Expert Review of Neurotherapeutics

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

Assessment of clinical outcomes in patients with post-traumatic stress disorder: analysis from the UK Medical Cannabis Registry

Manaswini Pillai, Simon Erridge, Lara Bapir, Martha Nicholas, Nishaanth Dalavaye, Carl Holvey, Ross Coomber, Daniela Barros, Urmila Bhoskar, Gracia Mwimba, Kavita Praveen, Chris Symeon, Simmi Sachdeva-Mohan, James J Rucker & Mikael H Sodergren

EXPERT REVIEW OF NEUROTHERAPEUTICS
https://doi.org/10.1080/14737175.2022.2155139

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS
Check for updates

Assessment of clinical outcomes in patients with post-traumatic stress disorder: analysis from the UK Medical Cannabis Registry

Manaswini Pillai[a], Simon Erridge[a,b], Lara Bapir[a], Martha Nicholas[a], Nishaanth Dalavaye[a], Carl Holvey[b], Ross Coomber[b,c], Daniela Barros[b], Urmila Bhoskar[b], Gracia Mwimba[b], Kavita Praveen[b], Chris Symeon[b], Simmi Sachdeva-Mohan[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]Department of Medicine, Sapphire Medical Clinics, London, UK; [c]Department of Trauma & Orthopaedics, 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

Background: The current paucity of clinical evidence limits the use of cannabis-based medicinal products (CBMPs) in post-traumatic stress disorder (PTSD). This study investigates health-related quality of life (HRQoL) changes and adverse events in patients prescribed CBMPs for PTSD.
Methods: A case-series of patients from the UK Medical Cannabis Registry was analyzed. HRQoL was assessed at 1-, 3-, and 6-months using validated patient reported outcome measures (PROMs). Adverse events were analyzed according to the Common Terminology Criteria for Adverse Events version 4.0. Statistical significance was defined as $p < 0.050$.
Results: Of 162 included patients, 88.89% (n = 144) were current/previous cannabis users. Median daily CBMP dosages were 5.00 (IQR: 0.00–70.00) mg of cannabidiol and 145.00 (IQR: 100.00–200.00) mg of Δ9-tetrahydrocannabinol. Significant improvements were observed in PTSD symptoms, sleep, and anxiety across all follow-up periods ($p < 0.050$). There were 220 (135.8%) adverse events reported by 33 patients (20.37%), with the majority graded mild or moderate in severity (n = 190, 117.28%). Insomnia and fatigue had the greatest incidence (n = 20, 12.35%).
Conclusions: Associated improvements in HRQoL were observed in patients who initiated CBMP therapy. Adverse events analysis suggests acceptability and safety up to 6 months. This study may inform randomized placebo-controlled trials, required to confirm causality and determine optimal dosing.

ARTICLE HISTORY
Received 23 August 2022
Accepted 1 December 2022

KEYWORDS
Cannabidiol; tetrahydrocannabinol; post-traumatic stress disorder; PTSD; medical cannabis

1. Introduction

Post-traumatic stress disorder (PTSD) is a debilitating condition defined by over 1 month of symptoms following trauma exposure, causing significant distress or functional impairment [1]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), symptoms are categorized into four subgroups of intrusions, avoidance, altered mood, and altered reactivity [1]. These may manifest as flashbacks, trigger avoidance, hyperarousal, depressive symptoms, and nightmares. PTSD affects between 5% and 10% of the population during their lifetimes [2] and is associated with other psychiatric disorders and physical health conditions [3–5]. Hence, there is a high socio-economic cost owing to increased reliance on health and social care, loss of productivity and impaired leisure activities [6].

Management of PTSD involves a biopsychosocial approach, with psychotherapy being the mainstay at present, although long-term effectiveness remains unclear [7,8]. The data on pharmacotherapy suggest that selective serotonin reuptake inhibitors (SSRIs) are not appropriate first-line agents if sustained long-term symptom improvement is intended [7]. Side-effects such as agitation may explain why SSRIs are poorly tolerated, since hyperarousal is a common symptom of PTSD [9]. Other pharmacological options that have also been evaluated for the treatment of PTSD include prazosin, an alpha-1 adrenoceptor antagonist [10], trazodone, a serotonin receptor antagonist and reuptake inhibitor [11], and agomelatine, a melatonin antagonist [12]. However, these have demonstrated variable efficacy. As such, there is a need for continued research into novel PTSD therapies that offer long-term symptom relief and minimal side-effects.

Cannabis-based medicinal products (CBMPs) have been suggested as a potential pharmacotherapeutic option to address this need. Cannabis plants, such as *Cannabis sativa*, contain two major phytocannabinoids: cannabidiol (CBD) and (−)-trans -Δ9-tetrahydrocannabinol (Δ9-THC), among other potentially active pharmaceutical ingredients [13]. Δ9-THC is a partial agonist of G-protein coupled receptors of the endocannabinoid system, cannabinoid receptors 1 and 2 (CB1/CB2), whilst CBD is a noncompetitive negative modulator of CB1 via allosteric binding [14]. CBD also acts by inhibiting fatty acid binding proteins required for cellular uptake of anandamide; this prevents the breakdown of the endocannabinoid by fatty acid amino hydrolase

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

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14737175.2022.2155139

[15]. CB1 receptors are concentrated in the central nervous system, particularly the presynaptic terminals in the cerebellum, basal ganglia, and hippocampus [16]. Agonism leads to the inhibition of gamma-aminobutyric acid (GABA) and glutamate neurotransmitter release [16]. This is one mechanism that mediates the cognitive, emotional, memory, and psychoactive effects of Δ9-THC [17].

Further effects of cannabinoids are mediated by non-CB1/2 targets such as peroxisome proliferator-activated receptors, transient receptor potential vanilloid type 1 (TRPV1), and serotonin (5-HT) receptors [18]. In vitro studies have shown that CBD is a 5-HT3 negative allosteric modulator and indirectly activates 5-HT1a receptors [19,20]. This may explain the anxiolytic effects of CBD, since 5-HT1a receptors from the median raphe nucleus can mediate fear extinction, whilst 5-HT3 receptors have anxiogenic effects [21]. As a result, CBD can counter the anxiogenic effects of the psychotomimetic component Δ9-THC [22]. TRPV1 receptors are found in relevant brain areas such as the dorsal periaqueductal gray matter, to facilitate anxiogenic responses via glutamate release [23]. CBD activates and desensitizes these receptors, whilst indirectly increasing levels of anandamide, which is also a TRPV1 agonist [23]. These mechanisms have been demonstrated to reduce learned fear expression and anxiety within *in vivo* models given CBD [22,23].

The key neurobiological changes witnessed in PTSD include structural synaptic enhancement in the amygdala during fear consolidation, leading to hypothalamic–pituitary–adrenal axis (HPA) stimulation via the paraventricular nucleus, and decreased connectivity to the ventromedial prefrontal cortex (vmPFC) [18,24]. This leads to greater emotional memory expression and reduced fear extinction to both threatening and non-threatening stimuli in PTSD [25]. CBMPs may counter these changes as demonstrated by preclinical evidence of enhanced amygdala-vmPFC connectivity [26,27], increased fear extinction retention [28], and alleviated PTSD sleep disturbances within *in vitro* and *in vivo* assessments of their effects [18,29].

