Taylor & Francis
Taylor & Francis Group



Expert Review of Clinical Pharmacology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierj20

UK Medical Cannabis Registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder

Mehmet Ergisi, Simon Erridge, Michael Harris, Michal Kawka, Devaki Nimalan, Oliver Salazar, Katerina Loupasaki, Rayyan Ali, Carl Holvey, Ross Coomber, Michael Platt, James J Rucker & Mikael H Sodergren

To cite this article: Mehmet Ergisi, Simon Erridge, Michael Harris, Michal Kawka, Devaki Nimalan, Oliver Salazar, Katerina Loupasaki, Rayyan Ali, Carl Holvey, Ross Coomber, Michael Platt, James J Rucker & Mikael H Sodergren (2022): UK Medical Cannabis Registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder, Expert Review of Clinical Pharmacology, DOI: 10.1080/17512433.2022.2020640

To link to this article: https://doi.org/10.1080/17512433.2022.2020640

© 2022 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

Published online: 18 Jan 2022.

Submit your article to this journal

Article views: 1245

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ierj20

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
https://doi.org/10.1080/17512433.2022.2020640

Taylor & Francis
Taylor & Francis Group

META-ANALYSIS

OPEN ACCESS Check for updates

UK Medical Cannabis Registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder

Mehmet Ergisi[a], Simon Erridge[a,b], Michael Harris[a], Michal Kawka [a], Devaki Nimalan[a], Oliver Salazar[a], Katerina Loupasaki[a], Rayyan Ali[a], Carl Holvey[b], Ross Coomber[b,c], Michael Platt[a,b], James J Rucker [b,d,e] and Mikael H Sodergren[a,b]

[a]Imperial College Medical Cannabis Research Group, Department of Surgery and Cancer, Imperial College London, London, UK; [b]Sapphire Medical Clinics, London, UK; [c]Trauma and Orthopaedic Department, St. George's Hospital NHS Trust, London, UK; [d]Department of Psychological Medicine, Kings College London, London, UK; [e]Centre for Affective Disorders, South London & Maudsley NHS Foundation Trust, London, UK

ABSTRACT

Objectives: Anxiety disorders are one of the most common reasons for seeking treatment with cannabis-based medicinal products (CBMPs). Current pharmacological treatments are variable in efficacy and the endocannabinoid system has been identified as a potential therapeutic target. This study aims to detail the changes in health-related quality-of-life (HRQoL) and clinical safety following CBMP therapy for generalized anxiety disorder.

Methods: A case series from the UK Medical Cannabis Registry was performed. Primary outcomes included changes from baseline in patient-reported outcome measures (the General Anxiety Disorder Scale (GAD-7), EQ-5D-5L (a measure of health-related quality of life), and Sleep Quality Scale (SQS)) at 1, 3 and 6 months. Statistical significance was defined as $p<0.050$.

Results: Sixty-seven patients were treated for generalized anxiety disorder. Statistically significant improvements were observed in GAD-7, EQ-5D-5L Index Value, EQ5D Visual Analog Scale, and SQS scores at 1, 3 and 6 months ($p<0.050$). Twenty-five (39.1%) patients reported adverse events during the follow-up period.

Conclusion: This study suggests that CBMPs may be associated with improvements in HRQoL outcomes when used as a treatment for generalized anxiety disorder. These findings must be treated with caution considering limitations of study design; however this data may help inform future clinical studies and practice.

Plain Language Summary

Anxiety disorders are the most prevalent psychiatric illness type in the United Kingdom, with 8.2 million cases reported in 2010. Generalized anxiety disorder (GAD), the most common anxiety disorder, debilitates, and so reduces the quality of life of those who suffer from the condition.

The efficacy of current treatments for GAD varies greatly from person-to-person. The endocannabinoid system in the human body is currently attracting a lot of attention in the scientific community as it can be targeted by chemicals in the cannabis plant to produce therapeutic effects in order to treat GAD. There is, however, a lack of studies investigating the effects of medicinal cannabis in GAD, and so this study aims to explore the drug's effect on quality of life in patients suffering from GAD.

Sixty-seven patients who attended the Sapphire Clinics for medicinal cannabis treatment for GAD were included in the study. The results from this study highlight that medicinal cannabis may improve generalized anxiety disorder, general health-related quality of life, and sleep-specific outcomes at 1, 3, and 6 months after starting treatment. There was also a low number of severe, disabling, and life-threatening adverse events experienced by patients. Although this study explores the effects of medicinal cannabis in a real clinical setting, the results were not compared to other types of treatment. Future studies with a comparator are therefore needed before concluding the true effects of medicinal cannabis in patients with GAD.

ARTICLE HISTORY
Received 28 July 2021
Accepted 5 November 2021

KEYWORDS
Medical cannabis; anxiety; psychiatry; cannabinoid; cannabidiol; tetrahydrocannabinol; health-related quality-of-life

1. Introduction

In 2010, there were 8.2 million cases of anxiety disorders, making it the most prevalent psychiatric illness type in the UK [1]. Generalized anxiety disorder (GAD), which is the most common anxiety disorder [2], is defined as persistent and excessive anxiety for a period of at least 6 months, characterized by constant worry and symptoms of restlessness and inability to concentrate and/or sleep [3,4]. GAD is associated with increased suicidality and unemployment, loss of productivity and self-worth, and increased health-care utilization [5–7]. In addition, those with GAD have reduced health-related quality of life (HRQoL) [8].

Current first-line pharmacological treatments for GAD include selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and pregabalin [9]. Whilst

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

The data from this study has been presented as a poster at the International Cannabinoid Research Society Conference, 2021.

© 2022 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

effective pharmaceutical options exist for the treatment of GAD, there is variability in medication response, side effects, and tolerance to medications and their side effects, resulting in many patients with refractory anxiety despite treatment [10,11]. Therefore, new pharmacological treatment options are required, particularly in those who have not benefited from pharmacotherapy or talking therapies. The endocannabinoid system, an endogenous system of neurotransmitters, enzymes and cannabinoid receptors, has shown promising pre-clinical data for drug development, supporting its role in modulating neuronal activity associated with anxiety [12,13].

