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Review article

# Medicinal cannabis in the management of anxiety disorders: A systematic review

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ABSTRACT

*Background:* With rising anxiety disorder diagnoses, many individuals are seeking alternatives to standard pharmacotherapies, like medicinal cannabis. This systematic review focuses exclusively on anxiety-related disorders and examines a wide range of cannabis-based preparations and interventions.

*Method:* We searched MEDLINE, EMBASE, CINAHL, and PsycInfo (October–December 2023) for peer-reviewed empirical studies, excluding case series, case studies, and review papers. Inclusion criteria were studies on adults (18+ years) diagnosed with anxiety-related disorders, examining the efficacy or effectiveness of medicinal cannabis. Studies on recreational cannabis or cannabis-use-disorder were excluded. The MASTER and QualSyst tools were used to assess bias.

*Results:* Fifty-seven studies met the inclusion criteria: 40 % cohort ($n = 23$), 30 % randomised controlled trials ($n = 17$), 18 % cross-sectional ($n = 10$), 12 % qualitative or other designs ($n = 7$). The MASTER scale revealed a high risk of bias, with a mean score of 62.9 (out of 100) due to inadequate reporting. Among the 13 highest-quality studies, 70 % ($n = 9$) reported a positive improvement for disorders including generalised anxiety disorder (GAD), social anxiety disorder (SAD), and post-traumatic stress disorder (PTSD). 30 % ($n = 4$) reported a negative result for conditions like obsessive-compulsive disorder, trichotillomania, test anxiety and SAD. Over 90 % of all studies, including lower quality studies, reported positive outcomes for CBD and THC-based cannabis. However, 53 % ($n = 30$) either omitted, or included self-reported data on either form and/or dosage.

*Conclusion:* Medicinal cannabis demonstrates potential in reducing anxiety symptoms, but the long-term benefits and overall impact on quality of life remain unclear. Further high-quality, longitudinal research with standardised dosing is needed.

## 1. Introduction

Anxiety ranks among the most common and disabling mental health conditions worldwide. According to the 2019 Global Burden of Diseases, Injury, and Risk Factor Study, it was identified as one of the two most disabling mental disorders and ranked among the top 25 leading causes of disease burden worldwide (Kessler et al., 2012; Surtees et al., 2003; Vos et al., 2020). Despite this, there remains a clear unmet need surrounding treatment and ongoing management of anxiety-related disorders (Bystritsky, 2006). In 2021, the countries with the highest globally age-standardised prevalence of anxiety disorders per 100 people percent were Portugal at 9.7 %, Brazil 9.0 %, Paraguay 8.4 %, Lebanon 8.3 % and Iran 8.2 % (IHME Global Burden of Disease, 2024). In Australia, anxiety was the most common mental health disorder in 2023 (Australian Bureau of Statistics, 2023). Anxiety and related disorders encompass a range of conditions, including generalised anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder

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(PTSD) and specific phobias (Kaczkurkin and Foa, 2022). For most anxiety-related disorders, lifetime morbidity risk is considerably greater than lifetime prevalence (Kessler et al., 2012). Anxiety disorders are widespread with lifetime prevalence ranging between 13.6 % and 28.8 % in Western countries (Michael et al., 2007). Furthermore, anxiety-related disorders significantly impact quality of life and psychosocial functioning (Mendlowicz and Stein, 2000; Olatunji et al., 2007).

First-line treatment for managing anxiety symptoms usually includes prescription of established psychotropic medication (such as benzodiazepines or antidepressants) and/or cognitive behavioural therapies (Bystritsky, 2006). Furthermore, Bystritsky (2006) reported that about 60 % of patients respond to mainstream treatments to a significant degree; however less than half of respondents achieved recovery (Bystritsky, 2006). Consequently, individuals may seek alternatives to psychological and pharmaceutical treatments due to poor compliance, perceived ineffectiveness, or concerns about pharmacotherapy side effects (Pellegrini and Ruggeri, 2007; Taylor et al., 2012). One such recent alternative treatment is medicinal cannabis, which is increasingly used as a treatment option for anxiety disorders (Berger et al., 2022a; Sarris et al., 2020).

Medicinal cannabis is a relatively new treatment that has not been widely approved. Countries that have approved its use include Uruguay (Alvarez et al., 2023), The Netherlands (Erkens et al., 2005; Hall et al., 2019), Australia (Therapeutic Goods Administration, 2022), along with several states in the United States (US), including California where it has been approved since 1990 (Johnson and Colby, 2023). Conditions that medicinal cannabis is used for currently include chronic pain, cancer pain, and multiple sclerosis (Blake et al., 2018; Haroutounian et al., 2016; Wade et al., 2004) and it is also being widely prescribed to treat anxiety disorders (Berger et al., 2022a; Sarris et al., 2020). The two most common compounds in medicinal cannabis-based products are cannabidiol (CBD) and tetrahydrocannabinol (THC). They share similar chemical structures but differ in mechanisms of action and effect on brain functions, with THC having greater psychoactive effects in humans (Stella, 2023). Modes of medicinal cannabis administration include smoking, vaporisation, oils, topicals or capsules (MacCallum and Russo, 2018).

Globally, anxiety-related disorders are among the most common conditions for which medicinal cannabis is prescribed (Sakal et al., 2022). In Australia, they are the second most common condition treated with prescribed cannabis (Department of Health, 2023), with GAD being the primary condition treated. While there is increasing use of medicinal cannabis, the evidence regarding its effectiveness for anxiety is conflicting and the range of anxiety disorders studied is limited. Some studies suggest that both CBD-and THC-based medicinal cannabis may be effective in managing anxiety symptoms (Sarris et al., 2020; Turna et al., 2019), and improving patients' quality of life (Ergisi et al., 2022). However, there is conflicting evidence indicating that THC-containing products may exacerbate anxiety symptoms (Berger et al., 2022a), and there is limited robust investigation of medicinal cannabis for anxiety disorders overall (Botsford et al., 2020; Hoch et al., 2019). This represents a concerning gap in the scientific knowledge given the emerging and increasingly widespread use of medicinal cannabis to treat anxiety.

Previous systematic reviews on medicinal cannabis primarily focused on a broad range of health conditions, including chronic pain, cancer, chemotherapy-induced nausea, and childhood epilepsy (National Academies of Sciences and Medicine, 2017). Several reviews also examined psychiatric conditions such as depression, attention-deficit hyperactivity disorder (ADHD), bipolar, schizophrenia, psychosis, personality disorders (Botsford et al., 2020; Hoch et al., 2019; Sarris et al., 2020), these reviews reported mixed findings and highlighted the need for further research. Reviews conducted on anxiety and depressive disorders have concluded that cannabidiol could be effective in reducing symptoms, however they emphasise the need for additional well-designed randomised controlled trials (RCTs) to establish efficacy (Black et al., 2019; Chadwick et al., 2020; Hasbi et al., 2023; Khan et al., 2020; Sarris et al., 2020). An additional review found that cannabis may decrease PTSD symptoms, particularly sleep disturbances; however the evidence was limited due to the included studies having a moderate to high risk of bias (Hindocha et al., 2020). Additionally, Han et al. (2024) and Bonaccorso et al. (2019), reported that CBD could be effective in the treatment of GAD and PTSD, however both studies had small clinical samples, highlighting the need for additional trials (Bonaccorso et al., 2019; Han et al., 2024). This review contributes to the growing body of literature by focusing exclusively on anxiety-related disorders, and encompassing a broad range of cannabis preparations and cannabinoid interventions.

This systematic review synthesised peer-reviewed literature investigating the use of medicinal cannabis for anxiety disorders to assess its effectiveness as a treatment option. We included a wide range of study designs, as well as various types of medicinal cannabis, dosages, and modes of administration.

## 2. Methods

The review was registered on PROSPERO – CRD42023487877. The review has followed the PRISMA guidelines for reporting (Page et al., 2021).

### 2.1. Eligibility criteria

Study design: All peer-reviewed quantitative, qualitative, mixed-methods, and empirical study designs were included except for case series, case studies, and review papers.

