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Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iern20

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To cite this article: John Warner-Levy, Simon Erridge, Evonne Clarke, Katy McLachlan, Ross Coomber, Muhammed Asghar, Karl Bexley, Urmila Bhoskar, Matthieu Crews, Andrea De Angelis, Muhammad Imran, Fariha Kamal, Laura Korb, Gracia Mwimba, Simmi Sachdeva-Mohan, Gabriel Shaya, James J Rucker & Mikael H Sodergren (2024) UK Medical Cannabis Registry: a cohort study of patients prescribed cannabis-based oils and dried flower for generalised anxiety disorder, Expert Review of Neurotherapeutics, 24:12, 1193-1202, DOI: 10.1080/14737175.2024.2423634

To link to this article: https://doi.org/10.1080/14737175.2024.2423634

EXPERT REVIEW OF NEUROTHERAPEUTICS
2024, VOL. 24, NO. 12, 1193–1202
https://doi.org/10.1080/14737175.2024.2423634

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ORIGINAL RESEARCH

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UK Medical Cannabis Registry: a cohort study of patients prescribed cannabis-based oils and dried flower for generalised anxiety disorder

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ABSTRACT

Background: Generalized anxiety disorder (GAD) is a common mental health condition. The endocannabinoid system has become a focus for new therapies, increasing interest in cannabis-based medicinal products (CBMPs). This study uses data from the UK Medical Cannabis Registry (UKMCR) to investigate real-world outcomes and safety of different CBMP formulations in GAD patients.

Methods: This study analyzed patient-reported outcomes from 302 GAD patients prescribed CBMPs (oil-based, dried flower, or a combination). Anxiety (GAD-7), sleep quality (SQS), and quality of life (EQ-5D-5 L) were assessed at 1, 3, 6, and 12 months. Adverse events were recorded.

Results: All CBMP formulations were associated with improvements in anxiety, sleep, and quality of life over 12 months ($p < 0.050$). At 12 months, there were no significant differences in outcomes between formulations ($p > 0.050$). The majority of reported adverse events ($n = 707$) were mild ($n = 343$) or moderate ($n = 285$) in severity, with no life-threatening events observed.

Conclusion: This study provides real-world evidence supporting the potential of CBMPs for improving GAD symptoms. Patients prescribed both oil-based and dried flower formulations have similar outcomes over 12 months. Further research is needed to determine the optimal CBMP formulation and long-term effects.

ARTICLE HISTORY
Received 13 June 2024
Accepted 28 October 2024

KEYWORDS
GAD; Cannabis; PROMs; GAD-7; cannabis-based medicinal products (CBMPs)

1. Introduction

Anxiety disorders, in particular generalized anxiety disorder (GAD), constitute a significant public health challenge, affecting millions of individuals [1]. GAD is characterized by excessive and often debilitating worry, typically accompanied by a range of physical symptoms, such as muscle tension, fatigue, sleep difficulties, and irritability [2]. GAD causes clinically significant distress and impairment [3], resulting in increased suicidality [4]. These symptoms can significantly impair an individual's health-related quality of life (HRQoL), affecting their ability to work, maintain relationships, and engage in daily activities. [5].

Current treatment approaches for GAD include psychological therapies and pharmacological interventions. Whilst cognitive-behavioral therapy has proven efficacy, its accessibility is often limited [6]. Therefore, pharmacological therapies form a key component of treatment regimes. Monoamine reuptake inhibitors, including selective serotonin uptake inhibitors (SSRIs), are commonly used as first-line therapeutics. However, a substantial proportion of patients do not achieve satisfactory symptom control with SSRIs or other first-line medications [7,8], highlighting the unmet need for novel pharmacotherapeutics. The endocannabinoid system has garnered increasing attention as a potential target for the treatment of anxiety disorders [9]. There is therefore growing interest in cannabis-based medicinal products (CBMPs), containing varying concentrations of cannabinoids, namely (-)-trans-Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [10,11].

THC is a partial agonist of cannabinoid receptors 1 (CB1) and 2 (CB2) [12]. CB1 receptors are predominantly expressed in the central nervous system on pre-synaptic terminals. Activation of CB1 receptors modulates the release of neurotransmitters, such as gamma-aminobutyric acid (GABA) and glutamate [13]. CB1 receptors are densely expressed in regions of the brain related to anxiety, including the prefrontal cortex, hippocampus, amygdala, and periaqueductal gray region [14]. Low-dose CB1 agonists have demonstrated anxiolytic properties, whilst CB1-deficiency or blockade of CB1 receptors is associated with heightened anxiety [14,15]. In addition, CB1 receptor activation can modulate the hypothalamic-pituitary-adrenal axis, which is central to the body's stress response [16]. However, there appears to be

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/14737175.2024.2423634

a bidirectional response in animals to exogenous CB1 agonists, such as THC, with high doses resulting in anxiogenic behaviors [14,15,17].

CBD, meanwhile, modulates anxiety through differing mechanisms. CBD does not directly bind to the CB1 receptor and instead has contrasting effects as a negative allosteric modulator and, according to pre-clinical data, an inhibitor of the breakdown of anandamide, an endogenous CB1 receptor agonist [16]. Preclinical studies, however, suggest that CBD may reduce fear and anxiety-related behaviors through non-CB receptor-dependent mechanisms. These mechanisms include transient receptor potential vanilloid 1 (TRPV1) channels and 5-hydroxytryptamine 1A (5-HT1A) receptors [18]. CBD is a TRPV1 agonist, but at sufficient doses causes desensitization of the channel. This mechanism in the prefrontal cortex of rats has been linked with anxiolytic properties of CBD [19]. Finally, CBD is an agonist of 5-HT1A, which has been linked with positive effects on both mood and anxiety in pre-clinical models [20].

Whilst the Royal College of Psychiatrists recognizes that CBMPs 'may be of potential benefit' in anxiety disorders, it highlights that there is a paucity of high-quality evidence supporting the use of CBMPs for psychiatric disorders [21]. A meta-analysis by Black and colleagues emphasizes this further [22]. Only two randomized controlled trials have considered the effects of CBMPs on individuals diagnosed with anxiety disorders to date. These were both of CBD isolate preparations at doses exceeding 300 mg for social anxiety. When combined, these do not show a significant effect on anxiety [22]. Studies examining the effects of preparations containing THC have shown a positive effect. However, these were entirely observational studies in individuals with chronic pain or multiple sclerosis [22]. Ultimately, due to the limitations of the available evidence, CBMPs are not considered in the routine treatment of anxiety disorders in the UK, except in individuals who have failed to benefit from licensed medications [23].