Cannabis sativa and *Cannabis indica*, the most prominent species of cannabis, contain at least 144 phytocannabinoids. Some of these act via endogenous cannabinoid receptors, whilst the mechanism of action of most is either via other receptors, or has yet to be characterized [14–16]. Of clinical interest, two phytocannabinoids have been the subject of a growing body of research: (–)-trans-Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [17]. THC is an agonist of G-protein coupled receptors, cannabinoid type 1 (CB1) and type 2 (CB2), which are predominantly found in the central nervous system and immune system, respectively [18–20]. CB1 receptors are located in regions of the brain such as the cerebellum, hippocampus, and basal ganglia; CB1 agonists result in the downregulation of neurotransmission, including via GABAergic and glutamatergic neurons [21,22]. This mechanism is thought to produce the resultant psychotropic effects of THC, including regulation of emotions, motor coordination, and cognition [21]. A primary target of CBD is fatty acid-binding proteins (FABPs), which are involved in the transport of anandamide to the enzyme fatty acid amide hydrolase (FAAH). FAAH breaks down anandamide, an endocannabinoid and CB1 receptor agonist [23]. CBD subsequently increases the concentration of anandamide at synapses, resulting in similar clinical effects to CB1 agonists [24]. This mechanism, in tandem with agonism of the serotonin 1A receptor and transient receptor potential vanilloid type 1, is thought to play a role in CBD's proposed anxiolytic effects [12,25]. The mechanisms of action of CBD are still to be fully elucidated, however [21]. CBD has also been linked with modulating both the therapeutic and adverse effects of THC, due to opposing direct action on CB1 and CB2 receptors [26–28].

As highlighted in a 2019 systematic review, most of the studies investigating the effects of cannabis-based medicinal products (CBMPs) in anxiety are among participants in which anxiety symptoms were secondary to another condition [29]. Only two clinical trials were identified for anxiety disorders, both of which compared CBD against placebo in social anxiety disorder (SAD) [29–31]. Although these studies reported that CBD improved anxiety compared to placebo during public speaking, the studies were limited by a small sample size [30,31]. In a recent review, CBMPs were not recommended for anxiety disorders due to a paucity of high-quality evidence [32]. Pilot clinical trials and observational studies, however, suggest promise by demonstrating improvement in anxiety among healthy volunteers and those with anxiety disorders, supported by mechanistic evidence from preclinical studies [20,33–35].

Currently, there is a high degree of methodological heterogeneity across the literature on CBMPs, such as formulations, routes of administration, and concentrations of constituent cannabinoids [36,37]. Crucially, there are several studies that evaluate use of illicit or recreational cannabis, which lack the regulation, and therefore consistency, of CBMPs [36,37]. This increases heterogeneity as the constitutive cannabinoid concentrations are at best inconsistent and at worst unknown [36,37]. Overall, much is yet to be discovered regarding clinical efficacy and potential adverse events.

Given the paucity of clinical data investigating the therapeutic effects of CBMPs, clinical case series can advance current clinical practice by observing preliminary trends within populations and in turn generating hypotheses for future RCTs. Herein, the primary aim of this formal, consecutive case series of UK patients was to explore the general HRQoL outcomes in patients treated for GAD. Supplementary aims included evaluation of adverse event frequency and dosage regimens.

2. Methods

2.1. Study design and participants

The UK Medical Cannabis Registry was set up in December 2019 and is the first prospective registry that records the pseudonymised data of medical cannabis patients, across the UK and Channel Islands and is managed by Sapphire Medical Clinics. The reporting of this observational study conformed to the STROBE guidelines [38]. Following the guidance of the NHS Health Research Authority and Research Ethics Committee, it was deemed that formal ethical approval was not required. Written and informed consent was completed by all participants.

In this formal, consecutive clinical case series, the effects of prescribed CBMPs were investigated in participants who attended Sapphire Medical Clinics for GAD. A variety of different CBMPs were prescribed, all of which met Good Manufacturing Practice, and were prescribed by a specialist in the condition, with the decision ratified by a multidisciplinary team, as per national guidance [39]. The formulations were either dry plant (flos or granulate) or oil (isolate phytocannabinoids or full-spectrum products containing cannabinoids, terpenes, and flavonoids). The oils were administered orally or sublingually, whilst dry plants were vaped. Vaping involves the use of an electronic device that heats the dry plant to turn it into a vapor, as opposed to smoke, which can be inhaled by the user. Furthermore, the strains were either *Cannabis sativa, Cannabis indica*, or a hybrid species.

This study describes an analysis for patients with a primary, secondary, or tertiary diagnosis of GAD determined by a trained health-care professional according to the DSM-5. The primary diagnosis was the condition designated by the clinician for which patients were being treated for with CBMPs. Secondary and tertiary diagnoses were those which had been confirmed clinically and in which treatment was also indicated alongside the primary presenting condition.

2.2. Data collection

Data were collected remotely whereby patients received patient-reported outcome measures (PROMs) and adverse event questionnaires electronically via an online web-based platform at baseline and 1-month, 3-month and 6-month follow-ups. Where patients had not provided a complete complement of data, they were contacted by a member of the research team to provide outstanding information retrospectively.

The following demographic data were collected at the initial assessment: age, sex, occupation, and Body Mass Index (kg/m^2). The primary diagnoses, other diagnoses where applicable, and comorbidities were recorded. The Charlson Comorbidity Index, a prognostic tool used to predict the ten-year mortality of patients, was calculated for each participant [40,41].

Smoking, alcohol, and cannabis status was collected, including smoking status, pack years, weekly alcohol consumption (units), cannabis use status, frequency of cannabis use for current users, and current quantity of cannabis consumption (g). To quantify the individual history of using illicit cannabis, a novel metric of 'cannabis gram years' was utilized, as previously described by our group [42].

Other medications under the following classes were also recorded: analgesics, anticoagulants, antidepressants, antidiabetic drugs, antimigraine drugs, antiplatelets, hypnotics, and anxiolytics. Using conversion factors cited by the British National Formulary, oral morphine equivalents were calculated for opioid medications. Details of the CBMP prescriptions were recorded at baseline and follow-up intervals, including company, formulation, CBD dose per day (mg), THC dose per day (mg), other active ingredients, dose of other active ingredients per day (mg), and strain.

The following PROMs were recorded at the baseline assessment and each follow-up interval for all adult patients, including those with GAD: General Anxiety Disorder Scale (GAD-7), EQ-5D-5L and Sleep Quality Scale (SQS).

The GAD-7, is a validated self-reported questionnaire designed to screen and measure severity for GAD [43]. Subjects are asked how often they have been bothered by each of the seven core symptoms of GAD over the last 2 weeks [43]. The options are 'not at all,' 'several days,' 'more than half the days,' and 'nearly every day,' with each option assigned a score of 0, 1, 2, and 3, respectively [43]. The total score is from 0 to 21, with thresholds of ≥5, ≥10, and ≥15 signifying mild, moderate, and severe anxiety symptoms, respectively [43].