Population: Studies included participants 18 years and older at the commencement of the study and clinically diagnosed as having an anxiety disorder including but not limited to GAD, SAD and phobias consistent with the Diagnostic and Statistical Manuel of Mental Disorders Fifth Edition DSM-V definition (American Psychiatric Association, 2013). We further included PTSD and OCD as they were previously categorised as anxiety disorders in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)(American Psychiatric Association, 1994).

Intervention: Studies that investigated any treatment with medicinal cannabis, including treatments using one or more of its compounds (such as THC, CBD, and synthetic varieties like Nabilone) were included.

Outcomes: The primary outcomes included anxiety (including symptoms) and quality of life. Outcomes were examined overall as well as by medicinal cannabis type (CBD and/or THC, where such information was available).

Exclusion criteria: Studies were excluded if they did not meet the predefined inclusion criteria, including ineligible study design ($n$ = 155), outcomes outside the scope of the study including cannabis use disorder ($n$ = 35), or interventions that did not include medicinal cannabis ($n$ = 29). Furthermore, studies not conducted in English were excluded ($n$ = 1). There was no restriction on year of publication.

### 2.2. Information sources

We searched MEDLINE, EMBASE, CINAHL, and PsycINFO for published peer-reviewed literature from inception until most recent available literature with the final search occurring on 13 December 2023. A search was conducted using related terms to medicinal cannabis, treatment/therapies and anxiety disorders as detailed in the PROSPERO protocol. Detailed search strategies are presented in supplementary materials Table 1. The search strategy was developed in consultation with a senior librarian at the University of Western Australia. Reference lists of all eligible studies were screened to identify possible additional relevant studies not identified by the database search. Previous reviews were screened to identify any potential missing studies for inclusion.