CBMPs are a heterogeneous class of medications that can either refer to isolated preparations of THC or CBD, or a diverse spectrum of other products potentially containing multiple active pharmaceutical ingredients. This heterogeneity and the challenges in studying CBMPs are responsible for the inconclusive clinical evidence in anxiety and other conditions [24]. Observational studies may help to address this by providing insights across different CBMP prescriptions and their outcomes to complement the results found in clinical trials. A large Australian longitudinal cohort study demonstrated the sustained safety and efficacy of orally administered CBMPs [25], while a study conducted on UK patients found that inhalation of flower preparations of CBMPs is associated with improvements in HRQoL [25]. However, there are limited direct comparisons of individuals prescribed different formulations of CBMPs. The UK Medical Cannabis Registry (UKMCR), established in 2019, serves as a repository for longitudinal observational data collected from patients receiving treatment with CBMPs [24]. This study utilizes data from the UKMCR to investigate different CBMP formulation prescribed in patients with GAD. The primary objective is to compare changes in these outcomes among individuals receiving oil-based, dried flower, or a combination of both CBMP formulations.

2. Materials and methods

2.1. Study overview

This research employed a cohort study design, focusing on individuals with a confirmed diagnosis of GAD who had been enrolled in the UK Medical Cannabis Registry (UKMCR) a minimum of 12 months prior to data extraction. The study specifically included patients who had been prescribed either an inhaled dried flower formulation, a sublingual/oral oil-based product, or a combination of both delivery methods.

It is important to note that within the UK healthcare system, CBMPs are subject to specific prescribing guidelines. These products are typically reserved for patients who have not experienced adequate symptom relief from at least two conventional treatment options [23]. The diagnosis of GAD and the documented history of prior therapies were verified through a review of primary care health records. Furthermore, the decision to initiate treatment with CBMPs is restricted to specialist physicians registered with the General Medical Council. In the context of anxiety disorders, this decision is typically made by a consultant psychiatrist in collaboration with a multidisciplinary team, ensuring a comprehensive evaluation of the patient's needs [23]. Currently, the majority of CBMP prescriptions originate from private healthcare settings.

All patients were enrolled on the UKMCR before 1 January 2022. Inclusion criteria involved patients over the age of 18 with a primary indication for CBMP use of the treatment of GAD, who had completed baseline patient-reported outcome measures (PROMs). Patients who had not recorded baseline PROMs, or who had a primary indication for CBMPs other than GAD were excluded. Data was extracted from the UKMCR on 9 January 2023.

Prior to enrollment, all patients provided written informed consent to participate in the study, completing required data collection through a bespoke online portal [26]. PROMs were collected at baseline through this portal and follow-up PROMs and adverse events were completed at 1, 3, 6, and 12 months after beginning CBMP treatment.

This study was provided with ethical approval (reference: 22/SW/0145) and was reported in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology guidance [27].

Baseline questionnaires collected demographic data. Occupations were classified using the International Standard Classification of Occupations [28]. Underlying health status was recorded using the Charlson comorbidity index [29]. Other comorbidities not listed in the Charlson comorbidity index were measured, including hypertension, arthritis, and epilepsy. Each comorbidity was confirmed using primary care health records. For each CBMP prescription, THC and CBD dosages were recorded as milligrams per 24 hours (mg/24 h). Cannabis history was collected by clinicians before patients were prescribed CBMPs. Gram years were used to quantify the lifetime cannabis history of ex- and current cannabis users [30].

2.2. PROMS

PROMs are validated, standardized questionnaires that collect health outcomes directly from patients. These questionnaires

generate numerical values which are then used to record patient information on symptoms of disease, HRQoL, and functional status [31]. The primary outcomes of the study were reflected by changes in PROMs related to and affected by GAD. These were: Generalized Anxiety Disorder-7 (GAD-7), Single-item Sleep Quality Scale (SQS), EQ-5D-5 L and Patient Global Impression of Change (PGIC).

2.2.1. Generalized anxiety disorder-7 (GAD-7)

GAD-7 is a seven-item, self-reported questionnaire which assesses generalized anxiety symptoms over the previous 2 weeks. Items record how often they are bothered by feeling nervous or on edge, as well as experiencing uncontrollable worry. Each item has a score between 0 and 3 where 0 indicates 'not at all,' while 3 indicates 'nearly every day.' These scores are combined to provide a total outcome from 0 to 21, where ≥5, ≥10 and ≥15 are cutoff values for mild, moderate, and severe anxiety, respectively [32]. A reduction in GAD-7 score of 4 or more is determined as clinically significant [33].

2.2.2. Single-item sleep quality scale (SQS)

SQS is a validated numerical rating system whereby participants rate their sleep quality over the past 7 days on a scale of 0 to 10, with '0' representing 'terrible' and '10' being equivalent to 'excellent' [34–36].

2.2.3. EQ-5D-5L

EQ-5D-5L is a global, brief quality of life questionnaire developed by EuroQoL, which measures patient health using 5 levels of severity across 5 dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression [37]. Patients score each domain between 1 and 5 where 1 indicates 'no problems,' and 5 indicates 'extreme problems.' These answers generate a 5-digit vector ranging from 11111 (full health) to 55555 (worst health) [38]. These vectors are then generalized to the UK population and displayed as an Index Value using the mapping function developed by van Hout et al., in line with National Institute of Health and Care Excellence (NICE) guidelines laid out in 2017 [39]. The Index Value has a maximum score of 1, with negative values representative of a health status deemed to be of poorer quality than death [40].

2.2.4. Patient global impression of change (PGIC)

PGIC is a seven-item, seven-point scale depicting a patient's rating of overall improvement [41] in quality of life since beginning treatment. Scores range from 1 indicating 'no change,' to 7 indicating 'a great deal better.'

2.3. Prescribed medication

The treating physician, using a shared decision-making model with the patient, decided on the CBMP prescribed and dose. The maximally tolerated dose at the time of data extraction was considered in this analysis. Other prescribed medications were categorized into 3 groups: antidepressants, benzodiazepines and gabapentinoids. Patient data regarding changes in prescriptions were collected at baseline and at 1, 3, 6, and 12 months of receiving CBMP treatment.

2.4. Adverse events

Adverse events reported by patients were classified and graded according to Common Terminology Criteria for Adverse Events version 4.0 and were recorded either contemporaneously by patients, prior to completion of PROMs, or during clinical consultations throughout the study period [42].

2.5. Missing data

To account for missing data, a baseline observation carried forward approach was utilized as a conservative measure to allow for pairwise analysis until 12 months for those individuals who were lost to follow-up.