The EQ-5D-5L is a self-reported questionnaire measuring HRQoL [44]. Subjects are asked to rate their quality of life on the day of completing the questionnaire across five domains: 'mobility,' 'self-care,' 'usual activities,' 'pain/discomfort,' and 'anxiety/depression' [44]. The five scores for each domain are from 1 to 5: (1) 'no problems', (2) 'slight problems', (3) 'moderate problems', (4) 'severe problems,' and (5) 'unable to' (mobility, self-care, usual activities) or 'extreme' (pain/discomfort, anxiety/depression) [44]. The scores from the five domains are combined to represent one of a possible 3125 health states [44]. The resulting health state is mapped to EQ-5D-5L index values validated for a UK population using methodology described by Van Hout et al., the preferred measure by NICE for assessing HRQoL [45,46]. Optimum health is given an index score of 1, whilst a negative index value represents a perceived health state worse than death [46]. Secondly, the EQ-visual analog scale (EQ-VAS) asks subjects to rate their overall health on the day of completing the questionnaire. A scale of 0–100 is used, with '0' indicating 'the worst health you can imagine' and '100' indicating 'the best health you can imagine' [44].

The sleep quality scale (SQS) is a questionnaire in which subjects rate their overall sleep quality in the last 7 days [47]. A scale of 0–10 is used, and the following sleep quality categories are formed: terrible (0), poor (1–3), fair (4–6), good (7–9), and excellent (10) [47].

Adverse events were collected at baseline and each follow-up interval through self-reporting, routine follow-up with clinician or direct questioning by the research team. These events and their severity were recorded in accordance with the Common Terminology Criteria for Adverse Events v4.0 [48].

Data were extracted on 23 March 2021. Cases were excluded if baseline PROMs were not completed by the participant or were enrolled in the registry for less than 1 month, providing insufficient opportunity to complete follow-up at 1 month.

2.3. Statistical analysis

Clinicopathological, as well as drug and alcohol data were analyzed using descriptive statistics. Demographic data were represented as the mean (± standard deviation (±SD)) or frequency (%), where appropriate. All other data were tested for normality using the Shapiro–Wilk test. Parametric data were presented as mean (±SD) whilst non-parametric data were presented as median (interquartile range [IQR]). For statistical analysis of PROMs, a paired t-test or the Wilcoxon rank sum test was used depending on whether data were parametric or non-parametric, respectively. PROMs from the 1, 3, and 6-month follow-ups were compared to the baseline scores of the participants included in each of the follow-up dates. Statistical Package for Social Sciences (SPSS) [IBM Statistics version 27 SPSS (New York, IL), USA] was used for the statistical analysis of the data. Statistical significance was defined as p-value<0.050.

3. Results

A total of 103 patients with GAD were recorded in the UK Medical Cannabis Registry at the time of extraction. Only 64 patients were included in the analysis for GAD after 36 patients were excluded for not completing baseline PROMs and 3 patients were excluded for not completing any follow-up data.

The mean age was 37.42 ± 13.01 whilst the female-to-male ratio was 1:2.05. The most frequently recorded occupation was 'unemployed' (n = 25; 39.1%). Twenty-four (37.5%), 28 (43.8%) and 12 (18.8%) patients had a primary, secondary, and tertiary diagnosis of GAD, respectively (Table 1).

Table 1. Demographic details of study participants (n = 64).

Demographic Details	n (%)/mean (± SD)
Sex	
Female	21 (32.8%)
Male	43 (67.2%)
Age (years)	37.42 ± 13.01
Body Mass Index (kg/m^2)	25.12 ± 5.09
Occupation	
Clerical support workers	2 (3.1%)
Elementary occupations	1 (1.6%)
Managers	1 (1.6%)
Plant and machine operators, and assemblers	1 (1.6%)
Professional	24 (37.3%)
Service and sales workers	2 (3.1%)
Skilled agricultural, forestry and fishery workers	1 (1.6%)
Technicians and associate professionals	3 (4.7%)
Other occupations*	29 (45.3%)
Unemployed	25 (39.1%)
Retired	1 (1.6%)
Student	1 (1.6%)

n: number of patients, *SD*: standard deviation, *GAD*: generalized anxiety disorder
*Other Occupations – The occupation was undefined for 2 patients (3.1%).

Table 3. CBMP dosing of study participants (n = 64).

Medication status	Baseline	1 Month	3 Month	6 Month
Number of patients recorded with a prescription	64	51	16	6
Number of patients who did not have recorded prescriptions	0	13	48	58
Median [IQR] CBD dosage (mg)	16.30 [1.00–20.00]	20.00 [2.00–40.00]	15.00 [4.75–50.00]	4.50 [0.00–20.00]
Median [IQR] THC dosage (mg)	13.00 [1.00–23.75]	32.00 [10.00–176.00]	20.50 [10.00–189.50]	28.00 [13.75–50.00]
Number of patients prescribed both THC and CBD (%)	58 (90.6%)	43 (84.3%)	12 (75.0%)	4 (66.7%)
Number of patients prescribed THC alone (%)	4 (6.3%)	6 (11.8%)	3 (18.8%)	2 (33.3%)
Number of patients prescribed CBD alone (%)	2 (3.1%)	2 (3.9%)	1 (6.3%)	0 (0.0%)

IQR: interquartile range, *CBD*: cannabidiol, *THC*: (–)-trans-Δ^9-tetrahydrocannabinol

Thirty-five (54.7%) participants were current cannabis users at the baseline assessment, of which 25 (39.1%) were daily cannabis users (Table 2). The median [IQR] daily cannabis consumption was 0.50 g/day [0.30–1.00].

The median number of CBMPs prescribed at each interval was 2. The majority of patients (n = 58, 90.6%) were prescribed both THC and CBD at the baseline assessment (Table 3). The most commonly prescribed therapy was Adven 50 (Curaleaf, Guernsey, UK). Thirty-six patients (56.2%) were on a medication for mental health disorders at baseline; 29 patients (45.3%) were on antidepressants, 3 patients (4.7%) were on anxiolytics, and 4 patients (6.3%) were on benzodiazepines or hypnotics.

3.1. Patient reported outcome measures

The results show statistically significant improvement in HRQoL at each of the three follow-up dates compared to the baseline data, as measured by the GAD-7, EQ5D-5L Index values, EQ-VAS and SQS ($p < 0.050$) (Table 4). There was also a statistically significant improvement, compared to baseline data, for the EQ-5D-5L Usual Activities and EQ-5D-5L Pain and Discomfort at the 3-month follow-up, and the EQ-5D-5L Anxiety and Depression at the 1, 3, and 6-month follow-ups ($p < 0.050$).