**Table 1**
Characteristics of the studies included in the review.

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| **High quality studies (low relative risk of bias)** | | | | | | | | | | |
| (Bapir et al., 2023) | UK | Prospective Observational CO | 1254<br>Anx Cohort (Female =346)<br>No Anx Cohort (Female=230) | Chronic pain patients (18+) with and without co-morbid anxiety. | **Compound(s):** THC, CBD (GMP-certified, prescription).<br>**Route:** Sublingual/oral and/or vaporised flower.<br>**Dose:** Median THC: 110 mg/day (IQR: 20–200 mg). Median CBD: 20 mg/day (IQR: 15–30 mg).<br>**Regimen/Duration:** Dosing frequency NR; administered daily; titration scheme NR.<br>**Duration:** Outcomes assessed at 1, 3, and 6 months post-initiation. | No anxiety (GAD-7 < 5) cohort. | Changes in PROMs: Pain (BPI, SF-MPQ-2, VAS), Health Related quality of life HRQoL (EQ-5D-5 L), anxiety (GAD-7), sleep (SQS), and opioid consumption. | 6 months (medium term) | **Anxiety Outcomes**<br>Significant improvements in all PROMS in the anxiety cohort ($p < 0.05$); greater HRQoL improvement in anxiety group (e.g., EQ-5D-5 L index: MD 0.2, $p < 0.001$). Minimal differences in pain outcomes between groups.<br>**Adverse Events**<br>Anxiety Cohort: 19.4 % ($n = 138$) experienced AE. Type of AE: fatigue 16.5 %, dry mouth 14.6 %.<br>No Anxiety Cohort" 16.8 % ($n = 91$) experienced AE. Type of AE: fatigue 14.4 %, somnolence 11.4 %.<br>AE severity both cohorts mild or moderate. | 82.05 |
| (Garcia-Romeu et al., 2022) | USA | Qualitative Survey | 808 (Female=63 %) | Medicinal cannabis users (18+) in an online setting. | **Compound(s):** Not pharmaceutical grade self-reported use CBD, THC; often CBD-dominant products.<br>**Route**: Oral oils, inhalation (vape or flower), edibles.<br>**Dose**: NR.<br>**Regimen/Duration**: NR. | Not applicable (qualitative study). | Physical symptoms, mental health, quality of life, medication reduction. | Not specified | The survey revealed that 55 % reported improvements in physical symptoms (e.g., pain, seizures, sleep quality), 29 % noted mental health benefits (e.g., reduced anxiety, improved mood), and 14 % experienced quality-of-life enhancements. A total of 12 % reduced medication or healthcare use. Most participants endorsed the perceived benefits despite concerns about cost (12 %), legal issues (10 %), and lack of support (16 %). | 19* |
| (Gournay et al., 2023) | USA | RCT Double-Blind, Randomised, | 63 (300 mg CBD group: 21<br>50 mg CBD group: | Adults (18–55), with self-reported | **Compound(s):** Prescription use CBD.<br>**Route:** Oral (soft gel | Placebo. | Worry severity (BMWS), anxiety symptoms (DASS-A). | 2 weeks (short term) | **Anxiety Outcomes**<br>Acute 300 mg CBD did not significantly | 97.43 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | placebo-controlled trial | 21<br>Placebo group: 21)<br>[Female =32]<br>Retention 100 % | elevated trait of worry. | capsules).<br>**Dose:** 300 mg/day (150 mg twice daily) or 50 mg/day (25 mg twice daily).<br>**Regimen/Duration:** Daily administration for 2 weeks.<br>**Product Type:** Pharmaceutical-grade hemp-derived CBD isolate in MCT oil. | | | | reduce worry severity compared to placebo ($p = 0.81$). Repeated 300 mg CBD did not significantly reduce worry ($p = 0.55$), but significantly reduced anxiety symptoms compared to placebo after 2 weeks ($p < 0.01$, $d = 1.37$). Mean BMWS scores dropped from 16.86±5.02 at baseline to 11.45 ±6.11 at week 2 in the 300 mg group - not statistically significant. DASS-A scores decreased from 8.35±3.50 at baseline to 3.15±3.33 for 300 mg group- significant improvement in anxiety symptoms.<br>**Adverse Events**<br>14 side effects possibly or related CBD<br>Placebo: Dry mouth (Distress rating 2), Nausea (Distress rating 3), Somnolence (drowsiness) (Distress rating 3)<br>50 mg CBD: Somnolence ((Distress rating 3–6), Light-headedness (Distress rating 7), Dry mouth (Distress rating 3–4), Headache (Distress rating 4)<br>300 mg CBD: Light-headedness (Distress rating 9) Nausea (Distress rating 4–9), Somnolence (Distress rating 3–7), Increased appetite (Distress rating 2). | |
| (Grant et al., 2022) | USA | RCT Randomised Double-Blind, placebo-controlled trial | 50 (Dronabinol: 25<br>Retention 56 %<br>Placebo group:25)<br>Retention 64 %<br>[Female =40] | Adult (18+) with trichotillomania ($n = 34$) or skin picking disorder ($n = 16$). | **Compound(s):** Pharmaceutical grade Dronabinol (synthetic THC).<br>**Route:** Oral.<br>**Dose:** 5–15mg/day.<br>**Regimen/Duration:** Up to 10 | Placebo. | Change in National Institute of Mental Health Trichotillomania Severity Scale Symptom (primary); | 10 weeks (medium term) | **Anxiety Outcomes**<br>DASS-A scores decreased from 8.35 ±3.50 to 3.15±3.33 for the 300 mg group. Significant | 87.18 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | weeks (titrated from 5mg/day to 5 mg TID over 4 weeks, maintained 6 weeks). | | CGI-I responder status. | | improvement in anxiety symptoms also observed.<br>**Adverse Events**<br>AEs 64 % Dronabinol compared 28 % placebo<br>Types AEs: sedation (20 %), dizziness (20 %), feeling "high" (16 %), dry mouth (16 %), cognitive blunting (16 %), anxiety (8 %), nausea/vomiting (4 %), sleep disturbance (4 %).<br>All mild to moderate. | |
| (Jetly et al., 2015) | Canada | RCT<br>Randomised, Double-Blind, placebo-controlled cross-over study | 10<br>(Male=10)<br>Retention 90 % | Male (18–65) Canadian military personnel with diagnosed PTSD and nightmares refractory to standard treatment. | **Compound(s):** Nabilone pharmaceutical-grade.<br>**Route**: Oral (capsule).<br>**Dose**: Titrated from 0.5 mg to a maximum of 3.0 mg.<br>**Regimen/Duration**: Nightly administration 1 hour before bedtime; 7-week treatment period (cross-over design with 2-week washout); dose titrated weekly based on tolerability and symptom suppression. | Placebo. | CAPS nightmare score, CGI-C, WBQ, sleep quality (CAPS falling/staying asleep), adverse events. | 7 weeks per treatment period, separated by 2-week washout (medium term) | **Anxiety Outcomes**<br>Mean CAPS nightmare reduction: Nabilone $-3.6 \pm 2.4$ vs Placebo $-1.0 \pm 2.1$ ($p = 0.03$). CGI-C: Nabilone $1.9 \pm 1.1$ vs Placebo $3.2 \pm 1.2$ ($p = 0.05$). WBQ: Nabilone $20.8 \pm 22.1$ vs Placebo $-0.4 \pm 20.6$ ($p = 0.04$). No effect on sleep quantity or quality ($p = 0.97$).<br>**Adverse Events**<br>Nabilone $n = 5$ 50 %<br>Placebo $n = 6$ 60 %<br>Types AEs in Nabilone: dry mouth $n = 6$, headache $n = 4$. | 87.18 |
| (Kayser et al., 2020) | USA | RCT<br>within-subject human lab study | 12<br>(Female=4)<br>Retention 86 % (12/14) | Adults (18+) with diagnosed OCD and prior cannabis experience. | **Compound(s):** Pharmaceutical-grade cannabis smoked THC, CBD, or placebo.<br>**Route**: Inhalation (smoked cannabis cigarette).<br>**Dose**: ~800 mg per cigarette; participants smoked 50 % of a cigarette per session.<br>**Regimen/Duration**: Three sessions (one per week); within-subject, randomised crossover design. Each session involved one of three cannabis varietals.<br>THC-dominant (7.0 % THC / 0.18 % CBD); CBD-dominant | Placebo cannabis (0 % THC/0 % CBD). | OCD symptoms (YBOCCS, OCD-VAS), state anxiety (STAI-S), cardiovascular measures. | Single session 3–4 h per session (immediate) | **Anxiety Outcomes**<br>THC significantly increased heart rate, blood pressure, and intoxication compared to placebo and CBD. Placebo significantly reduced anxiety immediately compared to THC and CBD ($p < 0.05$). There were no significant differences in OCD symptom reduction between THC, CBD, and placebo ($p < 0.05$).<br>**Adverse Events** | 92.31 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | (0.4 % THC / 10.4 % CBD); Placebo (0 % THC / 0 % CBD). | | | | Types: nervousness, dry mouth, $n = 1$ daily cannabis user experienced panic symptoms. | |