2.6. Statistical analysis

Data outlining patient demographics, medications, comorbidities, occupations, and drug and alcohol history were recorded by clinicians and summarized using descriptive statistics, which were also used to analyze adverse event data. PROMs were compared between a baseline of 1, 3, 6, and 12 months. Parametric data were represented using means (± standard deviation (SD)), while non-parametric data were represented using median values (interquartile range (IQR)).

Changes in PROMs in each cohort over time were assessed with a repeated measures analysis of variance (ANOVA). Statistically significant changes were interrogated with pairwise comparison with Bonferroni correction to control for potential family-wise error rate. A one-way ANOVA was used to compare the mean difference between patients treated with each type of CBMP after 12 months of treatment compared to baseline. If statistically significant differences from the ANOVA test were identified, then a post-hoc Tukey's honestly significant differences test was planned to perform a pairwise comparison between different treatment types.

A univariable and multivariable binary logistic regression model was used to calculate odds ratios (ORs) and associated 95% confidence intervals (CIs) for variables to determine the likelihood of patients achieving a clinically significant improvement in GAD-7 score (reduction ≥4) after 12 months of CBMP treatment. The variables included factors such as age, BMI, gender, cannabis exposure, prescription type, and THC and CBD dose. Univariable and multivariable regression models were also implemented to assess the effects of the same independent variables on the likelihood of experiencing an adverse event after 12 months of CBMP treatment.

Statistical significance was defined as $p < 0.050$. Statistical analysis was conducted using SPSS Statistics (version 28.0.0.0 IBM SPSS Inc., [New York, IL], U.S.A.) [43].

3. Results

3.1. Patient demographics, clinical history, and CBMP prescriptions

Three hundred and two patients who were prescribed CBMPs for GAD had completed baseline PROMs, and had been

enrolled on the UKMCR for a minimum of 12 months were identified.

Forty-three (14.23%), 167 (55.29%), and 92 (30.46%) GAD patients were prescribed oil-based, dried flower, or both formulations of CBMP. Median doses of CBD and THC were 55.00 (IQR: 20.00–55.00) mg/24 h and 5.00 (IQR: 5.00–10.00) mg/24 h for patients taking oils only; 10.00 (IQR: 5.00–20.00) mg/24 h and 200.00 (IQR: 125.00–300.00) mg/24 h for patients taking dried flower only; and 55.00 (IQR: 15.00–69.38) mg/24 h and 206.25 (IQR: 110.00–280.09) mg/24 h for patients prescribed both CBMPs. The most prescribed dried flower was Adven® EMT1 (Curaleaf International, United Kingdom), whilst the most prescribed medium-chain triglyceride-based oils were Adven® 50 mg/ml CBD and Adven® 20 mg/ml THC (Curaleaf International, United Kingdom). Table 1 presents descriptive data including patient demographics, clinical history, and prescription information in full.

The mean age of patients was 38.06 (±11.70) years. Most patients were male ($n = 210$: 69.54%), with most patients consuming cannabis up until commencing treatment ($n = 193$; 63.91%), and a considerable number had also used cannabis in the past ($n = 70$; 23.18%).

There were 267 (88.41%), 241 (79.80%), 206 (68.21%), and 153 (50.66%) complete PROM responses at 1, 3, 6, and 12 months, respectively. Table 2 presents a repeated measures ANOVA performed across all patients to analyze the effect of CBMP treatment across each time point. There were improvements in the GAD-7, SQS, EQ-5D-5L Index Value, EQ-5D-5L Usual Activities, EQ-5D-5L Pain & Discomfort, EQ-5D-5L Anxiety & Depression, and PGIC ($p < 0.001$). Pairwise comparison with Bonferroni correction in each PROM with a significant difference on repeated measures ANOVA showed that in all comparisons there was a difference at 1, 3, 6, and 12 months compared to baseline ($p < 0.001$). At 12 months, the GAD-7, SQS, EQ-5D-5L Index Value, and EQ-5D-5L Anxiety & Depression values worsened compared to prior 1, 3, and 6 month follow-ups ($p < 0.050$). Full pairwise comparisons are detailed in Supplementary Tables S1-S7. Supplementary table S8 details the results of repeated measures ANOVA according to treatment type.

Table 1. Patient data outlining demographic information, clinical history, and cannabis-based medicinal products.

Baseline characteristics	No. (%)/Mean ± SD/Median [IQR]
Prescription information	
Oils	
CBD, mg/24 h	55.00 [20.00–55.00]
THC, mg/24 h	5.00 [5.00–10.00]
Dried flower	
CBD mg/24 h	10.00 [5.00–20.00]
THC, mg/24 h	200.00 [125.00–300.00]
Oils and dried flower	
CBD, mg/24 h	55.00 [15.00–69.38]
THC, mg/24 h	206.25 [110.00–280.09]
Gender	
Male	210 (69.54)
Female	92 (30.46)
Age, years	38.06 ± 11.70
Body mass index (BMI), kg/m^2	26.85 ± 7.31
Occupation	
Unemployed	88 (29.14)
Professional	51 (16.89)
Managers	16 (5.30)
Other occupations	38 (12.58)
Elementary occupations	19 (6.29)
Technicians and associate professionals	15 (4.97)
Craft and related trades workers	16 (5.30)
Service and sales workers	18 (5.96)
Clerical support workers	14 (4.64)
Plant and machine operators and assemblers	1 (0.33)
Skilled agricultural, forestry and fishery workers	2 (0.66)
Cannabis status	
Current user	193 (63.91)
Cannabis naïve	39 (12.91)
Ex-user	70 (23.18)
Cannabis use, gram years	13.12 ± 17.80
Smoking status	
Current smoker	114 (37.75)
Ex-smoker	119 (39.40)
Non-smoker	69 (22.85)
Smoking pack years	8.50 [3.00-20.00]
Weekly alcohol consumption, units	0.00 [0.00-6.00]
Charlson comorbidity index	0.00 [0.00-0.00]

Data was collected and reported at baseline via clinicians and questionnaires. Median cannabis use in gram years was calculated according to the method outlined by Reagan et al [52]. BMI = body mass index, CBD = cannabidiol, THC = (-)-trans-Δ9-tetrahydrocannabinol.

3.2. Comparison of CBMP treatments

The change from baseline to 12 months in each PROM according to whether patients were prescribed oils only, dried flower only or both CBMPs is detailed in Table 3. There was no statistically significant difference between the three groups in any PROM ($p > 0.050$).

3.3. Logistic regression – GAD-7 scores after 12 months

Eighty-eight (29.14%) participants reported a minimal clinically important difference at 12 months.