At present, available evidence on CBMPs and PTSD is conflicting and difficult to synthesize owing to the use of selective cohorts, methodological heterogeneity, and underpowered studies. Whilst certain studies have reported significantly reduced PTSD symptom severity, improved sleep, and minimal adverse events (AEs), these were often limited due to small cohorts, short-term follow-up, and potential confounding from other psychotropic drug use [29–31]. Conversely, a longitudinal observational study of 2,276 veterans being treated in specialized PTSD programs found medical cannabis worsened violent behavior and substance use disorders [32]. Since excessive recreational cannabis consumption is shown to be associated with impaired fear extinction and downregulation of CB1 receptors, there is a need for long-term investigation [33].

The UK Medical Cannabis Registry (UKMCR) collects prospective data regarding outcome measures for patients receiving CBMP prescriptions in the UK. This paper analyzes the patient-reported outcome measures (PROMs) and AE data of PTSD patients prescribed CBMPs within the UKMCR, with the aim of identifying effects on health-related quality of life (HRQoL) and safety of use.

2. Methods

2.1. Study design

This study reports a case-series of patients diagnosed with PTSD, enrolled in the UKMCR. Patients provided written consent upon registration into the UKMCR, prior to baseline data collection. Formal ethical approval was not required for this study following guidance from the Health Research Authority. This paper is reported in line with strengthening the reporting of observational studies in epidemiology guidelines for observational studies [34].

2.2. Setting and participants

The UKMCR is the first UK patient registry to prospectively collect anonymized data regarding CBMP prescription formulations, patient demographics, PROMs, and AEs [35]. It was created in 2019 and is privately managed by the Sapphire Medical Clinics [35]. Participants are enrolled consecutively and asked to provide informed consent. The only screening criterion is whether participants have been prescribed CBMPs. Patients from the UKMCR were included in the analysis if PTSD was the primary indication for CBMP treatment. Exclusion criteria extended to those with incomplete baseline PROMs data and those who had started treatment less than 1-month prior to the date of data extraction and therefore had not reached the first follow-up milestone. There were no further exclusion criteria. The date of data extract from the UKMCR was 15 February 2022.

2.3. Data collection

Patient demographics completed on registration included age, gender, occupation, and body mass index (BMI). Data collected by clinicians during the initial consultation included medical history covering comorbidities such as those within the Charlson comorbidity index (CCI), and recreational and prescription drug use. The CCI is a validated measure of both short- and long-term mortality, widely used for identifying confounding due to comorbidities [36]. Scores 5 or above represent severe comorbidity, associated with 85% 1-year mortality [36]. Further recorded comorbidities include hypertension, depression and/or anxiety, arthritis, epilepsy, venous thromboembolism, and endocrine dysfunction. Secondary and tertiary indications for CBMP treatment were also recorded.

Recreational drug data included tobacco status, pack years, alcohol units consumed per week, previous cannabis status, and associated 'gram years.' This metric was calculated from weekly grams of cannabis and number of years of use, to assess the effects of both quantity and duration, as previously described by our group [35]. Patient prior cannabis exposure at the time of enrollment was classified into three categories of 'never used,' 'ex-user,' and 'current user.' Prescription drug data recorded included total daily dosage, start date, and, where relevant, end date; this allowed for identification of dosage changes/discontinuation following CBMP commencement.

This data was completed electronically by patients or contemporaneously by clinicians during initial clinical consultation. If information was still outstanding following clinical encounter, patients were contacted by members of the clinical and/or research team to complete missing data fields. CBMP details were recorded electronically from linked prescription data, detailing the formulation, relative Δ9-THC and CBD doses, strains, and route of administration. The dose of each CBMP was determined by multiplication of the concentration (mg/ml or mg/g) and the daily dose prescribed (ml/day or g/day). For both concentration and daily dose, some prescriptions are given within a range (e.g. 190–210 mg/g for concentration and 0.25–0.75 g/day for dose). Where present, the median value was taken (e.g. 200 mg/g and 0.50 g/day in the above example).

2.4. Outcome measures

Primary outcome measures analyzed were changes in PROMs from baseline to 1-, 3- and 6-month follow-up. Secondary outcomes were to analyze incidence of AEs and their severities.

The PROMs administered to all patients with PTSD include the Impact of Events Scale-Revised (IES-R), EQ-5D-5L, Single-Item Sleep Quality Scale (SQS), Generalized Anxiety Disorder-7 (GAD-7) and Patient Global Impression of Change (PGIC). Baseline questionnaire responses were recorded upon registration, with patients prompted to repeat surveys at follow-up periods, with 72-hourly reminders. Responses were completed using a remote electronic platform.

The IES-R is a 22-item questionnaire rating how distressing post-trauma difficulties had been in the past week, on a scale from 0 (not at all) to 4 (extremely). It is one of the most commonly used traumatic stress self-reporting measures [37]. It has been validated for a range of trauma etiologies [38]. Questions relate to three key PTSD symptom groups – hyperarousal, avoidance, and intrusions. A score of 24–32 signifies clinical concern for partial PTSD, 33 is considered the most probable cutoff for PTSD diagnosis [37]. Scores above 37 are at a severity that has demonstrated physiological effects, such as inducing immunosuppression [39]. Both test–retest reliability and internal consistency have been confirmed with scores of 0.89–0.94 and Cronbach's alpha = 0.95, respectively [40]. The scale also scored highly for validity and ease of use in clinical practice [38].

The EQ-5D-5L is the HRQoL measure recommended by the National Institute for Health and Care Excellence (NICE) [41,42]. Patients report current problems experienced in five domains on a scale ranging from ‘no problems’ (1) to ‘extreme problems’ (5). The domains consist of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores form a unique five-digit health state that can be translated into country-specific index values, wherein 1 represents perfect health, 0 represents HRQoL equivalent to death, and scores below 0 signify HRQoL worse than death [42]. Intraclass correlation coefficients of 0.65–0.91 in a previous analysis have demonstrated test–retest reliability of EQ-5D-5L for patients with PTSD [43].

The SQS utilizes a numerical rating scale from 0 (terrible) to 10 (excellent), to aid patients in self-assessing sleep quality over the past 7 days [44]. It benefits from more rapid sleep assessment than other common and lengthy questionnaires, such as the Pittsburgh Sleep Quality Index, whilst also demonstrating validity through strong correlations to these other scores [44].

GAD-7 evaluates seven aspects of generalized anxiety by the number of days they were experienced in the past fortnight. Each item is scored from 0 (‘not at all’) to 3 (‘nearly every day’), forming a total out of 21. Severity is assessed using cutoff scores at 5, 10, and 15, respectively, representing mild, moderate, and severe GAD [45]. The GAD-7 Cronbach’s value in a heterogeneous psychiatric sample ranged from a = 0.83–0.93, and it has been validated for several anxiety disorders, including PTSD [46].

The PGIC assesses perceived change since starting treatment in terms of activity limitations, symptoms, emotions, and overall quality of life, through two parts. The first (PGIC1) uses a seven-point scale from 1 (‘no change’) to 7 (‘a great deal better’), whilst the second (PGIC2) is a visual analog scale from 0 (‘much better’) to 10 (‘much worse’) [47]. This self-reported measure has been shown to correlate well with the clinician-administered version [48].

Adverse events data were recorded following the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE), to allow comprehensive reporting and grading comparable to other studies [49]. Severity is graded using unique clinical descriptions specific to each AE. Patients are prompted to self-report AEs remotely during completion of their PROMs. Clinicians can also update any AEs reported during clinical consultations.