Table 2. Smoking, alcohol and cannabis status of participants.

Smoking, alcohol and cannabis status	n (%)/median [IQR]
Smoking Status	
Current Smoker	15 (23.4%)
Pack Years	8.00 [2.00–10.00]
Ex-Smoker	12 (18.8%)
Pack Years	5.00 [2.00–10.00]
Non-Smoker	33 (51.6%)
Not reported	4 (6.3%)
Weekly Alcohol consumption (units)	1.00 [0.00–5.00]
Cannabis Status	
Current User	35 (54.7%)
Lifetime Quantity of Cannabis Consumption (Gram Years)	4.00 [1.00–6.50]
Current Quantity of Cannabis Consumption (g/day)	0.50 [0.30–1.00]
Ex-User	14 (21.9%)
Lifetime Quantity of Cannabis Consumption (Gram Years)	1.00 [0.40–1.00]
Non-User	14 (21.9%)
Not reported	1 (1.6%)
Frequency of Cannabis Use for Current Users	
Every Day	25 (39.1%)
Every Other Day	4 (6.3%)
1–2 Times Per Week	2 (3.1%)
>1 Times Per Month	1 (1.6%)
Not reported	3 (4.5%)

IQR: interquartile range, *GAD*: generalized anxiety disorder

3.2. Adverse events

Twenty-five (37.3%) adverse events were reported by 25 patients (Table 5). The most reported adverse events were dry mouth (n = 5, 7.5%) and somnolence (n = 4, 6.0%). Events were either mild (n = 13, 19.4%), moderate (n = 10, 14.9%) or severe (n = 1, 1.5%) in severity. Adverse events listed as 'other' were depression (n = 2, 3.0%), diarrhea (n = 2, 3.0%), anxiety (n = 1, 1.5%), paranoia (n = 1, 1.5%) and prolonged bleeding (n = 1, 1.5%). All adverse events were reported as having resolved by the time of the data extraction.

4. Discussion

In this study, HRQoL outcomes, adverse event frequency and dosage regimens of CBMPs were evaluated in a UK patient group with GAD. The results indicate that there may be an association between CBMPs and improved anxiety and HRQoL outcomes in patients with GAD, as measured by improvements up to 6 months compared to baseline scores in validated measures, including GAD-7, EQ-5D-5L Index Value, EQ-VAS and SQS. Adverse events were reported by 37.3% of patients, though most reported events were mild or moderate in severity.

Statistically significant improvement was found for anxiety outcomes at all follow-up dates compared to the baseline scores, as measured by the GAD-7 and EQ-5D-5L anxiety and depression subscale ($p < 0.050$). This is supported by preclinical studies that reported the anxiolytic effects of CBMPs, specifically CBD [49,50]. Whilst there is a paucity of clinical studies investigating the effects of CBMPs in GAD, the results are

Table 4. Paired baseline and follow up patient reported outcome measures.

Patient Reported Outcome Measures	Follow Up	n	Scores at Baseline	Scores at Follow Up	p-value
GAD-7	1 month	64	11.50 [7.00–19.00]	7.00 [4.00–14.00]	<0.001
	3 months	23	17.00 [10.00–21.00]	8.00 [6.00–12.00]	<0.001
	6 months	13	17.00 [14.00–21.00]	6.00 [4.00–12.50]	0.004
EQ-5D-5L Mobility	1 month	64	1.00 [1.00–2.00]	1.00 [1.00–2.00]	0.805
	3 months	23	1.00 [1.00–4.00]	1.00 [1.00–3.00]	0.739
	6 months	13	1.00 [1.00–3.00]	1.00 [1.00–3.00]	0.564
EQ-5D-5L Self Care	1 month	64	1.00 [1.00–2.00]	1.00 [1.00–2.00]	1.000
	3 months	23	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.408
	6 months	13	1.00 [1.00–3.00]	2.00 [1.00–2.50]	1.000
EQ-5D-5L Usual Activities	1 month	64	2.00 [1.00–3.75]	2.00 [1.00–3.00]	0.221
	3 months	23	3.00 [2.00–4.00]	3.00 [2.00–3.00]	0.022
	6 months	13	3.00 [2.50–4.50]	3.00 [1.50–4.00]	0.107
EQ-5D-5L Pain and Discomfort	1 month	64	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.058
	3 months	23	3.00 [2.00–4.00]	2.00 [1.00–3.00]	0.012
	6 months	13	3.00 [1.50–3.50]	2.00 [1.00–3.00]	0.058
EQ-5D-5L Anxiety and Depression	1 month	64	3.00 [2.00–4.00]	3.00 [2.00–3.00]	<0.001
	3 months	23	4.00 [3.00–5.00]	3.00 [2.00–3.00]	0.007
	6 months	13	4.00 [3.00–5.00]	2.00 [2.00–4.00]	0.019
EQ-VAS	1 month	64	50.00 [30.00–74.75]	60.00 [47.50–79.25]	0.005
	3 months	23	30.00 [21.00–50.00]	60.00 [50.00–80.00]	<0.001
	6 months	13	40.00 [20.50–50.00]	65.00 [50.00–80.00]	0.007
EQ-5D-5L Index Value	1 month	64	0.61 [0.29–0.79]	0.63 [0.44–0.82]	0.010
	3 months	23	0.36 [0.06–0.62]	0.59 [0.25–0.77]	0.020
	6 months	13	0.27 [0.09–0.68]	0.53 [0.38–0.86]	0.026
SQS	1 month	63	4.00 [2.00–6.00]	6.00 [4.00–8.00]	<0.001
	3 months	22	2.00 [1.00–5.00]	6.00 [4.75–7.00]	<0.001
	6 months	12	2.00 [1.25–5.00]	6.00 [5.00–7.00]	0.002

n: number of patients, GAD-7: Generalized Anxiety Disorder Scale, EQ-VAS: EQ Visual Analogue Scale, SQS: Sleep Quality Scale

Table 5. Reported adverse events by patients (n = 64).