To assess the factors associated with clinically significant improvements in anxiety symptoms, a logistic regression analysis was performed. Initially, a univariable model was employed to examine the relationship between various independent variables and the likelihood of achieving a meaningful reduction in GAD-7 scores after 12 months of CBMP treatment. However, none of the individual variables reached statistical significance ($p > 0.050$) in this initial analysis.

Subsequently, all variables were included in a multivariable logistic regression model to explore potential interactions and confounding effects (Supplementary Table S9). This revealed an association between the type of CBMP prescribed and the likelihood of achieving clinically significant improvements in GAD-7 scores at 12. Specifically, the odds ratio for achieving a clinically significant improvement in GAD-7 scores was 0.21 (95% CI: 0.05–0.94, $p = 0.041$) for the dried flower group and 0.19 (95% CI: 0.05–0.84, $p = 0.028$) for the combination therapy group, relative to the oil-only group. No other variables in the model demonstrated a significant association with clinically significant improvements in anxiety symptoms.

3.4. Adverse events

A total of 55 (18.25%) patients reported 707 adverse events, with dry mouth and insomnia being the most frequently reported ($n = 53$ each). Table 4 details the severity and

Table 2. Repeated measures ANOVA comparing baseline and follow-up scores for patient-reported outcome measures (PROMs).

	Baseline		1 month		3 months		6 months		12 months			
PROM	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F-value	*P*-value
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 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 Self-care	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 Anxiety and depression	3.39	1.11	2.72	1.08	2.75	1.10	2.76	1.14	2.95	1.18	38.11	<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	33.43	<0.001
PGIC			5.45	1.41	5.71	1.19	5.68	1.29	5.72	1.32	8.52	<0.001

Generalised anxiety disorder (GAD) patients recorded anxiety-specific PROMs at 1, 3, 6 and 12 months after commencing CBMP treatment. A one-way ANOVA analysis was used to compare the differences at each timepoint to baseline scores to identify improvements in PROMS after 12 months of CBMP treatment. Results are displayed using a mean and standard deviation (SD). GAD-7 = Generalised Anxiety Disorder-7, PGIC = Patient Global Impression of Change, SQS = Single-Item Sleep Quality Scale. *p < 0.050, **p < 0.010, ***p < 0.001.

Table 3. One-way ANOVA comparing patient-reported outcome measures (PROMs) after 12 months to baseline results for each treatment type.

	Oils		Dried Flower		Oils and Dried Flower			
PROM	Mean	SD	Mean	SD	Mean	SD	F-value	*P*-value
GAD-7	−1.58	3.70	−3.27	5.75	−3.30	5.50	1.80	0.167
SQS	0.72	1.84	1.14	2.43	1.23	2.24	0.75	0.474
EQ-5D-5L Index	0.06	0.16	0.09	0.20	0.09	0.22	0.39	0.681
EQ-5D-5 L Mobility	*0.047*	*0.43*	*-0.054*	*0.58*	*-0.17*	*0.69*	*2.24*	*0.109*
EQ-5D-5L Self-care	*-0.02*	*0.27*	*0.01*	*0.56*	*-0.065*	*0.63*	*0.59*	*0.556*
EQ-5D-5L – Usual activities	−0.19	0.55	−0.29	0.90	−0.33	0.93	0.38	0.682
EQ-5D-5L Pain and discomfort	−0.12	0.39	−0.21	0.70	−0.25	0.78	0.55	0.579
EQ-5D-5L Anxiety and depression	−0.30	0.83	−0.46	1.02	−0.46	1.01	0.44	0.643
PGIC	0.07	1.29	0.30	0.97	0.28	0.73	0.82	0.443

A one-way ANOVA was used to compare the differences in means after 12 months for each treatment type to test for significant differences between routes of administration based on PROM scores reported by GAD patients. SD = standard deviation. GAD-7 = Generalised Anxiety Disorder-7, SQS = Single-item sleep quality scale, PGIC = Patient Global Impression of Change.

Table 4. Adverse events as reported by participants ($n = 55$).

Adverse event	Mild	Moderate	Severe	Total (%)
Abdominal pain	7	2	1	10 (3.31%)
Akathisia	0	1	0	1 (0.33%)
Amnesia	9	17	6	32 (10.60%)
Anorexia	3	7	2	12 (3.97%)
Anxiety	2	4	6	12 (3.97%)
Ataxia	10	2	0	12 (3.97%)
Blurred Vision	17	2	0	19 (6.29%)
Bruxism	1	0	0	1 (0.33%)
Chest pain	2	0	0	2 (0.66%)
Cognitive disturbance	12	16	4	32 (10.60%)
Concentration impairment	22	24	2	48 (15.90%)
Confusion	16	5	2	23 (7.62%)
Constipation	10	1	0	11 (3.64%)
Delirium	9	5	6	20 (6.62%)
Depression	1	4	14	19 (6.29%)
Dizziness	14	11	4	29 (9.60%)
Dry mouth	35	18	0	53 (17.55%)
Dysgeusia	9	6	2	17 (5.63%)
Dyspepsia	7	21	3	31 (10.26%)
Fatigue	18	21	3	42 (13.91%)
Headache	18	11	3	32 (19.60%)
Insomnia	28	15	10	53 (17.55%)
Lethargy	18	18	0	36 (11.92%)
Nausea	25	3	2	30 (9.93%)
Paranoia	2	5	0	7 (2.32%)
Pharyngitis	0	10	0	10 (3.31%)
Seizure	0	0	2	2 (0.66%)
Sinus pain	1	0	0	2 (0.66%)
Sneezing	1	0	0	1 (0.33%)
Somnolence	0	36	6	42 (13.91%)
Tremor	5	3	0	8 (2.65%)
Upper respiratory infection	0	5	0	5 (1.66%)
Urinary tract infection	0	5	0	5 (1.66%)
Vertigo	7	6	1	14 (4.64%)
Vomiting	13	0	0	13 (4.30%)
Weight loss	20	1	0	21 (6.95%)
Total (%)	**343 (113.58%)**	**285 (94.37%)**	**79 (26.16%)**	**707 (234.11%)**

incidence of each adverse event. The majority of these adverse events were classified as mild ($n = 343$) or moderate ($n = 285$) in severity. A smaller proportion ($n = 79$) were categorized as severe. No life-threatening or disabling adverse events were observed in this cohort of patients.

3.5. Logistic regression – adverse events

Univariable analysis exploring individual factors revealed that prior cannabis use was associated with a lower likelihood of experiencing adverse events during CBMP treatment (Supplementary Table S10). Specifically, both former cannabis users (OR = 2.16, 95% CI: 1.08–4.29, $p = 0.029$) and individuals with no prior cannabis use (OR = 3.36, 95% CI: 1.53–7.38, $p = 0.003$) were more likely to report adverse events compared to those who were current cannabis users at the start of treatment.