2.5. Statistical analysis

All data were extracted from the UKMCR and the analysis was completed using Statistical Package for Social Sciences (SPSS) [IBM Statistics version 28 SPSS (New York, IL), USA]. Descriptive statistics were used to analyze demographic variables, drug and alcohol history, and frequency of adverse events reported. Analysis of PROMs consisted of comparisons between baseline data and PROMs at 1-, 3-, and 6-month follow-up. Sub-group analyses were also conducted according to prior cannabis exposure and gender. Initially, a Shapiro–Wilk test was used to determine the normality of data sets. Parametric data were analyzed using the student paired t-test, whilst the Wilcoxon rank-sum test was used if non-parametric. Effect sizes (r) were calculated for the Wilcoxon rank-sum test by dividing the Z-value by the square root of the number of participants (n) [50]. r values of 0.5, 0.3, and 0.1 indicate large, medium, and small effect sizes as described by Coolican [50]. Mean change in PROMs from baseline was compared between males and females using the independent samples t-test. Statistical significance was defined by p-values <0.050 and data were reported as mean ± standard deviation (±SD) or median and interquartile range (IQR) if parametric or non-parametric, respectively.

3. Results

3.1. Patient demographics

There were 162 patients identified from the UKMCR who met the inclusion criteria. The cohort had a mean age of 37.62

Table 1. Number of prescriptions within PTSD-related drug classes, with changes to prescriptions following commencement of CBMP treatment displayed.

Medication	Total	No Change	Stopped Taking	Reduced Dose	Increased Dose	New Medication
Antidepressants, n (%)	124	114 (91.94%)	10 (8.06%)	1 (0.81%)	3 (2.42%)	4 (3.23%)
Benzodiazepines, n (%)	28	27 (96.43%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (3.57%)
Insomnia-related, n (%)	14	14 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

(±9.85) years with a greater proportion of males (n = 97, 59.88%). Median BMI was 25.50 (22.80–31.20) kg/m^2. Half (n = 81; 50.00%) of the cohort were unemployed, with 67 (41.36%) employed and 14 (8.64%) of unspecified employment status. Median CCI score was 0.00 (0.00–0.00). The recorded incidence of the six further comorbidities was anxiety/depression (n = 108, 66.67%), arthritis (n = 16, 9.88%), endocrine dysfunction (n = 7, 4.47%), epilepsy (n = 3, 1.85%), hypertension (n = 7, 4.32%), and venous thromboembolism (n = 0, 0.00%).

Seventy-one (43.83%) patients had a secondary indication for CBMP prescription, of which anxiety was the most common (n = 39, 24.07%), as shown in Supplementary Table 1. Tertiary indications were present for 42 (25.93%) participants and largely consisted of depression (n = 18, 11.11%) and insomnia (n = 10, 6.17%).

Details of prior tobacco, alcohol, and cannabis consumption were recorded. Tobacco history was recorded for 125 (77.16%) patients, of whom 65 (40.12%) were current smokers, 60 (37.04%) were ex-smokers and 37 (22.84%) had never smoked. Median pack years of all smokers was 10.00 (4.00–19.50). With respect to alcohol consumption, the majority of the participants did not consume alcohol (n = 103, 63.58%), whilst 35.19% (n = 57) and 1.23% (n = 2) reported that they consumed alcohol or did not report their alcohol status, respectively. Median alcohol consumption per week was 0.00 (0.00–2.00) units. Most patients (n = 122, 75.31%) were current cannabis consumers at the point of starting treatment, whilst 13.58% (n = 22) were ex-users and 11.11% (n = 18) were cannabis naïve. Among current users, median cannabis gram years were 10.00 (2.43–25.00) and most patients were daily users (n = 103, 63.58%). The remaining patients reported use every other day (n = 10, 6.17%), 1–2 times per week (n = 7, 4.32%) and more or less than once per month (both n = 1, 0.62%).

3.2. Prescription data

Data on current prescriptions were available for 147 (90.74%) patients. There were 411 active CBMP prescriptions in total, with a median of 2.00 (2.00–3.00) prescriptions per patient. The most common CBMP therapies for oils were Adven 20 THC and Adven 50 CBD, and for flower was Adven EMT1 19% THC (Curaleaf International, Guernsey, UK). At the point of data extraction, median total daily dosages were 5.00 (0.00–70.00) mg of CBD and 145 (100.00–200.00) mg of Δ9-THC. Eighty patients (49.38%) used only flower inhaled by a vaporizer device. The remaining either administered via oral/sublingual use only (n = 19, 11.73%), or a combination of oral/sublingual preparations and inhaled flower (n = 48, 29.63%). For the latter using both oils and dried flower, median daily doses for oils were 45.00 (0.00–100.00) mg of CBD and 14.00 (10.00–20.00) mg of Δ9-THC and median daily doses for dried flower were 2.00 (0.00–5.00) mg of CBD and 137.50 (100.00–200.00) mg of Δ9-THC.

Regarding other prescribed medications, there were 424 active prescriptions, covering 147 different medications, for 118 patients (72.84%). Details of benzodiazepine, antidepressant, and insomnia-related prescriptions are displayed in Table 1. The most common medications included sertraline (n = 26, 16.05%), diazepam (n = 20, 12.35%) and quetiapine (n = 20, 12.35%). Following CBMP treatment, 10 (8.06%) patients previously prescribed antidepressants and 1 (3.57%) patient prescribed a benzodiazepine discontinued these medications.

3.3. Health-related quality of life

Analysis of paired baseline and follow-up PROMs is displayed in Table 2. Statistically significant improvements were seen in all domains of the IES-R, and both GAD7 and SQS, at all lengths of follow-up ($p < 0.050$). The EQ-5D-5L index score and both 'usual activities' and 'anxiety and/or depression' subscales also improved significantly at all follow-ups ($p < 0.050$). Significant improvements in the 'self-care' and 'pain and discomfort' subscales were seen at 1- and 3-month follow-up and the 'mobility' subscale at 3-months only ($p < 0.050$). There was a large effect size ($r = 0.50$) for the IES-R hyperarousal score at 3-month follow-up. All other IES-R and GAD7 scores had medium effect sizes. PGIC1 median scores were consistently 6.00 (5.00–6.00) at 1-, 3-, and 6-month follow-up, whilst median PGIC2 was 3.00 (2.00–3.00) at 1- and 3-month follow-up, and 2 (1.00–3.00) at 6-months (n = 128, 93, and 51 respectively).

Subgroup analysis of changes in the IES-R subscales and total score according to baseline cannabis status is displayed in Supplementary Table 2. Reductions in IES-R scores were demonstrated at all follow-up periods for the 'current user' group ($p < 0.001$), and at up to 6-month follow-up for the 'ex-user' group ($p < 0.050$). No significant improvements were seen in IES-R for the 'never used' group. Comparison in change in PROMs between the genders demonstrated a significant difference in only the SQS score at 3-month follow-up, where males had greater improvement ($p = 0.037$). Full details of gender subgroup analysis are displayed in Supplementary Table 3.

3.4. Adverse events

A total of 220 (135.80%) AEs were reported by 33 patients (20.37%) across 38 categories displayed in Table 3. The majority of AEs were either mild (n = 100, 61.73%) or moderate (n = 90, 55.56%) in severity, with no life-threatening/disabling events reported. Insomnia and fatigue both had the highest

Table 2. Change in PROMs from baseline to follow-up at 1-, 3-, and 6-months. Reported as median (IQR) *p < 0.050, **p < 0.010, ***p < 0.001.