| (Krediet et al., 2020) | The Netherlands | Focus Group Study | 7 (Male=7) | Male (42–66) military veterans with chronic PTSD treated with medical cannabis. | **Compound(s):** Prescription (pharmaceutical-grade cannabis) THC 1.3 % / CBD 2.0 %, THC 2.0 % / CBD <0.1 %, THC 22 % & 14 % / CBD <1 %,0.8 g/day, approx. every hour,1.4 g in the evening. **Route:** Oil, granulate, flower. **Dose:** Self-Reported 3–10 drops/day before sleep. **Regimen/Duration: R**anged 3 weeks to 6 months. | No direct comparison (qualitative study). | Experiences with administration, therapeutic effects (e.g., sleep quality, reduced anger, fewer nightmares), and adverse effects. | Not specified | Medical cannabis improved sleep quality, reduced nightmares, and enhanced relaxation. Minimal adverse effects reported. Dosage and strain optimisation were crucial. Partners highlighted improved patient well-being. Therapeutic effects varied across strains and doses. | 19* |
| (Kwee et al., 2022) | The Netherlands | RCT Double-Blinded | 80 (CBD: 39 Placebo: 41) [Female=32] | Patients (18–65) with treatment-refractory social anxiety disorder or panic disorder with agoraphobia. | **Compound(s):** CBD. **Route**: Oral. **Dose**: 300 mg per session, administered approximately 2 h before 8 weekly 90-minute therapist-assisted exposure in vivo sessions. **Duration**: 8 weeks. | Placebo (lactose capsules). | Fear Questionnaire (FQ), Beck Anxiety Inventory (BAI), other secondary measures. | 6 months (medium term) | **Anxiety Outcomes** No significant differences were observed between CBD and placebo groups in treatment outcomes (FQ: β=0.32, 95 % CI [−0.60, 1.25]). CBD did not enhance early treatment response, within-session fear extinction, or extinction learning. Adverse effects were comparable between groups. **Adverse Events** CBD group $n = 4$ Placebo $n = 6$ CBD group type: Dizziness, Drowsiness, Tiredness, Feeling of strong blood flow Placebo: Sweating, hot flushes, nausea, blurred vision, bad taste, Flu and gout attacks, Suicidal thoughts (led to discontinuation; only in placebo group), Recurrent tiredness, Drowsiness, Headaches. | 87.18 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| (Kwee et al., 2023) | The Netherlands | RCT | 69<br>(Completed fear conditioning task: 69<br>[Female=21]<br>Retention ranged 73 %–77 % | Patients (18+) with panic disorder with agoraphobia or social anxiety disorder. | **Compound(s):** Pharmaceutical-grade, prescription use CBD.<br>**Route**: Oral.<br>**Dose**: 300 mg.<br>**Regimen/Duration**: Once weekly, 2 h before exposure therapy session, for 8 consecutive weeks. | Placebo. | Fear acquisition, retention, re-extinction, subjective fear, shock expectancy, skin conductance, and startle responses. | 8 weeks<br>(medium term) | **Anxiety Outcomes**<br>CBD decreased shock expectancy at retention ($p = 0.004$ for CS+; $p = 0.03$ for CS-), no significant effects on fear-potentiated startle or skin conductance, CBD interfered with safety learning in female AD users ($p = 0.006$).<br>**Adverse Events**<br>NR. | 87.18 |
| (Masataka, 2019) | Japan | RCT | 37<br>(Placebo: 20, Female=5<br>Cannabis oil: 17, Female=6)<br>CBD retention 92 %<br>Placebo 100 % | Japanese adolescents (18–19) with diagnosed SAD, new to treatment. | **Compound(s):** Pharmaceutical grade CBD, isolate only.<br>**Route**: Oral.<br>**Dose**: 300 mg/day.<br>**Regimen/Duration**: Once daily in the afternoon, for 4 weeks. | Placebo group (olive oil). | Fear of Negative Evaluation (FNE), Liebowitz Social Anxiety Scale (LSAS). | 4 weeks + 6-month follow-up<br>(medium term) | **Anxiety Outcomes**<br>FNE Scores: Pre vs post-intervention for CBD group 24.4 ± 2.7 vs 19.1 ± 2.1; placebo group 23.5 ± 2.1 vs 23.3 ± 2.9; $p < 0.001$.<br>LSAS Scores: Pre vs post intervention for CBD group 74.2 ± 7.5 vs 62.1 ± 8.7; placebo group 69.9 ± 10.3 vs 66.8 ± 11.2; $p < 0.001$.<br>**Adverse Events**<br>Dropouts due to tolerability: 3 participants in the CBD group dropped out early due to disliking the taste or smell of the CBD oil.<br>Systematic assessment of side effects: NR<br>Reported adverse events: 0. | 100 |
| (Sachedina et al., 2022) | Canada | Retrospective CO | 7362<br>(Female = 3912) | Adults (18+) using medical cannabis with self-reported GAD. | **Compound(s):** Prescription use, non-pharmaceutical grade cannabis with varying THC/CBD content).<br>**Route**: NR.<br>**Dose**: NR.<br>**Regimen/Duration**: NR. | Compared to own baseline measures, assessing changes in outcomes over time. | GAD-7 (anxiety), PHQ-9 (depression). | 1 month to >24 months<br>(long term) | **Anxiety Outcomes**<br>Anxiety: GAD-7 scores decreased from baseline 11.1 ± 5.5 to >24 months 6.0 ± 5.0, MD=5.2, $p < 0.001$.<br>Most significant decreases occurred between baseline and 3 months for both anxiety and depression. Clinically significant improvements: GAD-7 decreased by >4 | 79.49 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | points (MCID) from 12 months onward for anxiety; PHQ-9 decreased by >5 points (MCID) from 18 months onward for depression. Baseline severity, being male, and older age were predictive of greater score improvements ($p < 0.05$). **Adverse Events** NR. | |
| (Souza et al., 2022) | Brazil | Clinical trial and observational study | 300 (CBD:100 Control: 200) [Female =232] | Frontline HCWs during COVID-19 (18+) (various roles). | **Compound(s):** Pharmaceutical-grade, CBD ≥99.6 % purity **Route:** Oral administration (dissolved in medium-chain triglyceride oil). **Dose:** 150 mg twice daily (total: 300 mg/day). **Regimen/Duration:** 28 consecutive days of administration, follow-up assessments at weeks 2, 4, 8, and 12. | Control group (no CBD). | GAD-7 (anxiety), PHQ-9 (depression), aMBI (burnout), PCL-5 (PTSD). | 12 weeks (medium term) | **Anxiety Outcomes** Significant reduction in anxiety (GAD-7): time effect ($p < 0.001$), group effect ($p = 0.03$), time-group interaction ($p = 0.01$); depressive symptoms (PHQ-9) reduced ($p = 0.03$ for group effect) and emotional exhaustion ($p = 0.004$ at week 4 and $p = 0.01$ at week 8); effects sustained up to 4 weeks post-treatment with minor adverse effects with CBD. **Adverse Events** Serious AEs: Elevated liver enzymes >3 × upper limit: 4 % of participants, Skin erythema diagnosed as pharmacodermia: 4 %, All serious adverse events resolved after discontinuation of CBD. Types AEs: Somnolence: 19 %, Diarrhea: 15 %, Increased appetite: 11 %, Fatigue: 10 %. | 97.43 |
| (Stanley et al., 2023) | USA | RCT Randomised, Double-Blind, placebo-controlled trial | 32 (Female =27 Retention 100 % | College students (18–55) with self-reported moderate-to-severe test anxiety. | **Compound(s):** Pharmaceutical-grade hemp CBD. **Route:** Oral (isolate in MCT oil with peppermint flavour). **Dose:** Single dose of 150 mg, 300 mg, or 600 mg. | Placebo. | Test anxiety (Visual Analog Scale), state anxiety (STAI-State), somatic symptoms (SSS-8), global impression of change, and | 1 session, 2.5 h (immediate) | **Anxiety Outcomes** No significant effect of CBD (any dose) on test anxiety, general anxiety, or test performance. 600 mg dose associated with | 82.05 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **Regimen/Duration:** Single administration, assessed over ~2.5-hour experimental session. | | academic performance. | | increased bodily anxiety symptoms compared to 150 mg and 300 mg. The results were not powered, and the effect was not statistically present. **Adverse Events** NR. | |
| (Weiss et al., 2023) | USA | RCT | 269 (across 6 timepoints 2:1 randomisation ratio) [Female =180] Retention 1 month = 71/7 % 193/269 3 month 69.9 % 188/269 12 month 59.9 % 161 | Adults (18–65) considering cannabis for medical symptoms (self-reported). | **Compound(s):** Self-reported cannabis products NR. **Route**: NR. **Dose**: NR. **Regimen/Duration**: Ad libitum use over 3 months (SCR group). | Waitlist control (WLC), no cannabis use for 3 months. | CEEQ-M scores, self-reported cannabis use, symptoms of pain, insomnia, anxiety, depression, and well-being. | 12 months (long term) | **Anxiety Outcomes** CEEQ-M showed stable psychometric properties (Cronbach's α: Symptom Relief factor=0.906, Atypical Beliefs factor=0.779). Expectancies did not predict symptom changes (e.g., pain, insomnia, anxiety, depression) or well-being at 3 or 12 months. Greater baseline cannabis use predicted positive changes in Symptom Relief ($\beta$=0.24, $p = 0.04$) and Atypical Beliefs ($\beta$=0.31, $p = 0.02$) expectancies. No significant predictive effects of baseline expectancies on clinical outcomes at 3 or 12 months ($p > 0.05$). **Adverse Events** NR. | 76.92 |