Multivariable analysis (Supplementary Table S11) confirmed the association between prior cannabis use and the likelihood of experiencing adverse events. Former cannabis users (OR = 2.46, 95% CI: 1.18–5.15, $p = 0.017$) and cannabis-naive patients (OR = 3.84, 95% CI: 1.52–9.72, $p = 0.004$) remained more likely to report adverse events compared to current cannabis users, even after adjusting for other variables.

3.6. Prescription medication

A total of 154 (50.99%) patients were prescribed antidepressants throughout the study (Table 5). 116 (74.32%) patients had no changes in medications over 12 months, while 21 (14.94%) stopped taking antidepressants and 5 (3.25%) patients had a reduced dose. 8 (5.19%) patients began treatment with antidepressants. Of the 36 patients taking benzodiazepines, 28 (77.78%) did not change their prescriptions, 6 (16.67%) patients stopped taking the medication and 1 (2.78%) patient reduced their dose, while a further 1 (2.78%) patient started benzodiazepines.

4. Discussion

This study presents the outcomes of 302 patients with GAD and prescribed CBMPs for a minimum of 12 months. This builds on previous research by our group using the UKMCR to assess the effects of CBMPs in GAD, following these patients over a longer period, demonstrating the persistence of clinical effects and safety profile [44]. This analysis demonstrates that treatment with CBMPs is broadly associated with improvements in GAD severity and EQ-5D-5L subscales for anxiety and depression after 12 months of treatment. Patients also experienced improvements in general HRQoL, sleep quality and other associated outcomes. At 12 months, however, the magnitude of this change was smaller compared to earlier follow-up assessments. On comparison of changes in outcomes from baseline at 12 months, there was no difference between the formulation of CBMPs. However, on multivariable logistic regression, those prescribed oils were most likely to report clinically significant improvement in symptoms of generalized anxiety compared to those who were prescribed a regimen including dried flower. Adverse events affected 18.25% of the study population, the majority being mild (343; 113.58%) or moderate (285; 94.37%). No life-threatening adverse events were recorded.

Patients prescribed CBMPs reported statistically significant improvements in GAD-specific PROMs after 12 months of treatment [45]. A meta-analysis by Black and colleagues demonstrated that CBMPs were associated with improvements in anxiety when pooling across a heterogenous range of medications and conditions [22]. However, studies examining the effects of CBD used doses more than the doses used in the present study. Meanwhile, no randomized trials assessed the impact of THC in a population with generalized anxiety as the primary indication for treatment [22]. Prior assessments have suggested that higher doses of THC are more closely associated with anxiogenic responses [14,15,17]. Therefore, whilst these results are supportive of the potential of CBMPs as demonstrated in the wider literature, there are discrepancies which will require further analysis to help determine the optimum doses of CBD and THC, as well as the interaction of other minor compounds present on reported outcomes. The multivariate analysis in the present analysis did not find a difference between those prescribed higher or lower than the median dose of THC and may therefore suggest the response to THC doses are individualized. Interestingly, those prescribed oils were more likely to report a clinically significant improvement in GAD-7 scores at 12 months, with this reaching statistical significance against both those prescribed dried flower and a combination of dried flower and oils (supplementary table S9). The reason for this is not clear from the present analysis but may be secondary to differing pharmacokinetic profiles of each administration method. Moreover, it could be secondary to lower doses of THC and higher doses of CBD in oils compared to dried flower that are not otherwise able to be adequately adjusted for within the present analysis.

Sleep disturbances are a hallmark of GAD, often exacerbating anxiety symptoms and contributing to a diminished quality of life [2,46]. In this study, participants reported significant improvements in their sleep quality at each assessment point, as measured by the SQS. This contrasts with findings from a study utilizing the Pittsburgh Sleep Quality Index to assess sleep quality in individuals with anxiety [47]. This found that while cannabis use was linked to heightened expectations of sleep improvement, there was limited evidence to suggest a direct correlation between cannabis use and actual

Table 5. Changes in prescription following 12 months of CBMP treatment.

Medication	Total	No Change	Stopped Taking	Reduced Dose	Increased Dose	New Medication
Antidepressants, n (%)	154	116 (74.32%)	23 (14.94%)	5 (3.25%)	1 (0.65%)	8 (5.19%)
Benzodiazepines, n (%)	36	28 (77.78%)	6 (16.67%)	1 (2.78%)	0 (0.00%)	1 (2.78%)
Gabapentinoids, n (%)	17	14 (82.35%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	2 (11.76%)

Medications were categorized into antidepressants, benzodiazepines and gabapentinoids. All data is represented as n (%).

improvements in sleep outcomes or subjective sleep efficiency [47]. The present study does, however, align with emerging evidence suggesting that CBMPs may positively influence sleep architecture and subjective sleep experiences [47–50]. One study found that vaporized CBMPs containing low doses of THC were associated with improvements in non-rapid eye movement sleep, potentially aiding sleep latency [48]. This effect may be aided by CBD [49]. Meanwhile, a review of clinical trials studying nabiximols, an oromucosal spray containing both CBD and THC, found that it was associated with improved sleep quality compared to placebo [50]. This may explain the improvements in sleep quality over time in this cohort.

Patients prescribed all three types of CBMP reported improvements in nonspecific HRQoL measures such as the EQ-5D-5L Index, and subgroups such as EQ-5D-5L anxiety and depression, and EQ-5D-5 L usual activities. Subgroup analysis revealed that all three groups also experienced improvements in anxiety and depression. This complements data from other studies of GAD: a case series of patients with depression and co-morbid anxiety enrolled on the UKMCR found a sustained improvement in EQ-5D-5L anxiety and depression/usual activities measures after 6 months of treatment with oils, dried flower, or both [51]. Another study of the UKMCR indicated that there is an association between improvements in chronic anxiety and improvements in HRQoL, and that CBMP treatment is linked to improvements in HRQoL [52]. These findings demonstrate a positive association between CBMP treatment and HRQoL.