	Severity of Adverse Event					
Adverse Events	Mild	Moderate	Severe	Life-threatening /disabling	Not Recorded	Total (%)
Other	4	2	0	0	1	7 (10.4%)
Dry mouth	3	1	1	0	0	5 (7.5%)
Somnolence	0	4	0	0	0	4 (6.0%)
Headache	2	0	0	0	0	2 (3.0%)
Constipation	0	1	0	0	0	1 (1.5%)
Dizziness	1	0	0	0	0	1 (1.5%)
Fatigue	0	1	0	0	0	1 (1.5%)
Insomnia	1	0	0	0	0	1 (1.5%)
Muscular weakness	1	0	0	0	0	1 (1.5%)
Nausea	1	0	0	0	0	1 (1.5%)
Vomiting	0	1	0	0	0	1 (1.5%)
Total	13 (19.4%)	10 (14.9%)	1 (1.5%)	0 (0.0%)	1 (1.5%)	25 (37.3%)

comparable to two studies in SAD which demonstrated a reduction in anxiety prior to anxiety provoking events [30,31]. Though the studies on SAD show a similar trend in anxiety improvement, they cannot be used as a direct comparison [30,31]. First, different PROMs were used to asses for changes in self-reported anxiety [30,31]. Second, the participants in those studies had never used CBMPs prior enrollment, whilst the majority of GAD patients in this study were cannabis consumers at baseline (54.7%) [30,31]. This is contrasted by a study by Hser et al. which found improvements in anxiety and sleep following reductions in cannabis consumption. However, this was in the setting of cannabis use disorder [51]. The effects of unregulated illicit cannabis used recreationally are expected to differ from the effects of CBMPs, which are regulated to ensure consistency of product, have lower THC doses and are taken in different settings. A previous analysis of all patients from the UK Medical Cannabis Registry from our group found that improvements were also seen in GAD-7 across all patients treated with CBMPs for several medical conditions [42]. This was not maintained in a narrow analysis of outcomes for chronic pain patients treated with a specific CBMP oil [52]. This deviation may be represented by underlying differences in condition, demographics or indeed the type of CBMP itself. These will all be assessed in future analyses of the registry.

In this study, the GAD patients experienced an improvement in HRQoL as displayed by a statistically significant increase in the EQ-5D-5L index value and EQ-VAS compared to the baseline scores ($p < 0.050$). Whilst this is the first study to detail the effects of CBMPs on HRQoL outcomes in GAD, the results are comparable to the initial study of the Medical Cannabis Registry which reported an increase in mean paired EQ-5D-5L index values and EQ-VAS scores at the 1-month and 3-month follow-ups across a range of conditions [42]. The findings are further supported by a study investigating the effects of CBD in a range of medical conditions, in which CBD resulted in an improvement of the EQ-VAS by 13.6 points [53]. It is worth noting that there was a decrease in median CBD

content from 1 month (20.00 mg) to 6 months (4.50 mg). This may be an incidental finding, especially given the low sample size at 6 months, though it does warrant future studies to investigate the association between CBD dosage and effects of anxiety.

This study suggests that CBMPs are associated with improvements in sleep quality at all time periods compared to baseline for all patient groups. A study by Ware et al. similarly found that nabilone, a synthetic THC analog, resulted in greater improvements to sleep compared to amitriptyline in patients with fibromyalgia [54]. Other studies, however, have had mixed findings for sleep outcomes. One study found that THC in combination with CBD may decrease stage 3 sleep, whilst THC in isolation may decrease sleep latency, measures that reflect sleep quantity and quality [55]. The combined findings may reflect the high degree of heterogeneity in studied CBMPs across studies. Focused study of sleep outcomes using CBMPs, which have shown promise in improving sleep outcomes in preclinical and clinical settings, in a GAD population will therefore be crucial.

To date, no studies have reported the follow-up of adverse events in patients with GAD treated with CBMPs for up to 6 months. A study by Gulbransen et al. investigating CBD in a range of conditions found an adverse event incidence of 9.9% [53], a stark difference to this study which reported adverse events in 37.3% of patients. This difference may reflect the comparatively low adverse event profile of CBD, which was the CBMP of choice in Gulbransen et al.'s study [53], whilst the majority of patients (90.6%) in the GAD group in this study were prescribed a combination of CBD and THC at the baseline assessment. This idea is supported by another study exploring Sativex, a CBMP with a CBD:THC ratio of 1.0:1.1, in subjects with multiple sclerosis-induced refractory epilepsy which found that 46.9% of the patients reported at least one adverse event [56]. The most commonly reported events were dizziness (14%), fatigue (5.9%) and somnolence (5.1%), which was comparable to the reported events in this study [56]. Moreover, the median follow-up duration in the study by Gulbransen et al. was 36 days, though the median for when the adverse events occurred in this study was 50 days after patients first started CBMP treatment, thus the longer interval may have been the reason for the greater number of patients with reported adverse events [53]. An interesting observation from the adverse events of the GAD group was that anxiety and paranoia were each reported by one patient. THC has previously been shown to induce anxiolytic properties at lower doses whilst a higher dose can be anxiogenic, causing anxiety and paranoia [35]. Two seminal studies from 1981 reported that dry mouth, headaches, and drowsiness were commonly reported adverse events following CBMP initiation for GAD, though ultimately long-term studies are warranted in this field [57,58].

Regarding dosing, an RCT with SAD patients comparing a single-dose of oral CBD (150 mg, 300 mg or 600 mg) or placebo, found that CBD displayed an inverted U-shaped dose–response curve in patients with SAD [34]. The 300 mg dose of CBD resulted in lower social anxiety ratings prior to a public speaking test, whereas the higher and lower doses failed to produce an effect [34]. This contrasts to the CBD dose in this study which was substantially lower at each follow-up assessment. This difference may be because most patients were treated with a combination of CBD and THC. However, this study did not investigate a dose-response relationship, so a conclusion cannot be made as to which doses were most effective.

There are inherent limitations to the present study. This is a case-series evaluation with data extraction performed on a discrete date. There is low internal validity due to the lack of blinding or control group, thus the true effect of CBMPs could not be ascertained. The low internal validity was amplified due to the many patients (56.2%) still on other medications, confounding the effect of CBMPs on the studied outcomes. Drug–drug interactions may have resulted in altered efficacy and adverse events. Internal validity was further limited due to the large portion of missing data, which reduced statistical power and introduced attrition bias [59]. Additionally, patients self-funded their treatment that was wholly private. This limited external validity as this population was not reflective of the entire UK population. However, a large proportion of patients (39.1%) were unemployed, suggesting that the cost of treatment did not preclude those of variable socioeconomic backgrounds. The inclusion of patients with a secondary and tertiary diagnosis of GAD was also a potential limitation. Given that the CBMPs were prescribed, and their dosage altered, to treat the primary diagnosis, these regimens may not have targeted their anxiety symptoms. This likely biased the results to the null and therefore understated any apparent effect on anxiety. Finally, retrospective data collection introduces recall bias. Thirty-five patients (54.7%) and 14 patients (21.9%) were ongoing and prior cannabis users, respectively, at the start of the study. This is an important limitation as previous studies have demonstrated a larger effect on HRQoL as measured with PROMs in cannabis naïve patients [52].