PROM	Followup month	n	Baseline Score median (IQR)	Follow-up Score median (IQR)	p-value	T-test statistic	Z-score	Effect size (r)
IES-R	1-month	127	19.00 (14.00–23.00)	16.00 (11.00–20.00)	<0.001***	5386.00	−4.82	−0.30
Avoidance	3-months	88	18.00 (14.00–22.00)	11.50 (6.25–17.00)	<0.001***	2976.00	−5.60	−0.42
	6-months	45	18.00 (13.50–21.00)	12.00 (7.00–16.50)	<0.001***	662.00	−3.80	−0.40
IES-R	1-month	127	23.00 (18.00–27.00)	15.00 (10.00–22.00)	<0.001***	6111.00	−6.74	−0.42
Intrusions	3-months	88	22.50 (17.00–26.75)	13.00 (6.25–19.00)	<0.001***	3219.50	−6.40	−0.48
	6-months	45	19.00 (12.00–23.50)	11.00 (5.00–17.00)	<0.001***	845.00	−4.49	−0.47
IES-R	1-month	127	18.00 (14.00–21.00)	12.00 (8.00–16.00)	<0.001***	6422.00	−7.07	−0.44
Hyperarousal	3-months	88	18.00 (12.00–20.00)	10.00 (5.25–15.00)	<0.001***	3200.50	−6.62	−0.50
	6-months	45	16.00 (9.50–19.00)	8.00 (5.00–14.00)	<0.001***	778.00	−4.10	−0.43
IES-R	1-month	127	59.00 (49.00–68.00)	44.00 (30.00–57.00)	<0.001***	6775.50	−6.76	−0.42
Total Score	3-months	88	58.00 (43.50–65.00)	34.00 (18.50–50.00)	<0.001***	3317.00	−6.53	−0.49
	6-months	45	56.00 (37.00–62.50)	32.00 (20.50–48.50)	<0.001***	914.50	−4.48	−0.47
EQ-5D-5L	1-month	133	1.00 (1.00–3.00)	1.00 (1.00–2.00)	0.300	507.50	−1.04	−0.06
Mobility	3-months	94	1.00 (1.00–3.00)	1.00 (1.00–2.00)	0.009**	275.00	−2.61	−0.19
	6-months	51	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.134	75.00	−1.50	−0.15
EQ-5D-5L	1-month	133	3.00 (2.00–4.00)	2.00 (1.50–3.00)	<0.001***	2802.00	−5.03	−0.31
Usual Activities	3-months	94	3.00 (2.00–3.00)	2.00 (1.00–3.00)	<0.001***	1695.00	−4.91	−0.36
	6-months	50	3.00 (1.00–3.00)	2.00 (1.00–2.25)	0.012*	369.00	−2.52	−0.25
EQ-5D-5L	1-month	133	2.00 (1.00–3.00)	2.00 (1.00–2.00)	0.044*	892.00	−2.02	−0.12
Self Care	3-months	94	2.00 (1.00–3.00)	1.00 (1.00–2.00)	0.017*	429.50	−2.39	−0.17
	6-months	50	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.334	50.50	−0.97	−0.10
EQ-5D-5L	1-month	133	3.00 (1.00–3.00)	2.00 (1.00–3.00)	<0.001***	1594.00	−3.40	−0.21
Pain and Discomfort	3-months	94	2.00 (1.00–3.00)	2.00 (1.00–3.00)	<0.001***	933.00	−3.80	−0.28
	6-months	50	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.584	168.50	−0.55	−0.05
EQ-5D-5L	1-month	133	4.00 (3.00–4.00)	3.00 (2.00–4.00)	<0.001***	3433.00	−6.05	−0.37
Anxiety and Depression	3-months	94	3.00 (3.00–4.00)	2.50 (2.00–3.00)	<0.001***	1841.00	−5.17	−0.38
	6-months	50	3.00 (2.00–4.00)	3.00 (2.00–3.00)	0.003**	464.00	−2.93	−0.29
EQ-5D-5L	1-month	133	0.42 (0.21–0.66)	0.59 (0.41–0.74)	<0.001***	6014.00	−6.01	−0.37
Index Value	3-months	94	0.51 (0.25–0.72)	0.71 (0.51–0.77)	<0.001***	3298.00	−5.58	−0.41
	6-months	50	0.59 (0.35–0.81)	0.69 (0.54–0.77)	0.024*	807.50	−2.25	−0.23
GAD7	1-month	133	15.00 (11.50–19.00)	8.00 (5.00–13.50)	<0.001***	6773.50	−7.73	−0.47
	3-months	94	15.00 (8.75–18.00)	7.00 (4.00–11.00)	<0.001***	3364.50	−6.74	−0.49
	6-months	50	13.50 (6.00–18.00)	7.00 (4.00–9.25)	<0.001***	965.50	−4.25	−0.43
SQS	1-month	133	3.00 (2.00–5.00)	6.00 (3.00–7.00)	<0.001***	5720.50	−6.69	−0.41
	3-months	94	3.50 (2.00–5.00)	5.00 (4.00–7.25)	<0.001***	2561.00	−5.10	−0.37
	6-months	50	4.00 (2.75–6.00)	6.00 (4.00–7.00)	0.037*	730.50	−2.09	−0.21

incidence among AEs (n = 20, 12.35%), followed by headache (n = 15; 9.26%), dry mouth (n = 15; 9.26%), and concentration impairment (n = 14; 8.64%). Median duration of AEs, where calculated, ranged from 1.00 to 10.50 days, with one case of severe paranoia lasting 75 days.

4. Discussion

This observational study found an association between initiation of CBMPs by patients with PTSD and improvements in PROMs administered from baseline to 3-month follow-up. PROMs covered several domains including specific PTSD symptom groups (intrusions, avoidance, hyperarousal), HRQoL, sleep quality, and anxiety. Further significant improvement at 6-month follow-up was demonstrated for all IES-R subscales, GAD7, SQS, and EQ-5D-5L index value scores ($p < 0.050$). AEs were reported by 20.37% of the cohort and were mainly mild or moderate, with insomnia and fatigue the most incident. No life-threatening/disabling AEs were reported.

Improvement in PTSD symptoms across follow-up was demonstrated by the validated IES-R ($p < 0.050$). At 3- and 6-month follow-up, IES-R total scores neared the 33-point threshold for PTSD diagnosis, compared to baseline scores above 50. This aligns with previously published findings. One retrospective study found over 75% reduction in clinician-assessed PTSD burden, with notable improvements in avoidance, hyperarousal, and reexperiencing criteria [51]. Cahill *et al*. demonstrated similar improvements in PTSD symptoms after 6-week CBMP treatment [52]. However, whilst 81.25% self-reported improvement, 18.75% of patients experienced deterioration, indicating greater variability in response to CBMP treatment [52]. Such variation could affect cohorts with greater proportions of cannabis-naive participants compared to our present study population, wherein 88.89% were current/previous cannabis users at baseline. On sub-group analysis, it was shown that the current/ex-user patients continued to report improved outcomes compared to baseline ($p < 0.050$), suggesting that there are supplementary benefits of CBMPs with respect to therapeutic efficacy above illicitly obtained cannabis and that these effects are not negated by pharmacological tolerance. Conversely, LaFrance *et al*. reported up to 67% short-term PTSD symptom reduction with cannabis self-medication, but no sustained long-term benefit [53]. Patients required increasing quantities of cannabis to achieve symptom relief, suggesting tolerance to its effects [53]. Potential reasons for contrasting results include methodological heterogeneity such as outcome measure timing, irregular patterns of use due to self-medication, patient self-identification with PTSD without verification of diagnosis, and single-item questions instead of validated PROM scales. Further evaluation of change in CBMP doses over time and correlation with clinical outcomes will be required to answer this question.