Results indicated that CBMPs were overall well-tolerated across the study as a small proportion (18.25%) of participants reported adverse events. The most common adverse event was dry mouth. This may be explained by the route of CBMP administration – most users were prescribed vaporized cannabis, as previous studies have shown that dry mouth is commonly associated with vaporized cannabis [53,54]. The most common severe adverse event was depression. As adverse events were not examined to determine whether they were treatment-related it is not possible to distinguish whether this was secondary to CBMPs or due to the co-occurrence of anxiety and depression in the same individual [55]. However, this does suggest that significant adverse mental health outcomes may occur during treatment with CBMPs, and this relationship should be examined further in randomized controlled trials. There was no reported incidence of cannabis use disorder in this cohort. In addition to assessment through reporting via adverse events, it would be helpful to use a screening tool to assess the risk of cannabis use disorder in a clinical population, as this is not well established compared to recreational cannabis use [56]. Unfortunately, currently available tools are not validated in clinical populations and would generate inappropriately high scores due to the weight placed on frequency of use [56]. Multivariable and univariable analysis determined that prior exposure to cannabis was associated with a lower probability of experiencing an adverse event. Ex-users and cannabis-naïve patients were more likely to experience an adverse event than current cannabis users, in line with previous research which reports that cannabis has less prominent effects in regular users, partially due to THC active maintenance which occurs when patients consume cannabis continuously [57,58]. This reinforces the results of the univariable and multivariable analysis and suggests an association between tolerance and continuous cannabis consumption.

The strengths of this study include a relatively large sample size as well as a long observation period compared to previous work, where previous studies have been limited to small sample sizes, short durations, and a homogenous selection of CBMPs [24]. The limitations of this study are largely attributed to the type of study conducted, as well as the data represented.

As an observational study, it is unable to establish causality between initiation of CBMPs and reported outcomes. The results of this study therefore cannot be generalized to the wider population. Another notable limitation is the lack of a control group, which means it cannot demonstrate whether improvements in PROMs are linked to CBMPs specifically or are associated with other factors or extreme outcomes due to regression to the mean. Within this study, the placebo effects of CBMPs may be enhanced due to the psychoactive and vasoactive effects of cannabinoids [59]. The study is subject to selection bias as patients enrolled in the UKMCR self-fund their treatment. In addition, most patients (63.8%) were current cannabis users before enrolling in the UKMCR and therefore may be more likely to report positive outcomes because of expectancy bias. Conversely, these individuals may be more likely to develop tolerance to the effects of cannabis [60]. One in two individuals were prescribed anti-depressants during the study. However, the effect of the pharmacokinetic and pharmacodynamic interaction of these medications was not able to be considered. There is attrition bias, with a loss to follow-up throughout the study. To address this missing data has been dealt with through a conservative methodology, carrying forward the baseline value, and biasing the results toward a null finding. PROMs are subject to recall bias, where patients may over- or understate their outcomes based on their perception of treatment. Self-reporting is also integral to determining previous cannabis exposure within observational studies. Finally, the analysis is subject to the limitations of data captured within the UK Medical Cannabis Registry and made available for this study. For example, additional mental health comorbidities beyond those detailed could not be considered. Moreover, only the maximum tolerated dose of CBD and THC at the point of data extraction was available. Ideally, it would be beneficial to track this dose throughout treatment.

5. Conclusion

In summary, these results demonstrate that treatment with CBMPs is associated with improved anxiety symptoms and HRQoL following 12 months of treatment. Whilst there were no changes between different formulations on direct comparison of the change in GAD-7 scores, on multivariable analysis those prescribed oils were more likely to report a clinically important difference. The size of the change is lower at 12 months compared to earlier follow-up periods emphasizing

the importance of longitudinal assessment in patients prescribed CBMPs. Further studies will be necessary to determine whether this is secondary to pharmacological tolerance and the implications of prescribing CBMPs beyond 12 months. This study also highlights the lack of severe and life-threatening events associated with CBMP treatment over 12 months. This data can be useful to help guide current clinical practice, suggesting oils may be preferable to dried flower when considering the optimal formulation when prescription CBMPs for GAD. Randomized controlled trials will ultimately be required to determine whether CBMPs are effective as a class of medications, and which is the most appropriate product for GAD.

Abbreviations

CB1	Cannabinoid receptor 1
CB2	Cannabinoid receptor 2
CBD	Cannabidiol
CBMPs	Cannabis-based medicinal products
GAD	Generalised Anxiety Disorder
GAD-7	Generalised Anxiety Disorder-7
HRQoL	Health-related quality of life
PGIC	Patient global impression of change
PROM	Patient-reported outcome measure
SQS	Single-item sleep quality scale
THC	(-)-trans-Δ9-tetrahydrocannabinol
TRPV1	Transient receptor potential vanilloid 1
UKMCR	UK Medical Cannabis Registry

Author contribution

All authors contributed to the study's conception and design. Material preparation and data collection were performed by J Warner-Levy, S Erridge, 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 J Warner-Levy, S Erridge, and MH Sodergren. The first draft of the manuscript was written by J Warner-Levy, 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.

Funding

This paper was not funded.

Declaration of interest

S Erridge is Research Director at Curaleaf Clinic, while E Clarke is a Patient Care Director and K McLachlan is Chief Pharmacist at the Curaleaf Clinic. R Coomber is the Operation's Director at the Curaleaf Clinic, while A De Angelis is a consultant neuropsychiatrist at the Curaleaf Clinic. M Asghar, K Bexley, U Bhoskar, M Crews, M Imran, F Kamal, L Korb, S Sachdeva-Mohan, G Shaya and G Mwimba 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.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Data availability statement

Data supporting this study's findings are available from the UK Medical Cannabis Registry. Restrictions are applied to the availability of these data. Data specifications and applications are available from the corresponding author.

Acknowledgments

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.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Fineberg NA, Haddad PM, Carpenter L, et al. The size, burden and cost of disorders of the brain in the UK. J Psychopharmacol. 2013 Sep 24;27(9):761–770. doi: 10.1177/0269881113495118
2. American Psychiatric Association, DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5™. 5th ed. American Psychiatric Publishing, Inc.; 2013. doi: 10.1176/appi.books.9780890425596
3. Revicki DA, Travers K, Wyrwich KW, et al. Humanistic and economic burden of generalized anxiety disorder in North America and Europe. J Affect Disord. 2012 Oct;140(2):103–112. doi: 10.1016/j.jad.2011.11.014
4. Khan A, Leventhal RM, Khan S, et al. Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. J Affect Disord. 2002 Apr;68(2–3):183–190. doi: 10.1016/S0165-0327(01)00354-8
5. Craske MG, Stein MB, Eley TC, et al. Anxiety disorders. Nat Rev Dis Primers. 2017 May 4;3(1):17024. doi: 10.1038/nrdp.2017.24
6. Baldwin DS, Waldman S, Allgulander C. Evidence-based pharmacological treatment of generalized anxiety disorder. Int J Neuropsychopharmacol. 2011 Jun 7;14(5):697–710. doi: 10.1017/S1461145710001434
   • **This paper reviews evidence-based pharmacological treatments for GAD.**
7. Bereza BG, Machado M, Ravindran AV, et al. Evidence-based review of clinical outcomes of guideline-recommended pharmacotherapies for generalized anxiety disorder. Can J Psychiatry. 2012 Aug 1;57(8):470–478. doi: 10.1177/070674371205700805
8. Slee A, Nazareth I, Bondaronek P, et al. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019 Feb;393(10173):768–777. doi: 10.1016/S0140-6736(18)31793-8
9. Ergisi M, Erridge S, Harris M, et al. UK medical cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder. Expert Rev Clin Pharmacol. 2022 Apr 3;15(4):487–495. doi: 10.1080/17512433.2022.2020640
10. Ligresti A, De Petrocellis L, Di Marzo V. From phytocannabinoids to cannabinoid receptors and endocannabinoids: pleiotropic physiological and pathological roles through complex pharmacology. Physiol Rev. 2016 Oct;96(4):1593–1659. doi: 10.1152/physrev.00002.2016

