early maladaptive schemas and anxiety in adolescence and Young adulthood: a systematic review and meta-analysis. *J Affect Disord*. 2021;295:1462–73.
17. Vorspan F, Mehtelli W, Dupuy G, Bloch V, Lépine JP. Anxiety and substance use disorders: co-occurrence and clinical issues. *Curr Psychiatry Rep*. 2015;17(2):4.

18. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med*. 2007;3(5 Suppl):S7–S10.
19. Chellappa SL, Aeschbach D. Sleep and anxiety: from mechanisms to interventions. *Sleep Med Rev*. 2022;61:101583.
20. Walker WH II, Walton JC, DeVries AC, Nelson RJ. Circadian rhythm disruption and mental health. *Transl Psychiatry*. 2020;10(1):28.
21. Baglioni C, Nanovska S, Regen W, Spiegelhalter K, Feige B, Nissen C, et al. Sleep and mental disorders: a meta-analysis of polysomnographic research. *Psychol Bull*. 2016;142(9):969–90.
22. Rogers AH, Wieman ST, Baker AW. Anxiety comorbidities: mood disorders, substance use disorders, and chronic medical illness. In: Bui E, Charney ME, Baker AW, editors. *Clinical handbook of anxiety disorders: from theory to practice*. Cham: Springer International Publishing; 2020. p. 77–103.
23. Maren S, Holmes A. Stress and fear extinction. *Neuropsychopharmacology*. 2016;41(1):58–79.
24. Graham BM, Milad MR. The study of fear extinction: implications for anxiety disorders. *Am J Psychiatry*. 2011;168(12):1255–65.
25. Strawn JR, Geraciotti L, Rajdev N, Clemenza K, Levine A. Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. *Expert Opin Pharmacother*. 2018;19(10):1057–70.
26. Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med*. 2008;359(26):2753–66.
27. Kaczkurkin AN, Foa EB. Cognitive-behavioral therapy for anxiety disorders: an update on the empirical evidence. *Dialogues Clin Neurosci*. 2015;17(3):337–46.
28. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. *Lancet*. 2019;393(10173):768–77.
29. Liu Y, Zhao J, Guo W. Emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. *Front Psychol*. 2018;9:2201.
30. Rodriguez BF, Weisberg RB, Pagano ME, Bruce SE, Spencer MA, Culppepper L, et al. Characteristics and predictors of full and partial recovery from generalized anxiety disorder in primary care patients. *J Nerv Ment Dis*. 2006;194(2):91–7.
31. Garakani A, Murrrough JW, Freire RC, Thom RP, Larkin K, Buono FD, et al. Pharmacotherapy of anxiety disorders: current and emerging treatment options. *Focus (Am Psychiatr Publ)*. 2021;19(2):222–42.
32. Bruce SE, Yonkers KA, Otto MW, Eisen JL, Weisberg RB, Pagano M, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *Am J Psychiatry*. 2005;162(6):1179–87.
33. Baldwin DS, Waldman S, Allgulander C. Evidence-based pharmacological treatment of generalized anxiety disorder. *Int J Neuropsychopharmacol*. 2011;14(5):697–710.
34. dos Reis Rosa Franco G, Smid S, Viegas C. Phytocannabinoids: general aspects and pharmacological potential in neurodegenerative diseases. *Curr Neuropharmacol*. 2021;19(4):449–64.
35. Kendall DA, Yudowski GA. Cannabinoid receptors in the central nervous system: their signaling and roles in disease. *Front Cell Neurosci*. 2016;10:294.
36. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. *Int J Mol Sci*. 2018;19(3):833.
37. Lu HC, Mackie K. An introduction to the endogenous cannabinoid system. *Biol Psychiatry*. 2016;79(7):516–25.
38. García-Gutiérrez MS, Navarrete F, Gasparyan A, Austrich-Olivares A, Sala F, Manzanares J. Cannabidiol: a potential new alternative for the treatment of anxiety, depression, and psychotic disorders. *Biomolecules*. 2020;10(11):1575.
39. Ibeas Bih C, Chen T, Nunn AV, Bazet M, Dallas M, Whalley BJ. Molecular targets of cannabidiol in neurological disorders. *Neurotherapeutics*. 2015;12(4):699–730.
40. Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimarães FS. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. *Philos Trans R Soc Lond B Biol Sci*. 2012;367(1607):3364–78.
41. Cristino L, Bisogno T, Di Marzo V. Cannabinoids and the expanded endocannabinoid system in neurological disorders. *Nat Rev Neurol*. 2020;16(1):9–29.
42. Papagianni EP, Stevenson CW. Cannabinoid regulation of fear and anxiety: an update. *Curr Psychiatry Rep*. 2019;21(6):38.
43. Silvestro S, Schepici G, Bramanti P, Mazon E. Molecular targets of cannabidiol in experimental models of neurological disease. *Molecules*. 2020;25(21):5186.
44. Garcia-Garcia AL, Newman-Tancredi A, Leonardo ED. 5-HT_{1A} [corrected] receptors in mood and anxiety: recent insights into autoreceptor versus heteroreceptor function. *Psychopharmacology (Berl)*. 2014;231(4):623–36.
45. Melas PA, Scherma M, Fratta W, Cifani C, Fadda P. Cannabidiol as a potential treatment for anxiety and mood disorders: molecular targets and epigenetic insights from preclinical research. *Int J Mol Sci*. 2021;22(4):1863.
46. Kesner AJ, Lovinger DM. Cannabinoids, endocannabinoids and sleep. *Front Mol Neurosci*. 2020;13:125.
47. Kaul M, Zee PC, Sahni AS. Effects of cannabinoids on sleep and their therapeutic potential for sleep disorders. *Neurotherapeutics*. 2021;18(1):217–27.
48. Black N, Stockings E, Campbell G, Tran LT, Zagic D, Hall WD, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *Lancet Psychiatry*. 2019;6(12):995–1010.
49. Ergisi M, Erridge S, Harris M, Kawka M, Nimalan D, Salazar O, et al. An updated analysis of clinical outcome measures across patients from the UK medical cannabis registry. *Cannabis Cannabinoid Res*. 2022;8(3):557–66.
50. Erridge S, Kerr-Gaffney J, Holvey C, Coomber R, Barros DAR, Bhoskar U, et al. Clinical outcome analysis of patients with autism spectrum disorder: analysis from the UK medical cannabis registry. *Ther Adv Psychopharmacol*. 2022;12:20451253221116240.
51. Erridge S, Salazar O, Kawka M, Holvey C, Coomber R, Usmani A, et al. An initial analysis of the UK medical cannabis registry: outcomes analysis of first 129 patients. *Neuropsychopharmacol Rep*. 2021;41(3):362–70.
52. Harris M, Erridge S, Ergisi M, Nimalan D, Kawka M, Salazar O, et al. UK medical cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions. *Expert Rev Clin Pharmacol*. 2022;15(4):473–85.
53. Ergisi M, Erridge S, Harris M, Kawka M, Nimalan D, Salazar O, et al. UK medical cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder. *Expert Rev Clin Pharmacol*. 2022;15(4):487–95.
54. Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36(6):1219–26.
55. Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *J Psychopharmacol*. 2011;25(1):121–30.
56. Walsh JH, Maddison KJ, Rankin T, Murray K, McArdle N, Ree MJ, et al. Treating insomnia symptoms with medicinal cannabis: a randomized, crossover trial of the efficacy of a cannabinoid medicine compared with placebo. *Sleep*. 2021;44(11):149.
57. Montero-Oleas N, Arevalo-Rodríguez I, Nuñez-González S, Viteri-García A, Simancas-Racines D. Therapeutic use of cannabis and

- cannabinoids: an evidence mapping and appraisal of systematic reviews. *BMC Complement Med Ther.* 2020;20(1):12.
58. Meier MH, Caspi A, Knodt AR, Hall W, Ambler A, Harrington H, et al. Long-term cannabis use and cognitive reserves and hippocampal volume in midlife. *Am J Psychiatry* 2022;179(5):362–74.
 59. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med.* 2007;147(8):573–7.
 60. Case P. The NICE guideline on medicinal cannabis: keeping Pandora's box shut tight? *Med Law Rev.* 2020;28(2):401–11.
 61. MHRA. The supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans 'specials'. London: The National Archives; 2020.