Similarly, it is important to be aware of the benefits of the study design. It is one of the first clinical studies investigating the therapeutic effects and adverse events of CBMPs in a sample of the UK population with GAD, which is underresearched in clinical studies. The results from the study can be subsequently used in the design of RCTs, improving efficiency and reducing associated costs of research by targeting specific conditions and CBMP formulations. Registry studies are also important in studying pharmacovigilance in the context of real-world conditions. Moreover, the results are of clinical significance for two reasons. First, questionnaires were self-reported and thus patients are best informed about how they feel and their symptoms. Second, regarding the GAD-7 results specifically, there was a change from severe generalized anxiety (score threshold of 10–15) at the baseline to moderate generalized anxiety (score threshold of 5–10) at each follow-up date.

The future of CBMP research demands RCTs to better identify causality between prescribed CBMP preparations and

outcomes. These must, however, consider the placebo effect garnered using CBMPs, specifically those with a THC concentration high enough to induce the psychoactive effects. This may cause overestimation of the therapeutic effects, and participants may be more alert to the development of adverse events. Future studies aim to investigate the effects of prior and current cannabis use on outcomes with CBMP prescriptions as 35 patients (54.7%) were cannabis users at the start of the study. It is important to distinguish this since prior cannabis use may result in tolerance and thus CBMPs may not provide any clinical benefits [60]. Conversely, these patients may have self-selected themselves as those with positive responses to CBMPs and continue to benefit after switching from unregulated, illicit cannabis. The effects of full-spectrum products versus isolate cannabinoids must also be compared, as full-spectrum products, containing other cannabinoids in addition to terpenes and flavonoids, may result in an altered therapeutic and adverse event profile [61].

5. Conclusion

Results from this study must be interpreted with caution due to the noted limitations, particularly its open-label nature. Nevertheless, this case series is the first of its kind in assessing the follow-up of patients with GAD prescribed CBMPs for up to 6 months. The results suggest that CBMPs may play a role in improving anxiety within the context of GAD, though these are preliminary findings and suggesting causation would be premature. Rather, this study should act as a foundation for future, more robust investigations to explore the topic and as an aid to current clinical practice. It also highlights the potential association between CBMPs and improved general HRQoL in those with GAD, in addition to the low incidence of severe or disabling adverse events associated with treatment for up to 6 months. In addition to comparative analysis of patients within the UK Medical Cannabis Registry on different CBMP prescriptions in the future, it is still essential that randomized controlled trials are performed in earnest to assess for the underlying causality for the associations displayed in this study.

Funding

This paper was not funded.

Declaration of interest

S Erridge has received paid consultancy work at Sapphire Medical Clinics. R Coomber, M Platt, J Rucker and M Sodergren are shareholders at Sapphire Medical Clinics. J Rucker has also received a funded fellowship (CS-2017-17-007) from the National Institute for Health Research (NIHR) and leads the Psychedelic Trials Group at King's College London. King's College London receives grant funding from COMPASS Pathways PLC to undertake phase 1 and phase 2 trials with psilocybin. COMPASS Pathways PLC has paid for J Rucker to attend trial-related meetings and conferences to present the results of research using psilocybin. J Rucker has undertaken paid consultancy work for Beckley PsyTech and Clerkenwell Health. Payments for consultancy work are received and managed by King's College London and J Rucker does not benefit personally. M Sodergren is the research director 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

A reviewer on this manuscript has disclosed that they are a scientific advisor for a cannabis-producing company. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Author contributions

M Ergisi, S Erridge, C Holvey, R Coomber, M Platt, JJ Rucker and MH Sodergren contributed to the study conception and design. M Ergisi, S Erridge, M Harris, M Kawka, D Nimalan, O Salazar, K Loupasaki, R Ali, C Holvey, M Platt and JJ Rucker contributed to the acquisition of data. M Ergisi, S Erridge, JJ Rucker and MH Sodergren contributed to the analysis and interpretation of data. M Harris, S Erridge and MH Sodergren contributed to the drafting of the manuscript. M Ergisi, S Erridge, M Harris, M Kawka, D Nimalan, O Salazar, K Loupasaki, R Ali, C Holvey, R Coomber, M Platt, JJ Rucker and MH Sodergren contributed to critical revision. JJ Rucker reviewed this article and made comments. All of the authors agreed to be accountable for all aspects of the work.

Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS.

Data availability

Data that support the findings of this study are available from the UK Medical Cannabis Registry. Restrictions apply to the availability of these data. Data specifications and applications are available from the corresponding author.

ORCID

Michal Kawka http://orcid.org/0000-0002-5826-8355
James J Rucker http://orcid.org/0000-0003-4647-8088