11. Ebbert JO, Scharf EL, Hurt RT. Medical cannabis. Mayo Clin Proc. 2018 Dec;93(12):1842–1847. doi: 10.1016/j.mayocp.2018.09.005
    - **This paper discusses the medical use of cannabis, focusing on its potential benefits and risks.**
12. Glass M, Northup JK. Agonist selective regulation of G proteins by cannabinoid CB_1 and CB_2 receptors. Mol Pharmacol. 1999 Dec 1;56(6):1362–1369. doi: 10.1124/mol.56.6.1362
13. Zou S, Kumar U. Cannabinoid receptors and the Endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci. 2018 Mar 13;19(3):833. doi: 10.3390/ijms19030833
14. Moreira FD, Aguiar DC, Terzian AL, et al. Cannabinoid type 1 receptors and transient receptor potential vanilloid type 1 channels in fear and anxiety—two sides of one coin? Neuroscience. 2012 Mar 1;204:186–192. doi: 10.1016/j.neuroscience.2011.08.046
15. Lutz B, Marsicano G, Maldonado R, et al. The endocannabinoid system in guarding against fear, anxiety and stress. Nat Rev Neurosci. 2015 Dec;16(12):705–718. doi: 10.1038/nrn4036
    - **This review paper discusses the role of the endocannabinoid system in protecting against fear, anxiety, and stress.**
16. Hasbi A, Madras BK, George SR. Endocannabinoid system and exogenous cannabinoids in depression and anxiety: a review. Brain Sci. 2023 Feb 14;13(2):325. doi: 10.3390/brainsci13020325
17. Childs E, Lutz JA, de Wit H. Dose-related effects of delta-9-thc on emotional responses to acute psychosocial stress. Drug Alcohol Depend. 2017 Aug 1;177:136–144. doi: 10.1016/j.drugalcdep.2017.03.030
    - **This study examines the dose-related effects of delta-9-THC on emotional responses to acute psychosocial stress.**
18. Campos AC, Moreira FA, Gomes FV, et al. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. Phil Trans R Soc B. 2012 Dec 5;367(1607):3364–3378. doi: 10.1098/rstb.2011.0389
19. Aguiar DC, Terzian AL, Guimarães FS, et al. Anxiolytic-like effects induced by blockade of transient receptor potential vanilloid type 1 (TRPV1) channels in the medial prefrontal cortex of rats. Psychopharmacology (Berl). 2009 Aug;205(2):217–225. doi: 10.1007/s00213-009-1532-5
20. Britch SC, Babalonis S, Walsh SL. Cannabidiol: pharmacology and therapeutic targets. Psychopharmacology (Berl). 2021 Jan;238(1):9–28. doi: 10.1007/s00213-020-05712-8
21. Royal College of Psychiatrists. Royal College of Psychiatrists. Position statement on cannabis-based medicinal products. 2019 [cited 2023 Aug 23]. Available from: https://www.rcpsych.ac.uk/docs/default-source/improving-care/better-mh-policy/position-statements/ps05_19.pdf?sfvrsn=2db968d3_2
    - **This reference gives a position statement on the use of cannabis-based medicinal products.**
22. Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry. 2019 Dec 1;6(12):995–1010. doi: 10.1016/S2215-0366(19)30401-8
23. UK Government. Guidance on cannabis-based products for medicinal use. 2020 [cited 2024 Aug 7]. Available from: https://assets.publishing.service.gov.uk/media/5e58eefb86650c53a363f77c/Cannabis_Guidance__unlicensed_CBPMs__updated_2020.pdf
24. Erridge S, Salazar O, Kawka M, et al. An initial analysis of the UK medical cannabis registry: outcomes analysis of first 129 patients. Neuropsychopharmacol Rep. 2021 Sep 14;41(3):362–370. doi: 10.1002/npr2.12183
25. Kawka M, Erridge S, Holvey C, et al. Clinical outcome data of first cohort of chronic pain patients treated with cannabis-Based sublingual oils in the United Kingdom: analysis from the UK medical cannabis registry. The J Clin Pharmacol. 2021 Dec 5;61(12):1545–1554. doi: 10.1002/jcph.1961
26. Tait J, Erridge S, Sodergren MH. UK medical cannabis registry: a patient evaluation. J Pain Palliat Care Pharmacother. 2023 Jun;37(2):170–177. doi: 10.1080/15360288.2023.2174633.
    - •• **This paper provides a patient evaluation from the UK Medical Cannabis Registry.**
27. •von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Bull World Health Organ. 2007 Nov;85(11):867–872. doi: 10.2471/BLT.07.045120
28. International Labour Organisation [Internet]. ISCO – international standard classification of occupations. Available from: https://www.ilo.org/public/english/bureau/stat/isco/isco08/index.htm
29. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987 Jan;40(5):373–383. doi: 10.1016/0021-9681(87)90171-8
30. Wetherill RR, Hager N, Guthier E, et al. Gram years: a method to standardize and quantify lifetime cannabis consumption. Cannabis Cannabinoid Res. 2016 Dec;1(1):216–217. doi: 10.1089/can.2016.0025
31. Churruca K, Pomare C, Ellis LA, et al. Patient-reported outcome measures (PROMs): a review of generic and condition-specific measures and a discussion of trends and issues. Health Expectations. [2021 Aug 5];24(4):1015–1024. doi: 10.1111/hex.13254
32. Williams N. The GAD-7 questionnaire. Occup Med (Chic Ill). 2014 Apr 1;64(3):224–224. doi: 10.1093/occmed/kqt161
33. Toussaint A, Hüsing P, Gumz A, 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. doi: 10.1016/j.jad.2020.01.032
34. Snyder E, Cai B, DeMuro C, et al. A New Single-Item Sleep Quality Scale: Results of Psychometric Evaluation in Patients With Chronic Primary Insomnia and Depression. J Clin Sleep Med. 2011;14(11):1849–1857. doi: 10.5664/jcsm.7478
35. Yi H, Shin K, Shin C. Development of the sleep quality scale. J Sleep Res. 2006 Sep;15(3):309–316. doi: 10.1111/j.1365-2869.2006.00544.x
36. Staner L. Sleep and anxiety disorders. Dialogues Clin Neurosci. 2003 Sep 30;5(3):249–258. doi: 10.31887/DCNS.2003.5.3/lstaner
37. Hinz A, Kohlmann T, Stöbel-Richter Y, et al. The quality of life questionnaire EQ-5D-5L: psychometric properties and normative values for the general German population. Qual Life Res. 2014 Mar 7;23(2):443–447. doi: 10.1007/s11136-013-0498-2
38. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012 Jul;15(5):708–715. doi: 10.1016/j.jval.2012.02.008
39. Mulhern B, Feng Y, Shah K, et al. Comparing the UK EQ-5D-3L and English EQ-5D-5L value sets. Pharmacoeconomics. 2018 Jun 23;36(6):699–713. doi: 10.1007/s40273-018-0628-3
40. Bernfort L, Gerdle B, Husberg M, et al. People in states worse than dead according to the EQ-5D UK value set: would they rather be dead? Qual Life Res. 2018 Jul;27(7):1827–1833. doi: 10.1007/s11136-018-1848-x
41. Ferguson L, Scheman J. Patient global impression of change scores within the context of a chronic pain rehabilitation program. J Pain. 2009 Apr;10(4):S73. doi: 10.1016/j.jpain.2009.01.258
42. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US national cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). JAMA Oncol. 2015 Nov 1;1(8):1051. doi: 10.1001/jamaoncol.2015.2639
43. IBM SPSS statistics for macintosh [Internet]. IBM Corp; 2021 [cited 2023 Aug 24: Available from: https://www.ibm.com/uk-en/analytics/spss-statistics-software
44. Rifkin-Zybutz R, Erridge S, Holvey C, et al. Clinical outcome data of anxiety patients treated with cannabis-based medicinal products in the United Kingdom: a cohort study from the UK medical cannabis registry. Psychopharmacology (Berl). 2023 Aug;240(8):1735–1745. doi: 10.1007/s00213-023-06399-3
    - •• **This cohort study provides real-world data on the clinical outcomes of anxiety patients treated with cannabis-based medicinal products.**
45. Wright M, Di Ciano P, Brands B. Use of cannabidiol for the treatment of anxiety: a short synthesis of pre-clinical and clinical evidence. Cannabis Cannabinoid Res. 2020 Sep 1;5(3):191–196. doi: 10.1089/can.2019.0052