Table 3. Incidence of all adverse events (AE) reported by patients (n = 33), classed by severity groups of mild, moderate, severe, and life-threatening/disabling (LT/D). Total values are reported as incidence n (%). Average duration of each AE is reported as median (IQR).

Adverse Events	Mild	Moderate	Severe	LT/D	Total n(%)	Median Duration, days
Abdominal pain (upper)	-	1	-	-	1 (0.62%)	5.00
Amnesia	3	2	-	-	5 (3.09%)	7.00 (5.00–11.00)
Anorexia	1	4	1	-	6 (3.70%)	7.00 (4.50–90.00)
Anxiety	2	1	2	-	5 (3.09%)	7.00 (1.00–42.00)
Arthritis	-	-	1	-	1 (0.62%)	7.00
Ataxia	3	1	-	-	4 (2.47%)	4.50 (2.00–7.00)
Blurred vision	3	1	-	-	4 (2.47%)	2.00 (1.25–5.75)
Cognitive Disturbance	3	2	2	-	7 (4.32%)	7.00 (7.00–14.00)
Confusion	3	3	1	-	7 (4.32%)	7.00 (1.00–7.00)
Concentration impairment	8	4	2	-	14 (8.64%)	6.00 (3.00–7.00)
Constipation	2	-	-	-	2 (1.23%)	2.50
Delirium	2	1	-	-	3 (1.85%)	7.00
Decreased Weight	6	2	-	-	8 (4.94%)	9.00 (3.25–49.75)
Diarrhea	1	-	-	-	1 (0.62%)	2.00
Distorted thoughts	-	1	-	-	1 (0.62%)	1.00
Dizziness	2	4	2	-	8 (4.94%)	2.00 (1.00–7.00)
Dry mouth	14	-	-	-	14 (8.64%)	7.00 (3.75–15.50)
Dysgeusia	2	-	1	-	3 (1.85%)	30.00
Dyspepsia	4	-	-	-	4 (2.47%)	1.00 (1.00–5.50)
Fatigue	8	10	2	-	20 (12.35%)	5.00 (3.00–7.00)
Headache	8	6	1	-	15 (9.26%)	4.00 (1.00–7.00)
Insomnia	3	10	7	-	20 (12.35%)	6.00 (4.25–10.00)
Intrusive thoughts	1	-	-	-	1 (0.62%)	0.00
Irritability	-	2	-	-	2 (1.23%)	3.50
Lethargy	8	5	-	-	13 (8.02%)	7.00 (4.00–9.50)
Muscular Weakness	3	1	1	-	5 (3.09%)	2.00 (1.50–5.50)
Nausea	3	5	1	-	9 (5.56%)	6.00 (2.50–8.50)
Nightmares	-	-	2	-	2 (1.23%)	5.00
Paranoia	-	-	1	-	1 (0.62%)	75.00
Pharyngitis	-	4	-	-	4 (2.47%)	10.50 (2.00–49.75)
Pyrexia	1	-	-	-	1 (0.62%)	1.00
Rash	1	1	-	-	2 (1.23%)	17.50
Respiratory Infection	-	1	-	-	1 (0.62%)	7.00
Somnolence	-	12	1	-	13 (8.02%)	4.00 (3.50–7.00)
Spasticity	2	-	-	-	2 (1.23%)	2.50
Tremor	2	2	-	-	4 (2.47%)	5.50 (3.25–16.00)
Vertigo	1	3	1	-	5 (3.09%)	2.00 (1.00–33.50)
Vomiting	-	1	1	-	2 (1.23%)	3.50
Total	**100 (61.73%)**	**90 (55.56%)**	**30 (18.52%)**	**0 (0.00%)**	**220 (135.80%)**	

During this study, patients were prescribed regimens with higher Δ9-THC doses compared to CBD. Previous studies have suggested that higher proportions of Δ9-THC:CBD regimens result in optimum PTSD outcomes [52,54,55]. Rabinak *et al*. conducted a randomized controlled trial (RCT) wherein Δ9-THC administration reduced threat-responses and emotional expression, by increasing amygdala-vmPFC connectivity [56]. This may explain the preference toward higher Δ9-THC ratio preparations, though multi-arm RCTs are required to confirm the optimal dose and route of administration of CBMPs in PTSD. Sub-group analysis by gender revealed no significant differences in PROMs improvement. This aligns with analysis from Bolsoni et al., demonstrating no difference in responses of PTSD patients to trauma recall following CBD administration [57]. Whilst some pre-clinical studies have reported sex differences in anti-depressant effects of CBD and there are known neurobiological sex-differences in PTSD, there is little clinical evidence at present [58]. The use of gender rather than sex in this study, however, could limit analysis with respect to sex-differences.

Anxiolytic effects were suggested through improvements in both the GAD-7 and EQ-5D-5L 'anxiety and depression' subscale ($p < 0.050$). This is in line with previous analyses of all patients, and those with GAD, in the UKMCR [35,59]. Reductions in GAD-7 scores represent changes in symptom burden from 'severe' to 'mild' GAD. In this way, the diverse targets of CBMPs may be particularly beneficial in PTSD patients with co-existing anxiety, since anxiety was a non-primary indication for 27.16% and a recorded comorbidity for 66.67% of the cohort. These findings are corroborated by a case series of CBD use for anxiety/sleep disorders [60], and an observational study reporting significantly greater anxiety reduction in medicinal cannabis users over control 'non-users' at 3-month follow-up ($p < 0.001$) [61]. Studies specifically regarding PTSD mirror these improvements [52,54,62]. Anxiolytic effects of CBMPs have been explained by the aforementioned prevention of anandamide hydrolysis by CBD, as well as agonism at serotonin-1a and transient receptor potential vanilloid type 1 receptors in pertinent brain regions such as the median raphe nucleus and dorsal periaqueductal gray matter, respectively, [15–18]. Contrastingly, a secondary analysis of cannabis use disorder highlighted significant improvement in anxiety and depression with cannabis use reduction ($p < 0.050$) [63]. Whilst CBMPs differ from recreational cannabis in their often-lower Δ9-THC concentrations, regulated composition, and reduced variability [64], and there are inherent differences between patients with cannabis use disorder, further investigation is required to assess the therapeutic window for CBMPs prescribed for PTSD.

Reductions in symptom burden, reflected by EQ-5D-5L index values ($p < 0.050$), corroborate HRQoL improvements from other analyses of the UKMCR [35,59], and a similar Canadian registry analysis [52]. Le *et al*. determined the minimal clinically important difference in EQ-5D-5L index values for PTSD to range from 0.03 to 0.05 [65]. As such, calculated median increases of 0.10–0.20 represent important patient HRQoL benefit. Improved 'usual activities' subscale scores corroborate a reported 59% reduction in social and family life impacts for military and police veterans [66]. Benefits to both patients and their partners, outlined by a qualitative focus group study, further exemplify this broad impact on HRQoL [67]. Both studies also highlight medication reductions as meaningful patient outcomes. This is evidenced herein by high PGIC scores and 8.87% of patients prescribed antidepressants either discontinuing or reducing dosage. Regarding 'pain and discomfort' subscale improvements, clinical data suggest comorbid chronic pain affects up to 80% of PTSD patients owing to similar neurobiological vulnerabilities and mutual maintenance underpinning the two [68,69]. Alongside existing evidence indicating CBMP utility in chronic pain, this may provide a further indication for medical cannabis in PTSD [29,52,61,62,66]. Subgroup analysis of those with comorbid chronic pain could elucidate any particular benefit from CBMP therapy.