| (Zabik et al., 2023) | USA | RCT Randomised, Double-Blind, placebo-controlled study | 71 (Healthy controls: 26 Trauma exposed controls:26 Trauma exposed adults with PTSD:19) [Female =35] Retention 82.6 % | Trauma-exposed adults, PTSD and non-PTSD controls (21–45). | **Compound(s):** Pharmaceutical grade THC dronabinol. **Route**: Oral capsule. **Dose**: 7.5 mg single dose. **Regimen/Duration**: Single administration. | Placebo. | fMRI activation in vmPFC, amygdala; fear conditioning and extinction measures. | ~3-day experimental protocol (short term) | **Anxiety Outcomes** Mean BMWS scores dropped from 16.86 ±5.02 at baseline to 11.45±6.11 at week 2 in the 300 mg group (not statistically significant). **Adverse Events** NR. | 89.74 |
| **Low quality studies (moderate to high relative risk of bias)** | | | | | | | | | | |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| (Altman et al., 2023) | USA | Observational, CS | 455 (Female=296) | Adults (18+) with self-reported anxiety symptoms (not formally diagnosed) using CBD, recruited online. | **Compound(s):** Self-reported, non-prescription, non-pharmaceutical grade product CBD. **Route**: Edibles [45.1 %], vaping [30.3 %], topicals [29.7 %], sublingual [28.8 %], smoking, pills, other). **Dose**: NR. **Regimen/Duration**: Weekly (23.3 %) daily (19.8 %), monthly (19.8 %); Duration ≥ 1 year (29.2 %), ≥ 6 months and < 1 years (27.9 %), a month (19.6 %). Titration scheme NR. | No comparison group (descriptive). | Anxiety symptoms (DASS-21) CBD expectancies. | Not applicable | **Anxiety Outcomes** Anxiety scores significantly reduced under CBD expectancies (11.06 to 4.59, $p < 0.001$). Anxiety-related CBD expectancies explained 29 % of variance ($p < 0.001$). **Adverse Events** NR. | 17.95 |
| (Ashare et al., 2022) | USA | CS | 210 (Female =114) | Patients (18+) with mixed diagnostic criteria physician certified diagnosis and certified for medical cannabis use in Pennsylvania in state-regulated medical marijuana dispensaries. | **Compound(s):** Non-pharmaceutical grade, non-prescription but certified use THC and/or CBD-containing products). **Route**: NR. **Dose**: NR. **Regimen/Duration**: Duration – Baseline data only, Titration scheme NR. | Non-use of cannabis (retrospective self-report). | Symptom severity (anxiety, pain, sleep disturbance, depression), quality of life (FACIT-Pal), and impact of medications. | Not applicable | **Anxiety Outcomes** Using cannabis reduced symptom severity in 91 % of cases. Patients certified for pain reported higher QoL (FACT-G score: 70.6 ± 1.9 than those certified for anxiety 67.1 ± 2.2, $p = 0.25$). Those using opioids or benzodiazepines reported significantly lower QoL (FACT-G score: 62.7 ± 2.7 compared to non-users 70.5 ± 1.4, $p = 0.01$). Symptoms like anxiety and sleep disturbance showed >90 % self-reported improvement. **Adverse Events** NR. | 30.77 |
| (Bergamaschi et al., 2011) | Brazil | RCT Double-Blind | 24 (SAD CBD:12 Placebo: 12) (Female =6 CBD and Placebo Retention 100 % | Treatment-naïve adults (18+) with diagnosed Social Anxiety Disorder (SAD) and healthy controls (HC). | **Compound(s):** CBD pharmaceutical grade, ≥99.9 % pure). **Route:** Oral (encapsulated oil preparation). **Dose:** 600 mg single dose or placebo. **Regimen/Duration:** One-time administration, given 90 min prior to anxiety induction (simulated public speaking task). | Healthy controls without medication. | Anxiety, cognitive impairment, discomfort, alertness (Visual Analogue Mood Scale VAMS); negative self-statements (SSPS-N); physiological measures (e.g., heart rate, skin conductance). | Single session, exact time NR (immediate) | **Anxiety Outcomes** CBD group vs Placebo group: Significant reductions in anxiety (VAMS anxiety factor, $p < 0.001$), cognitive impairment (VAMS cognitive impairment factor, $p = 0.009$), discomfort (VAMS discomfort factor, $p = 0.029$), and negative self-statements (SSPS-N, $p = 0.001$) during | 71.79 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | speech performance. No significant difference between the CBD group and HC in these measures. **Adverse Events** NR. | |
| (Berger et al., 2022b) | Australia | Open-Label single arm interventional study | 31 (Female = NR) | Young people (12–25) with treatment-resistant anxiety disorders in a clinical setting. | **1. Compound(s):** Prescription pharmaceutical-grade CBD (isolate). **Route:** Oral, oil, wafers, or capsule forms. **Dose:** 200–800 mg/day (open-label trial). **Regimen/Duration**: Daily dosing for 12 weeks (open-label trial) also includes other studies with single or 4-week dosing. **2. Compound(s):** THC, THC/CBD combinations. **Route:** Oral (oils/capsules) or vaporised herbal cannabis. **Dose:** NR; THC doses ≥20–30 mg/day noted as potentially anxiogenic. **Regimen/Duration:** NR. **Product type:** Prescription herbal cannabis or extracts **3. Compound(s):** Pharmaceutical-grade Nabilone / Dronabinol (THC analogues). **Route:** Oral. **Dose:** NR. **Regimen/Duration:** NR. | Compared to own baseline measures, assessing changes in outcomes over time. | OASIS (Overall Anxiety Severity and Impairment Scale), HARS (Hamilton Anxiety Rating Scale), QIDS-A17 (Quick Inventory of Depressive Symptoms), SOFAS (Social and Occupational Functioning Assessment Scale). | 12 weeks (primary outcome) and 26 weeks (extended follow-up) (medium term) | **Anxiety Outcomes** Anxiety severity (OASIS) decreased by 42.6 % ($p < 0.0001$), social functioning improved by 11.3 % ($p = 0.04$), and 40 % achieved at least 50 % reduction in OASIS. **Adverse Events** 80.6 % 1 adverse event, 61.3 % possibly related to CBD. Most common: fatigue, low mood, hot flushes, cold chills, drowsiness, nausea, diarrhea, dry mouth, insomnia, increase/decreased appetite Mild to moderate AE, no serious AE. | 48.72 |
| (Bolsoni et al., 2022) | Brazil | RCT Double-Blind Placebo-Controlled Trial | 33 (CBD: 17; Female =13 Placebo: 16; Female =25) Retention 100 % | Adults (18–60) with diagnosed PTSD. | **Compound(s):** Pharmaceutical grade CBD. **Route:** Oral (gelatine capsule). **Dose:** 300 mg (single dose, 99.6 % purity). **Regimen:** Administered once, 90 min before trauma recall (Day 2); no titration; duration: single administration with follow-up 7 days later. | Placebo (corn oil). | VAMS (anxiety, sedation, cognitive impairment, discomfort), STAI-E. | 1-week post-intervention (short term) | **Anxiety Outcomes** Mean increase in VAMS Cognitive Impairment scores post-trauma recall was lower with CBD compared to placebo (CBD: 49.15±13.01 vs Placebo: 53.41±15.78, $p = 0.03$, MD=−4.26). The effect persisted 1-week post-intervention (CBD: 45.79±12.79 vs Placebo: 52.19±14.55, $p = 0.04$, MD −6.4). No significant effect of CBD was observed on VAMS Anxiety scores | 74.36 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | (CBD: 54.94±15.05 vs Placebo: 55.00±12.57, $p > 0.05$). CBD demonstrated limited overall impact on PTSD symptoms but showed potential to reduce cognitive impairments associated with traumatic memory recall, potentially linked to memory reconsolidation mechanisms. **Adverse Events** NR. | |