46. Monti JM, Monti D. Sleep disturbance in generalized anxiety disorder and its treatment. Sleep Med Rev. 2000 Jun;4(3):263–276. doi: 10.1053/smrv.1999.0096
47. Winiger EA, Hitchcock LN, Bryan AD, et al. Cannabis use and sleep: expectations, outcomes, and the role of age. Addict Behav. 2021;112:112. doi: 10.1016/j.addbeh.2020.106642
48. Mondino A, Cavelli M, González J, et al. Acute effect of vaporized cannabis on sleep and electrocortical activity. Pharmacol Biochem Behav. 2019 Apr;179:113–123. doi: 10.1016/j.pbb.2019.02.012
49. Kaul M, Zee PC, Sahni AS. Effects of cannabinoids on sleep and their therapeutic potential for sleep disorders. Neurotherapeutics. 2021 Jan 12;18(1):217–227. doi: 10.1007/s13311-021-01013-w
50. Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from Therapeutic clinical trials ofSativex®, a cannabis-based medicine. Chem Biodivers. 2007 Aug;4(8):1729–1743. doi: 10.1002/cbdv.200790150
51. Mangoo S, Erridge S, Holvey C, et al. Assessment of clinical outcomes of medicinal cannabis therapy for depression: analysis from the UK medical cannabis registry. Expert Rev Neurother. 2022 Nov 2;22(11–12):995–1008. doi: 10.1080/14737175.2022.2161894
•• **This study provides an analysis of clinical outcomes for patients using medicinal cannabis for depression, based on data from the UK Medical Cannabis Registry.**
52. Olsson F, Erridge S, Tait J, et al. An observational study of safety and clinical outcome measures across patient groups in the United Kingdom medical cannabis registry. Expert Rev Clin Pharmacol. 2023 Mar 4;16(3):257–266. doi: 10.1080/17512433.2023.2183841
53. Joshi S, Ashley M. Cannabis: a joint problem for patients and the dental profession. Br Dent J. 2016 Jun 10;220(11):597–601. doi: 10.1038/sj.bdj.2016.416
54. Bywood PMJ, McMillan J. Medicinal Cannabis Evidence Review Update. Institute for Safety, Compensation and Recovery Research (ISCRR); 2022. https://research.iscrr.com.au/__data/assets/pdf_file/0010/2823238/303_Medicinal-cannabis-update.pdf
55. Jacobson NC, Newman MG. Anxiety and depression as bidirectional risk factors for one another: a meta-analysis of longitudinal studies. Psychol Bull. 2017 Nov;143(11):1155. doi: 10.1037/bul0000111
56. López-Pelayo H, Batalla A, Balcells MM, et al. Assessment of cannabis use disorders: a systematic review of screening and diagnostic instruments. Psychol Med. 2015 Apr;45(6):1121–1133. doi: 10.1017/S0033291714002463
57. Colizzi M, Bhattacharyya S. Cannabis use and the development of tolerance: a systematic review of human evidence. Neurosci Biobehav Rev. 2018 Oct;93:1–25. doi: 10.1016/j.neubiorev.2018.07.014
58. Ramaekers JG, Mason NL, Theunissen EL. Blunted highs: pharmacodynamic and behavioral models of cannabis tolerance. Eur Neuropsychopharmacol. 2020 Jul;36:191–205. doi: 10.1016/j.euroneuro.2020.01.006
59. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: The Current State of Evidence and Recommendations for Research. Washington D.C: National Academies Press; 2017.
60. Bapir L, Erridge S, Nicholas M, et al. Comparing the effects of medical cannabis for chronic pain patients with and without co-morbid anxiety: a cohort study. Expert Rev Neurother. 2023 Mar 4;23(3):281–295. doi: 10.1080/14737175.2023.2181696