Regarding sleep quality, significant improvements across follow-ups ($p < 0.050$) add to the existing body of research demonstrating beneficial associations of CBMPs with sleep quality [31], insomnia [29] and nightmares [70,71] in PTSD. These fall within the core PTSD symptoms of hyperarousal and intrusions, and as such, is a clinically relevant finding in most patients [72]. Effective treatment is paramount since sleep quality has been identified as both a predicting factor for PTSD development and a perpetuating factor that impacts overall outcomes [72]. This has been linked to two main theorized mechanisms. One relates nightmares to increased waking due to respiratory disturbances and aberrant limb movements [72,73]. The second implicates memory processing in the hippocampus and cerebral cortex during sleep; fearful memories may be continuously reactivated and preferentially consolidated due to the neuroendocrine and inflammatory responses elicited [72,73]. CBMPs could be effective in countering both mechanisms, via suppression of wakeful phenomena, and promotion of extinction learning through impaired aversive memories retrieval [73]. However, cannabinoid effects on sleep are complex. Nicholson *et al*. suggested that Δ9-THC alone does not affect polysomnography and led to greater morning sleepiness, but in combination with CBD, caused fewer awakenings [74]. Assessment of wakefulness suggested that Δ9-THC had sedating effects and CBD alerting effects [74]. However, this placebo-controlled trial involved eight healthy individuals, so the small sample size and population background may limit application to PTSD pathology. Therefore, optimal dosage to alleviate sleep disturbance in PTSD, while balancing sedative and alerting effects must be determined.

The need to identify the optimal dosage is exemplified further when examining AE incidence. Largely mild or moderate severity AEs were reported with resolution within 10.50 days, suggesting safety of use. The AE incidence of 135.80% was greater than the 57.94% reported in a prior study by Cahill et al., though in both studies, the same proportion (20%) of patients reported AEs [52]. This may be partially explained by protocol differences as patients were asked to select a side effect they had experienced from a predetermined list of 17, not allowing for a broad range of adverse events, such as those reported by participants in the present study. The frequency and types of AEs are comparable to other studies wherein sedation/sleepiness and dry mouth were the most common [29,52]. As aforementioned, this could be a consequence of high Δ9-THC contents, which exert sedating effects [74]. Tolerance to Δ9-THC effects following chronic use has been suggested to cause insomnia, though longer-term analysis is required to evaluate risks/incidence of tolerance [75]. Moreover, insomnia is a common sequalae of PTSD and therefore may be misattributed as an AE, rather than secondary to the underlying disease.

In contrast to the present study, Bonn-Miller *et al*. reported a higher frequency of patients experiencing AEs (60.8–61.7%), consisting mainly of cough, throat irritation, and anxiety [54]. The lack of such bronchopulmonary AEs in this study, despite 79.01% of patients using vaporizer devices, may relate to the different compositions of vaporized and smoked cannabis [76]. A large proportion of patients with previous cannabis exposure may have developed tolerance to some AEs, or found these more acceptable. However, these AEs could affect the acceptability of treatment if extended to a cannabis-naive cohort. Interestingly, Jetly *et al*. found a higher proportion of patients experienced AEs when receiving placebo compared to the synthetic cannabinoid nabilone, drawing into question whether all reported AEs are treatment-related, though this would only cause an overestimation of AEs [71]. As such, AEs analyzed suggest safety and acceptability, though confirmation through larger RCTs with extended follow-up is necessary.

Limitations should be considered when interpreting findings. Firstly, the observational study design prevents causality determination owing to the lack of placebo control and blinding, which increase reporting bias due to the subjective nature of PROMs [54]. Cannabis exerts greater placebo effects due to societal impressions, shown to affect previous users most due to the expectancy of effect, highlighting the need for placebo-controlled trials [77]. However, effective blinding in CBMP research can be difficult to achieve, and observational studies provide cost-effective, real-world evidence to support confirmation through future RCTs [78]. Secondly, whilst biometric and socioeconomic demographics were similar to national PTSD surveys [79], the cohort was not generalizable due to selection bias evident in the proportion of previous/current cannabis users. This increases the likelihood of overstated benefits and underrepresentation of AEs, as reflected in the subgroup analysis of IES-R changes by cannabis status [80]. Finally, a follow-up beyond 6-months was not possible due to limited PROMs data. The decreased sample size at consecutive follow-ups represents both fewer patients having completed longer-term treatment, and loss to follow-up. Moreover, the limited availability of CBD and THC dose at each follow-up time period limits the analysis further. This is especially true of analyzing the effects of cannabis-naïve populations, for which only five patients had completed 6-months of follow-up. The resulting attrition bias could have predisposed toward positive findings.

5. Conclusion

This observational study suggests an association between CBMP treatment and improvement in PTSD-specific, HRQoL, sleep, and anxiety outcomes at up to 6-month follow-up ($p < 0.050$). Treatment safety assessed via AE incidence demonstrated minimal severity and no life-threatening events, in line with evidence from similar patient cohorts. Alongside positive changes in PROMs, this suggests CBMPs were well-tolerated and adverse events manageable. Moreover, patients with previous exposure to cannabis continue to benefit after initiating treatment with CBMPs. However, owing to limitations discussed in this study, definitive conclusions on efficacy or causality are limited and results should be interpreted considering the subjectivity of PROMs. Nevertheless, this study can serve to inform future randomized placebo-controlled trials with the aim of confirming these promising effects, whilst informing current clinical practice. Future work should also focus on including objective measures, determining optimal dosages and conducting comparisons to existing treatments to better inform prescribing of add-on or sole CBMP therapy.

Declaration of interests

S Erridge, C Holvey, R Coomber, JJ Rucker, and MH Sodergren are the founding clinicians of Sapphire Medical Clinics, which is the first clinic registered with the CQC to evaluate patients for medical cannabis in England. R Coomber and MH Sodergren are directors at Sapphire Medical Clinics. S Erridge undertakes paid consultancy work at Sapphire Medical Clinics. C Holvey, D Barros, U Bhoskar, G Mwimba, K Praveen, C Symeon, S Sachdeva-Mohan, and JJ Rucker are employees of Sapphire Medical Clinics. MH Sodergren is also Chief Medical Officer at Curaleaf International. JJ Rucker is funded by a fellowship (CS-2017-17-007) from the National Institute for Health Research (NIHR). 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.

Authors' contributions

Conception and design of the study – M Pillai, S Erridge, JJ Rucker, MH Sodergren. Acquisition of data – M Pillai, S Erridge, L Bapir, M Nicholas, N Dalavaye, C Holvey, R Coomber, D Barros, U Bhoskar, G Mwimba, K Praveen, C Symeon, S Sachdeva-Mohan, JJ Rucker. Analysis and interpretation of the data – M Pillai, S Erridge, JJ Rucker, MH Sodergren. Drafting of the paper – M Pillai, S Erridge, L Bapir, M Nicholas, N Dalavaye, JJ Rucker, MH Sodergren. Critical revisions for intellectual content – M Pillai, S Erridge, L Bapir, M Nicholas, N Dalavaye, C Holvey, R Coomber, D Barros, U Bhoskar, G Mwimba, K Praveen, C Symeon, S Sachdeva-Mohan, JJ Rucker, MH Sodergren. All authors have approved the final version to be published and agree to be accountable for all aspects of the work.