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 [Internet]. J Psychopharmacol. 2013 [cited 2021 Apr 19];27(9):761–770. Available from. SAGE Publications. /pmc/articles/PMC3778981/
2. Remes O, Wainwright N, Surtees P, et al. Generalised anxiety disorder and hospital admissions: findings from a large, population cohort study. BMJ Open. Internet]. 2018 Oct 1 [cited 2021 Oct 26];8 (10):e018539. Available from https://bmjopen.bmj.com/content/8/10/e018539
3. NHS England. Adult psychiatric morbidity survey: survey of mental health and wellbeing, England. 2016;
4. DeMartini J, Patel G, Fancher TL. Generalized anxiety disorder. Ann Intern Med. Internet]. 2019 Apr 2 [cited 2021 May 14];170(7):ITC49–64. Available from. https://pubmed.ncbi.nlm.nih.gov/30934083/
5. Kroenke K, Spitzer RL, Williams JBW, et al. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med. Internet]. 2007 Mar 6 [cited 2021 Apr 19];146 (5):317–325. Available from. https://pubmed.ncbi.nlm.nih.gov/17339617/
6. 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. Internet]. 2002 [cited 2021 Apr 19];68(2–3):183–190. Available from. https://pubmed.ncbi.nlm.nih.gov/12063146/
7. Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: a meta-analytic review [Internet]. Clin Psychol Rev. 2007 [cited 2021 Apr 19];27(5):572–581. Available from: https://pubmed.ncbi.nlm.nih.gov/17343963/
8. Revicki DA, Travers K, Wyrwich KW, et al. Humanistic and economic burden of generalized anxiety disorder in North America and Europe [Internet]. J Affect Disord. 2012 [cited 2021 May 14];140(2):103–112. Available from: https://pubmed.ncbi.nlm.nih.gov/22154706/
9. National Institute of Health and Care Excellence. Generalized anxiety disorder: scenario: management of a person with generalized anxiety disorder. 2021. [cited 01 July 2021]; Available from: https://cks.nice.org.uk/topics/generalized-anxiety-disorder/management/management/
10. Griebel G, Holmes A. 50 years of hurdles and hope in anxiolytic drug discovery. Nat Publ Gr. 2013. cited 2021 Apr 19]; Available from 2021 Apr 19. Internet: www.nature.com/reviews/drugdisc
11. Slee A, Nazareth I, Bondaronek P, et al. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019 Feb 23 [cited 2021 May 21];393(10173):768–777. Available from: http://www.thelancet.com/article/S0140673618317938/fulltext
Network meta-analysis of the efficacy of curent pharmacological treatments for generalised anxiety disorder
12. Skelley JW, Deas CM, Curren Z, et al. Use of cannabidiol in anxiety and anxiety-related disorders. J Am Pharm Assoc. 2020;60(1):253–261. Elsevier B.V.
A review outlining the use of CBD in anxiety and anxiety-related disorders.
13. Papagianni EP, Stevenson CW. Cannabinoid regulation of fear and anxiety: an update. Curr Psychiatry Rep. 2019;21(6):1. Current Medicine Group LLC
14. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis [Internet]. JAMA. 2015 [cited 2021 May 3];313(24):2456–2473.Available from. American Medical Association. https://pubmed.ncbi.nlm.nih.gov/26103030/
15. Hanuš LO, Meyer SM, Muñoz E, et al. Phytocannabinoids: a unified critical inventory [Internet]. Nat Prod Rep Royal Society of Chemistry. 2016 [cited 2021 May 4];33(12):1357–1392. Available from: https://pubmed.ncbi.nlm.nih.gov/27722705/
16. Baron EP. Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it's been … [Internet]. Headache. Blackwell Publishing Inc. 2015[cited 2021 May 4]; 55:885–916. Available from. https://pubmed.ncbi.nlm.nih.gov/26015168/
17. Elsaid S, Kloiber S, Le Foll B. Effects of cannabidiol (CBD) in neuropsychiatric disorders: a review of pre-clinical and clinical findings. In: Progress in Molecular Biology and Translational Science [Internet]. Elsevier B.V.; 2019 [cited 2021 May 4]. p. 25–75. Available from: https://pubmed.ncbi.nlm.nih.gov/31601406/
18. Condie R, Herring A, Koh WS, et al. Cannabinoid inhibition of adenylate cyclase-mediated signal transduction and interleukin 2 (IL-2) expression in the murine T-cell line, EL4.IL-2. J Biol Chem. Internet]. 1996 [cited 2021 May 17];271(22):13175–13183. Available from. https://pubmed.ncbi.nlm.nih.gov/8662742/
19. Klumpers LE, Thacker DL. A brief background on cannabis: from plant to medical indications. J AOAC Int. Internet]. 2019 Mar 1 [cited 2021 May 17];102(2):412–420. Available from. https://pubmed.ncbi.nlm.nih.gov/30139415/
20. Fusar-Poli P, Crippa J, Bhattacharyya S, et al. Distinct effects of A9-Tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry. Internet]. 2009 Jan [cited 2021 May 5];66(1):95–105. Available from. https://pubmed.ncbi.nlm.nih.gov/19124693/
21. Ebbert JO, Scharf EL, Hurt RT. Medical Cannabis [Internet]. Mayo Clin Proc Elsevier Ltd. 2018 [cited 2021 May 4];93(12):1842–1847. Available from: https://pubmed.ncbi.nlm.nih.gov/30522595/
22. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system [Internet]. Int J Mol Sci. 2018 [cited 2021 May 17]. Available from 2021 May 17];19(3): 833. MDPI AG. https://pubmed.ncbi.nlm.nih.gov/29533978/
23. Elmes MW, Kaczocha M, Berger WT, et al. Fatty acid-binding proteins (FABPs) are intracellular carriers for Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). J Biol Chem. Internet]. 2015 Apr 3 [cited 2021 Oct 26];290(14):8711–8721. Available from. https://pubmed.ncbi.nlm.nih.gov/25666611/
24. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. Internet]. 2001 [cited 2021 Oct 26];134(4):845–852. Available from. https://pubmed.ncbi.nlm.nih.gov/11606325/
25. Blessing EM, Steenkamp MM, Manzanares J, et al. Cannabidiol as a potential treatment for anxiety disorders [Internet]. Neurotherapeutics Springer New York LLC. 2015 [cited 2021 May 4];12(4):825–836. Available from: https://pubmed.ncbi.nlm.nih.gov/26341731/
26. Englund A, Morrison PD, Nottage J, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol. Internet]. 2013 Jan 5 [cited 2021 May 4];27(1):19–27. Available from. []; ():.
27. Dalton WS, Martz R, Lemberger L, et al. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. Clin Pharmacol Ther. Internet]. 1976 [cited 2021 May 4];19(3):300–309. Available from. https://pubmed.ncbi.nlm.nih.gov/770048/
28. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. Internet]. 2010 Feb [cited 2021 May 4];35(3):764–774. Available from. https://pubmed.ncbi.nlm.nih.gov/19924114/
29. 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 Internet]. 2019 Dec 1 [cited 2021 May 18];6(12):995–1010. Available from. http://www.thelancet.com/article/S2215036619304018/fulltext
30. Bergamaschi MM, Queiroz RHC, Chagas MHN, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-nave social phobia patients. Neuropsychopharmacology. Internet]. 2011 May [cited 2021 May 5];36(6):1219–1226. Available from. https://pubmed.ncbi.nlm.nih.gov/21307846/
31. Crippa JAS, Nogueira Derenusson G, Borduqui Ferrari T, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol. Internet]. 2011 Jan [cited 2021 May 18];25(1):121–130. Available from. https://pubmed.ncbi.nlm.nih.gov/20829306/
32. Klimkiewicz A, Jasinska A. The health effects of cannabis and cannabinoids. Psychiatria. Internet]. 2018 Jun 27 [cited 2021 May 5];15(2):88–92. Available from. https://pubmed.ncbi.nlm.nih.gov/28182367/
33. De Souza Crippa JA, Zuardi AW, Garrido GEJ, et al. Effects of Cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology Internet]. 2004 Oct 29 [cited 2021 May 5];29(2):417–426. Available from. http://www.acnp.org/
34. Linares IM, Zuardi AW, Pereira LC, et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. Rev Bras Psiquiatr Internet]. 2019 Jan 1 [cited 2021 May 18];41(1):9–14. Available from. https://pubmed.ncbi.nlm.nih.gov/30328956/
35. Zuardi AW, Shirakawa I, Finkelfarb E, et al. Action of cannabidiol on the anxiety and other effects produced by δ9-THC in normal subjects. Psychopharmacology (Berl). Internet]. 1982 Mar [cited 2021 May 5];76(3):245–250. Available from. https://pubmed.ncbi.nlm.nih.gov/6285406/