 62. Brusselaers N, Lagergren J. The Charlson comorbidity index in registry-based research. *Methods Inf Med.* 2017;56(5):401–6.
 63. Tait J, Erridge S, Sodergren MH. UK medical cannabis registry: a patient evaluation. *J Pain Palliat Care Pharmacother.* 2023;37(2):170–7.
 64. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006;166(10):1092–7.
 65. Toussaint A, Hüsing P, Gumz A, Wingenfeld K, Härter M, Schramm E, et al. Sensitivity to change and minimal clinically important difference of the 7-item generalized anxiety disorder questionnaire (GAD-7). *J Affect Disord.* 2020;265:395–401.
 66. Lee C, Round JM, Hanlon JG, Hyshka E, Dyck JRB, Eurich DT. Generalized anxiety disorder 7-item (GAD-7) scores in medically authorized cannabis patients-Ontario and Alberta, Canada. *Can J Psychiatry.* 2022;67(6):470–80.
 67. Snyder E, Cai B, DeMuro C, Morrison MF, Ball W. A new single-item sleep quality scale: results of psychometric evaluation in patients 30th chronic primary insomnia and depression. *J Clin Sleep Med.* 2018;14(11):1849–57.
 68. NICE. Position statement on use of the EQ-5D-5L value set for England. 2019. Available from: <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l>. [Accessed 27 Feb 2023].
 69. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health.* 2012;15(5):708–15.
 70. Scott W, McCracken LM. Patients' impression of change following treatment for chronic pain: global, specific, a single dimension, or many? *J Pain.* 2015;16(6):518–26.
 71. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol.* 2003;13(3):176–81.
 72. Kaiser KA, Affuso O, Beasley TM, Allison DB. Getting carried away: a note showing baseline observation carried forward (BOCF) results can be calculated from published complete-cases results. *Int J Obes (Lond).* 2012;36(6):886–9.
 73. van Ginkel JR, Kroonenberg PM. Analysis of variance of multiply imputed data. *Multivariate Behav Res.* 2014;49(1):78–91.
 74. Kwak SG, Kim JH. Central limit theorem: the cornerstone of modern statistics. *Korean J Anesthesiol.* 2017;70(2):144–56.
 75. Tait J, Erridge S, Holvey C, Coomber R, Usmani A, Sajad M, et al. Clinical outcome data of chronic pain patients treated with cannabis-based oils and dried flower from the UK medical cannabis registry. *Expert Rev Neurother.* 2023;23(4):413–23.
 76. Lavender I, McGregor IS, Suraev A, Grunstein RR, Hoyos CM. Cannabinoids, insomnia, and other sleep disorders. *Chest.* 2022;162(2):452–65.
 77. Probst G, Vislă A, Flückiger C. Patients' symptoms and strengths as predictors of long-term outcomes of CBT for generalized anxiety disorder – A three-level, multi-predictor analysis. *J Anxiety Disord.* 2022;92:102635.
 78. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med.* 2011;5(1):1–8.
 79. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology.* 2010;35(3):764–74.
 80. Pillai M, Erridge S, Bapir L, Nicholas M, Dalavaye N, Holvey C, et al. Assessment of clinical outcomes in patients with post-traumatic stress disorder: analysis from the UK medical cannabis registry. *Expert Rev Neurother.* 2022;22(11–12):1009–18.
 81. D'Souza DC, Ranganathan M, Braley G, Gueorguieva R, Zimolo Z, Cooper T, et al. Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology.* 2008;33(10):2505–16.
 82. Ramaekers JG, Mason NL, Theunissen EL. Blunted highs: pharmacodynamic and behavioral models of cannabis tolerance. *Eur Neuropsychopharmacol.* 2020;36:191–205.
 83. Kocis PT, Vrana KE. Delta-9-tetrahydrocannabinol and cannabidiol drug-drug interactions. *Med Cannabis Cannabinoids.* 2020;3(1):61–73.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Murphy M, Erridge S, Holvey C, Coomber R, Rucker JJ, Sodergren MH. A cohort study comparing the effects of medical cannabis for anxiety patients with and without comorbid sleep disturbance. *Neuropsychopharmacol Rep.* 2023;00:1–14. <https://doi.org/10.1002/npr2.12407>