| (Bonn-Miller et al., 2022) | USA | Longitudinal Observational CO | 150 (Cannabis users: 75 Controls: 75) Female =40 | Adults (18+) diagnosed PTSD (veterans and non-veterans). | **Compound(s):** THC-dominant dispensary obtained cannabis **Routes:** Mixed routes (primarily inhalation of smoked flower; concentrates, edibles, tinctures). **Dose:** 1.75 g/day *THC 24 %), concentrates 0.29 g/day (THC 72 %), edibles 72mg/day THC self-directed use, minimum once weekly, ongoing over 12 months 91 % used THC dominant products, 4 % used CBD dominant, 4 % used balance THC: CBD. **Regimen/duration:** NR. | Non-cannabis users. | PTSD symptom severity Clinician-Administered PTSD Scale (CAPS-5), remission rates, psychosocial functioning (IPF), sleep quality (Pittsburgh Sleep Quality Index PSQI, ISI), and physical activity (IPAQ). | 1 year (assessments every 3 months) (long term) | **Anxiety Outcomes** Cannabis user's vs Controls: Greater reduction in PTSD symptom severity (CAPS-5: group × time interaction β=0.32, $p = 0.02$) and remission rates (hazard ratio=2.57, $p = 0.03$). Improvements in hyperarousal symptoms (CAPS-5 subscale, $p = 0.02$) and trends in avoidance ($p = 0.06$). No significant changes in psychosocial functioning, sleep-specific measures, or physical activity. Cannabis users were more likely [HR 2.57, $p = 0.03$] to no longer meet the criteria for PTSD diagnosis. **Adverse Events** NR. | 71.79 |
| (Bruce et al., 2021) | USA | CS | 367 (Female =201) | Adults (18+) self-reported chronic condition, registered medical cannabis users. | **Compound(s):** Self-reported (smoked flower). **Route:** Vaporization, edibles, topicals, or combination. **Dose:** NR. **Regimen/Duration:** Self-directed use; current use in past 30 days required; frequency and duration not standardised NR. | No cannabis use. | Perceived efficacy of medical cannabis in treating pain, anxiety, depression, and insomnia over past 30 days. | Not applicable | **Anxiety Outcomes** Medical cannabis (MC) was most frequently used for pain (74.9 %), followed by anxiety (65.7 %), insomnia (56.4 %). MC efficacy for anxiety 3.36±0.73, and insomnia 3.17 ±0.83. Perceived | 30.77 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
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| | | | | | | | | | efficacy increased with the number of co-occurring symptoms treated, with significant variations in perceived efficacy for anxiety ($p < 0.01$) based on symptom burden.<br>**Adverse Events**<br>NR. | |
| (Cahill et al., 2021) | Canada | Observational, prospective CO | 214 (Female =71) | Newly registered medical cannabis patients (19–79) in Canada. | **Compound(s):** Self-reported use THC, CBD, balanced CBD: THC.<br>**Route**: Various (dried herb, oil, soft gels, vaporisers).<br>**Dose**: NR.<br>**Regimen/Duration:** Duration 6 weeks. | Compared to own baseline measures, assessing changes in outcomes over time. | EQ-5D-5 L (QOL), POQ-SF (pain), DASS-21 (anxiety/ depression/stress), SPRINT (PTSD), PSQI (sleep disorders). | 6 weeks (medium term) | **Quality of Life Outcomes**<br>Quality of life (EQ-VAS) scores showed significant improvement (MD 8.3, $p < 0.001$). PTSD symptoms improved significantly with SPRINT total scores decreasing from 16.8 ± 4.2 at baseline to 12.5 ± 3.9 at follow-up ($p < 0.001$). Quality of life (EQ-VAS) scores improved (MD 10.2, $p < 0.001$). Sleep disorders, including restless leg syndrome, showed significant improvement in PSQI global scores, with scores decreasing from 10.3 ± 2.7 at baseline to 8.6 ± 2.8 at follow-up ($p < 0.01$). There was no significant change in quality of life (EQ-VAS) scores for this group ($p < 0.05$).<br>**Anxiety Outcomes**<br>Patients with anxiety did not show significant changes in the DASS-21 anxiety subscale scores, which decreased from 15.2 ± 4.1 at baseline to 14.3 ± 4.0 at follow-up ($p = 0.07$), but quality of life (EQ-VAS) scores significantly improved (MD 7.9, $p < 0.001$). | 51.28 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | **Adverse Events** 20.1 % ($n = 43$) experienced side effects Types: dry mouth $n =$ 27 cases 21.8 %, sleepiness $n = 18$ cases 14.5 %, restlessness $n$ = 9 7.3 % decreased memory $n = 9$ 7.3 %. | |
| (Cameron et al., 2014) | Canada | Retrospective Observational Study (Chart Review) | 104 (All Male) | Male inmates (19–55) with serious diagnosed mental illness in correctional settings. | **Compound(s):** Pharmaceutical grade, prescription Nabilone. **Route:** Oral (powder in water or capsule). **Dose:** Initial; mean 1.4 mg/day; Final dose: mean 4.0 mg/day (range 0.5–6.0 mg). **Regimen/Duration:** Typically, nightly; divided dosing used in 16.3 % of patients. Mean duration 11.2 weeks (range: 1 day–36 weeks). | Compared to own baseline measures, assessing changes in outcomes over time. | Hours of sleep, nightmares per week, PTSD symptoms (PCL-C), Global Assessment of Functioning (GAF), subjective chronic pain improvement, medications discontinued, adverse effects, abuse potential. | 1–36 weeks (medium term) | **Anxiety Outcomes** Nabilone significantly increased sleep hours from 5.0 ± 1.4 to 7.2 ± 1.2 ($p < 0.001$) and reduced nightmares per week from 5.2 ± 2.2 to 0.9 ± 1.8 ($p <$ 0.001). PTSD symptoms decreased (PCL-C scores: 54.7 ± 13.0 to 38.8 ± 7.1, $p <$ 0.001). GAF scores improved from 45.0 ± 6.9 to 58.2 ± 8.4 ($p <$ 0.001). **Adverse Events** Occurred $n = 31$ (29.8 %), discontinued due to AE $n = 10$ (9.6 %) Types: sedation 12.5 %, dry mouth 6.7 %, feeling "intoxicated" 3.8 %, orthostatic hypotension 1.9 %, agitation 1.9 %, headache 1 %. | 46.15 |
| (Chan et al., 2017) | Canada | Prospective Observational CO | 588 (Female=131) | Patients (18+) with self-reported PTSD using medical cannabis in an online setting. | **Compound(s):** NR. **Route:** NR. **Dose:** NR. **Regimen/Duration:** Patients surveyed at baseline, 4 months, and 10 months after initiating cannabis from a single provider. Duration up to 10 months. | Compared to own baseline measures, assessing changes in outcomes over time. | Pain severity, quality of life (QOL), comorbid conditions, side effects. | 4 and 10 months (long term) | **Anxiety Outcomes** At 4 months, 79.1 % of patients reported improved anxiety, 15 % saw no change, and 11.1 % experienced worsening symptoms ($p = 0.096$). By 10 months, improvements rose to 83.3 %, with 5.6 % reporting no change and 11.1 % worsening ($p = 0.268$) Quality of Life Improvements general mood improved significantly at both follow-ups ($p < 0.001$), | 33.33 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | with more patients reporting a "positive" or "very positive" mood.<br>**Quality of Life Outcomes**<br>Quality of life also improved, with significant gains in mood ($p < 0.001$), reduced "bad" or "very bad" QOL reports from 43.6 % at baseline to 17.9 % at follow-ups ($p = 0.03$), and better sleep quality ($p = 0.002$). Concentration improved significantly ($p = 0.006$).<br>**Adverse Events**<br>115 side effects.<br>Types (Mild to moderate): dry mouth 23 %, psychoactive effects 13 %, sleepiness 12.2 %, red/irritated eyes 7.8 %, heart palpitation 6.1 %, decreased memory 6.1 %.<br>Severe (for those who reported it) dry mouth 13.6 %, psychoactive effects 13.3 %, sleepiness 7.7 %. | |
| (Crippa et al., 2011) | Brazil and UK | RCT<br>Double-Blind, Randomised, crossover trial | 10<br>(Male=10)<br>Retention 100 % | Treatment-naïve men (20–33) with diagnosed generalised social anxiety disorder (SAD) no comorbidities, severe SAD based on BSPS and SPIN scales. | **Compound(s):** Pharmaceutical grade CBD, 99.99 % purity.<br>**Route:** Oral.<br>**Dose:** 400 mg single dose.<br>**Regimen/Duration:** Single administration in a double-blind, placebo-controlled, crossover design with one-week washout. | Placebo. | Subjective anxiety (VAMS), regional cerebral blood flow (rCBF) assessed via SPECT imaging. | 1 week between sessions<br>specific time NR<br>(short term) | **Anxiety Outcomes**<br>CBD significantly reduced subjective anxiety ($p < 0.001$), with MDs at various time points (e.g., pre-stress: −8.3, post-stress: −11.3).<br>Reduced rCBF in the left parahippocampal gyrus and hippocampus ($p < 0.001$) and increased rCBF in the right posterior cingulate gyrus ($p < 0.001$).<br>**Adverse Events**<br>NR. | 66.6 |