Reviewer disclosures

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

Funding

This paper was not funded.

Data availability statement

Data that support the findings of this study are available from the UK Medical Cannabis Registry (https://ukmedicalcannabisregistry.com/). Restrictions apply to the availability of these data. Data specifications and applications are available from the corresponding author.

Ethical approval

In the UK, formal ethics approval is not required for research database analysis as detailed by the UK Health Research Authority.

Patient consent

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

Previous publication

This original paper has not been previously published or simultaneously submitted for publication elsewhere. The data have been presented as a poster at the International Cannabinoid Research Society Conference, 2022.

ORCID

Mikael H Sodergren http://orcid.org/0000-0002-7141-3924

References

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

(1) American Psychiatric Association. Trauma and stressor-related disorders. *Diagnostic and statistical manual of mental disorders (5th ed.)*. 2013.
2. Yehuda R, Hoge CW, McFarlane AC, et al. Post-traumatic stress disorder. Nat Rev Dis Primers. 2015;1(1):15057.
3. Sareen J. Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. Can J Psychiatry. 2014;59(9):460–467 [cited Aug 1 2022]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4168808/
4. Edmondson D, Kronish IM, Shaffer JA, et al. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. Am Heart J. 2013;166(5):806–814.
5. Song H, Fang F, Tomasson G, et al. Association of stress-related disorders with subsequent autoimmune disease. JAMA. 2018;319 (23):2388–2400.
6. McGowan I. The economic burden of PTSD. A brief review of salient literature. Int J Psychiatry Ment Health. 2019; 20–26. DOI:10.36811/ijpmh.2019.110003.
7. Merz J, Schwarzer G, Gerger H. Comparative efficacy and acceptability of pharmacological, psychotherapeutic, and combination treatments in adults with posttraumatic stress disorder: a network meta-analysis. JAMA psychiatry. 2019;76(9):904–913.
8. Bisson JI, Roberts NP, Andrew M, et al. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. Cochrane Database Syst Rev. 2013;12:CD003388.
9. Etten MLV, Taylor S. Comparative efficacy of treatments for post-traumatic stress disorder: a meta-analysis. Clin Psychol Psychother. 1998;5(3):126–144.
10. De Berardis D, Marini S, Serroni N, et al. Targeting the noradrenergic system in posttraumatic stress disorder: a systematic review and meta-analysis of prazosin trials. Curr Drug Targets. 2015;16 (10):1094–106.
11. Berardis D, Fornaro M, Ventriglio A, et al. Trazodone add-on in COVID-19-related selective serotonin reuptake inhibitor-resistant

post-traumatic stress disorder in healthcare workers: two case reports. Clin Psychopharmacol Neurosci. 2021;19(4):780–785.
12. De Berardis D, Conti CM, Marini S, et al. Is there a role for agomelatine in the treatment of anxiety disorders? A review of published data. Int J Immunopathol Pharmacol. 2013;26(2):299–304. 3.
13. Andre CM, Hausman J, Guerriero G. Cannabis sativa: the plant of the thousand and one molecules. Front Plant Sci. 2016;7:19. DOI:10.3389/fpls.2016.00019
14. Laprairie RB, Bagher AM, Kelly ME, et al. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 2015;172(20):4790–4805.
15. 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. 2015;290(14):8711–8721.
16. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci. 2018;19(3):833.
- **comprehensive review of endocannabinoid signalling within the central nervous system and action of phyto- and endocannabinoids**
17. Kumar RN, Chambers WA, Pertwee RG. Pharmacological actions and therapeutic uses of cannabis and cannabinoids. Anaesthesia. 2001;56(11):1059–1068.
18. Hill MN, Campolongo P, Yehuda R, et al. Integrating endocannabinoid signaling and cannabinoids into the biology and treatment of posttraumatic stress disorder. Neuropsychopharmacol. 2018;43(1):80–102.
19. Campos AC, Moreira FA, Gomes FV, et al. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. Philos Trans R Soc B. 2012;367(1607):3364–3378.
20. Rock EM, Bolognini D, Limebeer CL, et al. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT(1A) somatodendritic autoreceptors in the dorsal raphe nucleus. Br J Pharmacol. 2012;165(8):2620–2634.
21. Silvestro S, Schepici G, Bramanti P, et al. Molecular targets of cannabidiol in experimental models of neurological disease. Molecules. 2020;25(21):10.3390/molecules25215186.
22. Papagianni EP, Stevenson CW. Cannabinoid regulation of fear and anxiety: an update. Curr Psychiatry Rep. 2019;21(6):38.
23. Melas PA, Scherma M, Fratta W, et al. Cannabidiol as a potential treatment for anxiety and mood disorders: molecular targets and epigenetic insights from preclinical research. Int J Mol Sci. 2021;22(4):1863.
24. Ressler KJ, Berretta S, Bolshakov VY, et al. Post-traumatic stress disorder: clinical and translational neuroscience from cells to circuits. Nat Rev Neurol. 2022;1–16. doi: 10.1038/s41582-022-00635-8.
25. Mechoulam R, Parker LA. The endocannabinoid system and the brain. Annu Rev Psychol. 2013;64(1):21–47.
26. Rabinak CA, Angstadt M, Lyons M, et al. Cannabinoid modulation of prefrontal-limbic activation during fear extinction learning and recall in humans. Neurobiol Learn Mem. 2014;113:125–134
- **Detailing fear extinction via cannabinoids, the proposed mechanism of action through which cannabinoids have been identified as a novel therapeutic for post-traumatic stress disorder**
27. Dincheva I, Drysdale AT, Hartley CA, et al. FAAH genetic variation enhances fronto-amygdala function in mouse and human. Nat Commun. 2015;6(1):6395.
28. Rabinak CA, Angstadt M, Sripada CS, et al. Cannabinoid facilitation of fear extinction memory recall in humans. Neuropharmacology. 2013;64(1):396–402.
29. Cameron C, Watson D, Robinson J. Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: a retrospective evaluation. J Clin Psychopharmacol. 2014;34(5):559–564.
30. Elms L, Shannon S, Hughes S, et al. Cannabidiol in the treatment of post-traumatic stress disorder: a case series. J Altern Complement Med. 2019;25(4):392–397.
31. Roitman P, Mechoulam R, Cooper-Kazaz R, et al. Preliminary, open-label, pilot study of add-on oral Δ9-tetrahydrocannabinol in chronic post-traumatic stress disorder. Clin Drug Investig. 2014;34(8):587–591.
32. Wilkinson ST, Stefanovics E, Rosenheck RA. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with PTSD. J Clin Psychiatry. 2015;76(9):1174–80.
33. Hirvonen J, Goodwin RS, Li C, et al. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. Mol Psychiatry. 2012;17(6):642–649.
34. 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. Int J Surg. 2014;12(12):1495–1499.
35. 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;41(3):362–370.
36. Roffman CE, Buchanan J, Allison GT. Charlson comorbidities index. J Physiother. 2016;62(3):171.
37. Creamer M, Bell R, Failla S. Psychometric properties of the impact of event scale—Revised. Behav Res Ther. 2003;41(12):1489–1496.
38. Bowen-Salter H, Kernot J, Baker A, et al. Self-reported outcome measures for adults with post-traumatic stress disorder: towards recommendations for clinical practice. Aust J Psychol. 2021;73(3):282–292.
39. Kawamura N, Kim Y, Asukai N. Suppression of cellular immunity in men with a past history of posttraumatic stress disorder. Am J Psychiatry. 2001;158(3):484–486.
40. Steel JL, Dunlavy AC, Stillman J, et al. Measuring depression and PTSD after trauma: common scales and checklists. Injury. 2011;42(3):288–300.
41. *Position statement on use of the EQ-5D-5L value set for England (updated October 2019) | Technology appraisal guidance | NICE guidance | Our programmes | What we do | About*. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l [cited 2022 Apr 28].
42. van Hout B, Janssen MF, Feng Y, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708–715.
43. Dams J, Rimane E, Steil R, et al. Reliability, validity and responsiveness of the EQ-5D-5L in assessing and valuing health status in adolescents and young adults with posttraumatic stress disorder: a randomized controlled trail. Psychiatr Q. 2021;92(2):459–471.
44. 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. 2018;14(11):1849–1857.
45. Spitzer RL, Kroenke K, Williams JBW, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Internal Med. 2006;166(10):1092–1097.
46. Johnson SU, Ulvenes PG, Øktedalen T, et al. Psychometric properties of the General Anxiety Disorder 7-item (GAD-7) scale in a heterogeneous psychiatric sample. Front Psychol. 2019;10:1473. DOI:10.3389/fpsyg.2019.01713.
47. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther. 2004;27(1):26–35.
48. Swanenburg J, Gruber C, Brunner F, et al. Patients' and therapists' perception of change following physiotherapy in an orthopedic hospital's outpatient clinic. Physiother Theory Pract. 2015;31(4):293–298.
49. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003;13(3):176–181.
50. Coolican H. Research methods and statistics in psychology. 7th ed. London: Routledge; 2018.

51. Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico medical cannabis program. J Psychoactive Drugs. 2014;46(1):73–77.
52. Cahill SP, Lunn SE, Diaz P, et al. Evaluation of patient reported safety and efficacy of cannabis from a survey of medical cannabis patients in Canada. Front Public Health. 2021;9. DOI:10.3389/fpubh.2021.626853.
53. LaFrance EM, Glodosky NC, Bonn-Miller M, et al. Short and long-term effects of cannabis on symptoms of post-traumatic stress disorder. J Affect Disord. 2020;274 298–304. DOI:10.1016/j.jad.2020.05.132.
54. Bonn-Miller MO, Sisley S, Riggs P, et al. The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: a randomized cross-over clinical trial. PloS One. 2021;16(3): e0246990.
55. Loflin MJE, Babson K, Sottile J, et al. A cross-sectional examination of choice and behavior of veterans with access to free medicinal cannabis. Am J Drug Alcohol Abuse. 2019;45(5):506–513.
56. Rabinak CA, Blanchette A, Zabik NL, et al. Cannabinoid modulation of corticolimbic activation to threat in trauma-exposed adults: a preliminary study. Psychopharmacology (Berl). 2020;237 (6):1813–1826.
57. Bolsoni LM, Crippa JAS, Hallak JEC, et al. The anxiolytic effect of cannabidiol depends on the nature of the trauma when patients with post-traumatic stress disorder recall their trigger event. Rev Bras psiquiatr (Sao Paulo, Brazil: 1999). 2022;44(3):298–307.
58. Matheson J, Bourgault Z, Le Foll B. Sex differences in the neuropsychiatric effects and pharmacokinetics of cannabidiol: a scoping review. Biomolecules. 2022;12(10):1462.
59. 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;15 (4):487–495.
    - **Case series of outcomes for people prescribed medical cannabis for generalised anxiety disorder in the UK.**
60. Shannon S, Lewis N, Lee H, et al. Cannabidiol in anxiety and sleep: a large case series. Perm J. 2019;23(1):18–41.
61. Martin EL, Strickland JC, Schlienz NJ, et al. Antidepressant and anxiolytic effects of medicinal cannabis use in an observational trial. Front Psychiatry. 2021;12:729800.
62. Drost L, DeAngelis C, Lam H, et al. Efficacy of different varieties of medical cannabis in relieving symptoms in post-traumatic stress disorder (PTSD) patients. J Pain Manage. 2017;10(4):415–422.
63. Hser Y, 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. 2017;81:53–58.
64. Baratta F, Simiele M, Pignata I, et al. Cannabis-based oral formulations for medical purposes: preparation, quality and stability. Pharmaceuticals. 2021;14(2):171.
65. Le QA, Doctor JN, Zoellner LA, et al. Minimal clinically important differences for the EQ-5D and QWB-SA in Post-traumatic Stress Disorder (PTSD): results from a Doubly Randomized Preference Trial (DRPT). Health Qual Life Outcomes. 2013;11(59):10.1186/1477-7525-11–59.
66. Smith P, Slaven M, Shaw E, et al. Medical cannabis use in military and police veterans diagnosed with post-traumatic stress disorder (PTSD). J Pain Manage. 2017;10(4):397–405.
67. Krediet E, Janssen DG, Heerdink ER, et al. Experiences with medical cannabis in the treatment of veterans with PTSD: results from a focus group discussion. Eur Neuropsychopharmacol. 2020;36:244–254.
68. Otis JD, Keane TM, Kerns RD. An examination of the relationship between chronic pain and post-traumatic stress disorder. J Rehabil Res Dev. 2003;40(5):397–405.
69. Asmundson GJG, Coons MJ, Taylor S, et al. PTSD and the experience of pain: research and clinical implications of shared vulnerability and mutual maintenance models. Can J Psychiatry. 2002;47 (10):930–937.
70. Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). CNS Neuroscience & Therapeutics. 2009;15(1):84–88. *CNS neuroscience & therapeutics.*
71. Jetly R, Heber A, Fraser G, et al. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology. 2015;51:51 585–8.
72. Lancel M, van Marle HJF, Van Veen MM, et al. Disturbed sleep in PTSD: thinking beyond nightmares. Front Psychiatry. 2021;12:767760.
73. Mamelak M. Nightmares and the Cannabinoids. Curr Neuropharmacol. 2020;18(8):754–768.
74. Nicholson AN, Turner C, Stone BM, et al. Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. J Clin Psychopharmacol. 2004;24(3):305–313.
75. Babson KA, Sottile J, Morabito DC. Cannabinoids, and sleep: a review of the literature. Curr Psychiatry Rep. 2017;19(4):23.
76. Loflin M, Earleywine M. No smoke, no fire: what the initial literature suggests regarding vapourized cannabis and respiratory risk. Can J Respir Ther. 2015;51(1):7–9.
77. Loflin MJE, Earleywine M, Farmer S, et al. Placebo effects of edible cannabis: reported intoxication effects at a 30-minute delay. J Psychoactive Drugs. 2017;49(5):393–397.
78. Casarett D. The achilles heel of medical cannabis research-inadequate blinding of placebo-controlled trials. JAMA Intern Med. 2018;178(1):9–10.
79. Fear NT, Bridges S, Hatch S, et al. Posttraumatic stress disorder. In: NHS Digital, editor,Adult psychiatric morbidity survey 2014. England: Government Office; 2016. p. 106–130.
80. Kluzek S, Dean B, Wartolowska KA. Patient-reported outcome measures (PROMs) as proof of treatment efficacy. BMJ Evid Based Med. 2022;27(3):153–155.