36. Häuser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management – an overview of systematic reviews [Internet]. European Journal of Pain (United Kingdom). Blackwell Publishing Ltd. 2018[cited 2021 May 4]; 22 (3):455–470. Available from. https://pubmed.ncbi.nlm.nih.gov/29034533/
37. Montero-Oleas N, Arevalo-Rodriguez I, Nuñez-González S, et al. Therapeutic use of cannabis and cannabinoids: an evidence mapping and appraisal of systematic reviews. BMC Complement Med Ther. Internet]. 2020 Dec [cited 2021 May 4];20(1). Available from. https://pubmed.ncbi.nlm.nih.gov/32020875/
38. 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. J Clin Epidemiol. Internet]. 2008 Apr [cited 2021 Apr 26];61(4):344–349. Available from. https://pubmed.ncbi.nlm.nih.gov/18313558/
39. Medicines and Healthcare products Regulatory Agency. The supply of unlicensed cannabis-based products for medicinal use in humans. 2020. [cited 01 July 2021]; Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/869284/Cannabis_Guidance__unlicensed_CBPMs__updated_2020.pdf
40. Brusselaers N, Lagergren J. The charlson comorbidity index in registry-based research: which version to use? Methods Inf Med. Internet]. 2017 [cited 2021 Apr 26];56(5):401–406. Available from. https://pubmed.ncbi.nlm.nih.gov/29582935/
41. Quan H, Li B, Couris CM, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol Internet]. 2011 Mar 15 [cited 2021 Apr 26];173(6):676–682. Available from. https://pubmed.ncbi.nlm.nih.gov/21330339/
42. Erridge S, Salazar O, Kawka M, et al., An initial analysis of the UK medical cannabis registry: outcomes analysis of first 129 patients. Neuropsychopharmacol Reports. 41(3): 362–370. 2021.
The first study reporting data from the Medical Cannabis Registry.
43. Löwe B, Decker O, Müller S, et al. Validation and standardization of the generalized anxiety disorder screener (GAD-7) in the general population. Med Care. Internet]. 2008 Feb [cited 2021 Apr 26];46 (3):266–274. Available from. https://pubmed.ncbi.nlm.nih.gov/18388841/
44. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. Internet]. 2011 Dec [cited 2021 May 4];20(10):1727–1736. Available from. https://pubmed.ncbi.nlm.nih.gov/21479777/
45. National Institute for Health and Care Excellence. Position statement on the use of the EQ-5D-5L value set for england. 2019;
46. 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 Heal. Internet]. 2012 Jul [cited 2021 May 4];15(5):708–715. Available from. https://pubmed.ncbi.nlm.nih.gov/22867780/
47. 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. Internet]. 2018 Nov 15 [cited 2021 Apr 26];14(11):1849–1857. Available from. /pmc/articles/PMC6223557/
48. Trotti A, Colevas AD, Setser A, et al. Seminars in radiation oncology [Internet]. May 10 2003; Available from:https://pubmed.ncbi.nlm.nih.gov/12903007/
49. Guimarães FS, Chiaretti TM, Graeff FG, et al. Antianxiety effect of cannabidiol in the elevated plus-maze. Psychopharmacology (Berl). Internet]. 1990 Apr [cited 2021 May 18];100(4):558–559. Available from. https://pubmed.ncbi.nlm.nih.gov/1969666/
50. Onaivi ES, Green MR, Martin BR. Pharmacological characterization of cannabinoids in the elevated plus maze. J Pharmacol Exp Ther. 1990;253(3):1002–1009.
51. Hser YI, Mooney LJ, Huang D, et al. Reductions in cannabis use are associated with improvements in anxiety, depression, and sleep quality, but not quality of life. J Subst Abuse Treat. Internet]. 2017 Oct 1 [cited 2021 Oct 26];81:53–58. Available from. https://pubmed.ncbi.nlm.nih.gov/28847455/
52. 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. J Clin Pharmacol. 2021 Oct 5 [cited 2021 Oct 26]; Available from 2021 Oct 26];61(12):1545–1554. Internet: https://pubmed.ncbi.nlm.nih.gov/34473850/
53. Gulbransen G, Xu W, Arroll B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. BJGP Open Internet]. 2020 [cited 2021 May 3];4(1). Available from:1010. https://pubmed.ncbi.nlm.nih.gov/32019776/
A study which is referenced to compare to the health-related quality of life and adverse events data of this study
54. Ware MA, Fitzcharles MA, Joseph L, et al. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg. Internet]. 2010 [cited 2021 May 18];110(2):604–610. Available from. https://pubmed.ncbi.nlm.nih.gov/20007734/
55. Nicholson AN, Turner C, Stone BM, et al. Effect of Δ-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. J Clin Psychopharmacol. Internet]. 2004 Jun [cited 2021 May 18];24(3):305–313. Available from. https://pubmed.ncbi.nlm.nih.gov/15118485/
56. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol. Internet]. 2011 Sep [cited 2021 May 18];18(9):1122–1131. Available from. https://pubmed.ncbi.nlm.nih.gov/21362108/
57. Glass RM, Uhlenhuth EH, Hartel FW, et al. Single-dose study of nabilone in anxious volunteers. J Clin Pharmacol. Internet]. 1981 [cited 2021 May 18];21(S1). Available from.;():383S–396S. https://pubmed.ncbi.nlm.nih.gov/6117576/
58. Fabre LF, McLendon D. The efficacy and safety of Nabilone (A Synthetic Cannabinoid) in the treatment of anxiety. J Clin Pharmacol. Internet]. 1981 Aug 9 [cited 2021 May 18];21 (S1):377S–382S. Available from. https://pubmed.ncbi.nlm.nih.gov/6117575/
59. Kang H. The prevention and handling of the missing data [Internet]. Korean J Anesthesiol Korean Society of Anesthesiologists. 2013 [cited 2021 May 14];64(5):402–406. Available from: /pmc/articles/PMC3668100/
60. Ramaekers JG, Van Wel JH, Spronk DB, et al. Cannabis and tolerance: acute drug impairment as a function of cannabis use history. Sci Rep. Internet]. 2016 May 26 [cited 2021 May 18];6(1):1–9. Available from.;(). www.nature.com/scientificreports
61. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects [Internet]. Br J Pharmacol. 2011 [cited 2021 May 18];163:1344–1364. Available from: https://pubmed.ncbi.nlm.nih.gov/21749363/