| (Dahlgren et al., 2022) | USA | Open-label phase 2 clinical | 14<br>(Female =11) | Adults (18+) with diagnosed | **Compound(s):** Pharmaceutical-grade, | Baseline assessments. | Beck Anxiety Inventory (BAI), | 4 weeks<br>(short term) | **Anxiety Outcomes**<br>Anxiety significantly | 51.28 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | trial (single arm) | | moderate-to-severe anxiety in a clinical setting. | prescription full spectrum MCT oil, CBD: THC with emulsifier.<br>**Route**: Sublingual.<br>**Dose**: Targeted dose of ~30 mg/day CBD and <1 mg/day THC (mean actual use: 34.73 ± 6.03 mg/day CBD; 0.80 ± 0.14 mg/day THC).<br>**Regimen/Duration**: 1 mL sublingually 3x/day for 4 weeks (average treatment duration: 31.07 ± 3.67 days). | | Overall Anxiety Severity and Impairment Scale (OASIS), cognitive function assessments. | | reduced at week 4 relative to baseline (BAI: MD −16.21, 95 % CI [−21.03, −11.40], $p < 0.001$; OASIS: MD −7.93, 95 % CI [−9.79, −6.07], $p < 0.001$). Clinically significant anxiety reduction (≥15 %) achieved by 78.6 % of participants by week 1 and 100 % by week 3. Cognitive assessments showed improved executive function with faster response times on Stroop Interference condition (MD −11.36 s, 95 % CI [−17.66, −5.05], $p = 0.002$) and Multi-Source Interference Task (MD −66.53, 95 % CI [−109.23, −23.82], $p = 0.006$).<br>**Adverse Events**<br>Mild<br>Types: fatigue 3 21.4 %, sleep more 2 (14.3 %), sleep less 1 (7.1 %), increased energy 3 (21.4 %), more talkative 2 (14.3 %), less talkative 1 (7.1 %), dry mouth 3 (21.4 %), cognitive cloudiness 2 (14.3 %, memory problems 1 (7.1 %), difficulty concentrating 1 (7.1 %), decreased appetite 1 (7.1 %), increased appetite 1 (7.1 %), weight gain 1 (7.1 %), constipation 1 (7.1 %), acid reflux 1 (7.1 %), anxiety 1 (7.1 %), decreased alcohol use 1 (7.1 %), increased libido 1 (7.1 %)<br>Moderate 1 (7.1 %) – increased energy, appetite, acid reflux. | |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| (Dugosh et al., 2023) | USA | Prospective Observational CO | 108 (Female =77) | Adults (18+) with self-reported anxiety or PTSD qualifying for medical marijuana. | **Compound(s):** NR. **Route:** NR. **Dose:** NR. **Regimen/Duration:** Initiation of MM program with 3-month follow-up; duration 3 months. | Compared to own baseline measures, assessing changes in outcomes over time. | Anxiety severity (GAD-7), prescription medication usage. | 3 months (medium term) | **Anxiety Outcomes** Significant reduction in GAD-7 scores from baseline to Month 3 ($p < 0.001$); 32 % reduced anxiety medication use, more likely among those on benzodiazepines (67 % vs 24 %; $p < 0.05$). **Adverse Events** NR. | 44.74 |
| (Erridge et al., 2023) | UK | Prospective CO | 1378 (Female =733) | Patients (18+) listed on the UK Medical Cannabis Registry (UKMCR). | **Compounds:** CBD 50 mg/mL, THC 20 mg/mL (sublingual/ oral MCT oil). Dried Flower (200 mg/g THC <10 mg/g CBD). **Route**: Oral/sublingual oils, inhaled dried flower. **Dose** (Median): Oils – CBD 20 mg/day [20–50], THC 10 mg/ day [5–11.6]; Dried Flower – CBD 7.5 mg/day [5–15], THC 167.5 mg/day [100–200]; Oils + Flower – CBD 27.5 mg/ day [20–55], THC 112 mg/ day [105–195]. **Regimen/Duration**: Titrated to optimal dose; follow-up at 1, 3, 6, and 12 months. | Compared to own baseline measures, assessing changes in outcomes over time. | GAD-7, SQS, EQ-5D-5 L index values, opioid use reduction, adverse events. | 12 months (long term) | **Anxiety Outcomes** Significant improvement in GAD-7 scores for all patients (MD: oils 1.15, dried flower 3.49, oils and dried flower 2.48, $p < 0.001$). Significant improvement in SQS scores (MD: oils −1.01, dried flower −1.55, oils and dried flower −1.61, $p < 0.001$). **Quality of Life Outcomes** Significant improvement in EQ-5D-5 L index values (MD: oils 0.16, dried flower 0.14, oils and dried flower 0.14, $p < 0.001$). Opioid prescription reduced by 6.26 % at 6 months ($p = 0.039$). **Adverse Events** Total AEs $n = 3663$, patients reporting AEs 297 (21.55 % of sample) Mild $n = 1560$ (42.59 %) Moderate 1584 (43.24 %) Severe 517 (14.11 %) Life threatening 2 events (0.05 %) 1 case of psychosis, 2 euphoria. Most common types: fatigue 271 (19.67 %), somnolence 250 | 46.15 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | (18.14 %), dry mouth 246 (17.85 %), lethargy 221 (16.04 %), headache 205 (14.88 %)<br>Oil only highest AE incidence. | |
| (Fabre and McLendon, 1981) | USA | 1) Open-label single arm intervention study<br>2) RCT Double-Blind | 25<br>(Open-label: 5, Male=5)<br>Retention 100 %<br>(Double-blind: 20, Male=15, Female=5)<br>Placebo 50 %<br>Nabilone 100 % | Adults (18–60) with diagnosed psychoneurotic anxiety. | **Compound(s):** Pharmaceutical-grade, prescription use Nabilone.<br>**Route**: Oral (capsule).<br>**Dose**:<br>• *Open-label*: Flexible dosing 2–8 mg/day (initial 1 mg BID, titrated individually); mean final dose 2.8 mg/day.<br>• *Double-blind*: Fixed dose 1 mg TID (3 mg/day), with one deviation (1 mg/day).<br>**Regimen/Duration**: 28-day treatment following 4-day washout period. | Placebo. | Hamilton Anxiety Rating Scale, Self-Rating Symptom Scale, Patient's, and Physician's Global Impressions. | 28 days (short term) | **Anxiety Outcomes**<br>Study 1: Significant reduction in Hamilton Anxiety total scores ($p < 0.001$), somatic anxiety ($p < 0.001$), and psychic anxiety ($p < 0.001$). All patients reported improvement on clinical and patient global impressions.<br>Study 2: Nabilone significantly reduced Hamilton Anxiety scores ($p < 0.001$) and SCL-56 anxiety and depression subscales ($p < 0.001$). Placebo group had higher dropout rates due to lack of symptom relief ($p = 0.03$).<br>**Adverse Events**<br>Study 1<br>N = 5 one side effect Types: dry mouth ($n = 5$), drowsiness ($n = 1$), feeling slowed down ($n = 3$), spaced out feeling ($n = 1$), headaches ($n = 1$), dry eyes ($n = 1$).<br>Study 2<br>Types: dry mouth mild ($n = 5$), moderate ($n = 9$), severe ($n = 4$), dry eyes $n = 5$, drowsiness ($n = 3$), headaches and insomnia ($n = 1$). | 30.77 |
| (Faraj et al., 2023) | USA | Quasi-Experimental Study | 374<br>(30-day: 175, Female =136<br>60-day: 199, Female =146) | Adults (18+) experiencing high baseline stress (self-reported average ~8/10). | **Compound(s):** CBD.<br>**Route**: Oral (sublingual tincture).<br>**Dose**: Self-reported Variable, at-will use (15–70 mg/day.<br>**Regimen/Duration**: (1) 1000 mg CBD isolate oil (15–30 days), followed by (2) 1000 mg broad-spectrum CBD oil | Within-subject comparison of CBD isolate and broad-spectrum products. | Self-reported stress, product effectiveness, taste, quality, adverse effects, and overall impression. | 30- or 60-day regimens (medium term) | **Anxiety Outcomes**<br>Broad Spectrum vs Isolate: Broad spectrum CBD was rated more effective for stress management ($p < 0.001$) and perceived as having greater ability to | 71.79 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | (15–30 days), depending on assignment to a 30- or 60-day program. | | | | manage stress ($p <$ 0.001). Participants rated its overall impression more favourably in the 30-day regimen ($p <$ 0.001). Supports the "entourage effect. Participants overall impression of CBD: 75 % overall impression as extremely favourable, 18 % as very favourable, 6 % somewhat favourable, 1 % as neither favourable nor unfavourable. In the 60-day regimen 100 % of participants rated both products of CBD and THC as extremely favourable. **Adverse Events** 30-day $n = 10$ 60-day $n = 7$ Types: lethargy $n = 4$, nausea $n = 2$, increased appetite $n =$ 2, Irritability, Headache, Feeling "spacey", Visual disturbances, Light sensitivity, Cough, Scratchy throat, Bad dreams, Upset stomach, Loose stools, Tachycardia. | |
| (Greer et al., 2014) | USA | Retrospective observational study (chart review) | 80 (Gender = NR) | Adults (18+) with confirmed PTSD diagnosis applying for medical cannabis. | **Compound(s):** NR. **Route**: Inhalation (smoked). **Dose**: NR. **Regimen/Duration**: Retrospective self-report comparing symptom severity during periods of cannabis use vs non-use; cannabis use was regular but exact duration and frequency NR. | No cannabis use. | CAPS scores. | Not applicable | **Anxiety Outcomes** Patients reported a significant reduction in total CAPS scores when using cannabis 22.5 ± 16.9 compared to when not using cannabis 98.8 ± 17.6, with a reduction of 75.3 % ($p < 0.001$). Symptom cluster analysis revealed significant reductions in re-experiencing from 29.5 ± 6.4 to 7.3 ± 5.9 ($p < 0.0001$), avoidance/numbing | 43.59 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | from 38.2 ± 8.4 to 8.7 ± 8.0 ($p < 0.001$), and hyperarousal from 31.0 ± 6.2 to 6.6 ± 6.0 ($p < 0.001$). Cannabis was associated with reductions in PTSD symptom severity across all symptom clusters, highlighting its potential efficacy in managing PTSD symptoms.<br>**Adverse Events**<br>NR. | |
| (Hundal et al., 2018) | UK | RCT Randomised, Double-blind, Placebo-Controlled trial | 32 (Female=16) Retention 100 % | Non-clinical volunteers (18–50) with high paranoia traits. | **Compound(s):** Cannabidiol CBD, pharmaceutical-grade synthetic.<br>**Route**: Oral.<br>**Dose**: 600 mg.<br>**Regimen/Duration**: Single dose, 130 min prior to exposure to a virtual-reality (VR) stress paradigm (one-time administration). | Placebo. | Anxiety (BAI), paranoia (SSPS, CAPE), physiological measures (cortisol, heart rate, BP), and cognitive measures (Digit-span, recall tests). | Immediate (VR session) exact time NR (immediate) | **Anxiety Outcomes**<br>Anxiety: BAI scores increased with CBD compared to placebo ($p < 0.05$) with a trend toward higher anxiety in VR ($p = 0.09$).<br>Paranoia: No significant effects of CBD on SSPS ($p = 0.15$) or CAPE ($p = 0.7$). Physiological measures: VR-induced increases in cortisol, heart rate, and systolic BP were not mitigated by CBD. Cognitive measures: No significant Session by Treatment interactions across digit-span, immediate or delayed recall (all $p > 0.1$).<br>Conclusion: CBD (600 mg) did not exhibit anxiolytic or anti-paranoia effects under VR.<br>**Adverse Events**<br>Mild<br>Placebo: tiredness $n = 4$<br>CBD group: tiredness $n = 5$, light headedness $n = 2$, nausea $n = 2$, abdominal discomfort $n = 1$, increased appetite $n = 2$. | 69.23 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| (Kalaba and Ware, 2022) | Canada | Prospective Observational CO | 629 (Female=369) | Adults (18+) using medical cannabis for various symptoms. | **Compound(s):** THC-dominant, CBD-dominant, and balanced THC:CBD cannabis products (plant-derived). **Route**: Inhaled (vape, dried flower) or oral (oil, soft gels). **Dose**: Self-reported varies widely; oral doses reported in mL (e.g., ~0.1–0.3 mL typical single dose); inhaled doses reported as number of "puffs" (variable and not standardised). **Regimen/Duration**: Self-administered; variable frequency and titration over time. | Pre-cannabis symptom severity and demographic subgroups. | Symptom severity scores (0–10 scale), cannabis product type and dose, self-titration patterns. | 5–12 months (long term) | **Anxiety Outcomes** (Anxiety) symptom severity decreased ($p < 0.001$) from baseline after cannabis use, with an average reduction of 2.8 points. Reductions were sustained over time, with noticeable effects starting from the first session and persisting for up to 12 months. Dosages of CBD-dominant products for anxiety increased over time ($p < 0.05$), suggesting self-titration to enhance perceived effectiveness. **Adverse Events** NR. | 41.02 |
| (Kimless et al., 2022) | USA | CS | 202 (Female=75 Male= 75 NB=3) | Adults (21+) Certified diagnosed with a range of disorders and medical cannabis patients. | **Compound** Prescription use THC alone (39.1 %) and THC-dominant (36.6 %); CBD-dominant (2.5 %), CBD alone (1.0 %). **Route**: Inhalation—vaporization of oils/concentrates (48.0 %) or vaporised flower (41.6 %). **Dose**: NR. **Regimen/Duration**: Median use 4.5 years (54.5 months); 59.4 % reported using several times per day. | No comparison group (descriptive). | Symptom improvement, side effects, and barriers to access. | Not applicable | **Anxiety Outcomes** Anxiety disorders were the most common qualifying condition (50.1 %) and comorbid condition (69.3 %). Patients reported an average 79.2 % improvement in symptoms, with 74.8 % stating cannabis improved anxiety and 72.8 % stating improved sleep quality. **Adverse Events** $N = 11$ Types: Anxiety/ nervousness/paranoia, changes in perception or memory problems, concentration problems. mood changes, Nausea/ vomiting Mean number of side effects reported (among those with any): 2.8. | 35.90 |
| (LaFrance et al., 2020) | USA | Retrospective Observational CO | 404 (Female=220) | Medical cannabis users (18+) self-identifying as PTSD | **Compound(s):** Not prescription or pharmaceutical grade | Pre- vs. post-cannabis | Changes in PTSD symptoms (intrusions, | 31 months (long term) | **Anxiety Outcomes** Cannabis use reduced symptoms | 31.58 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | patients online and app-based. | cannabis. Mean THC = 14.88 % (SD = 6.79; range = 0–84.4 %); Mean CBD = 2.43 % (SD = 5.12; range = 0–25 %). **Route**: Inhalation (smoke, vape, dab) only. **Dose**: Self-reported mean of 9.27 puffs per session (SD = 5.86; range = 1–30). **Regimen/Duration**: NR. | symptom ratings. | flashbacks, irritability, anxiety); effects of dose, gender, time, THC/CBD content. | | immediately: intrusions (−62.48 %, $p < 0.001$), flashbacks (−50.79 %, $p < 0.001$), irritability (−66.52 %, $p < 0.001$), and anxiety (−57.19 %, $p < 0.001$). No long-term improvement in baseline symptoms was observed (anxiety baseline ratings, β=0.002, $p = 0.14$). Higher doses for anxiety over time indicated potential tolerance (β=0.02, $p = 0.04$). Later sessions showed greater relief for intrusions (β=−0.14, $p = 0.04$) and irritability (β=−0.21, $p = 0.001$). **Adverse Events** NR. | |
| (Lee et al., 2022) | Canada | Observational CO | 37,303 (initial GAD-7, Female=20,147) 5075 (follow-up GAD-7, Female=2799) | Adults (18+) with GAD authorised to use medical cannabis. | **Compound(s):** Prescription use cannabis specific compound NR. **Route:** Oral (oil) or Inhaled (smoked/vaporised). **Dose:** NR. **Regimen/Duration:** Up to 3.2 years; mean follow-up 282 days (SD 264). | Compared to own baseline measures, assessing changes in outcomes over time. | GAD-7 score changes over time. | Up to 3.2 years (long term) | **Anxiety Outcomes** Statistically significant decrease in GAD-7 scores (MD −0.23 [95 % CI −0.28, −0.17], $p < 0.001$). 90.8 % had no change in GAD-7 scores, 3.7 % showed a clinically significant decrease (≥4 points), and 1.3 % showed a clinically significant increase. Improvements were most notable in the 6–12-month period (MD −0.50 [95 % CI −0.67, −0.34], $p < 0.001$) but did not meet clinical significance thresholds. **Adverse Events** NR. | 74.36 |
| (Lintzeris et al., 2018) | Australia | CS (anonymous) online survey (convenience sample) | 1748 (Female=545) | Adults (18+) using cannabis not clinically diagnosed for medical purposes in the past | **Compound(s): C**annabis (unspecified compound). **Route:** Inhaled (83.4 %). **Dose:** NR. **Regimen/Duration:** Self- | No comparison group (descriptive). | Indications for use, perceived benefits and harms, consumer perspectives on regulation. | Not applicable | **Anxiety Outcomes** For anxiety, 50.7 % of participants reported using medical cannabis, and 71 % | 53.85 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 12 months in an online setting. | reported mean of 9.8 years (SD 12.5 years) with mean use in past 28 days of 19.9 days (SD 10). | | | | reported that their anxiety symptoms had "very much" or "much" improved. 1 % reported worsening anxiety.<br>**Adverse Events**<br>Common side effects reported (out of 1302 respondents): Increased appetite: 74.0 % (severe in 6.1 %), Drowsiness: 67.1 % (severe in 1.8 %), Ocular irritation: 40.7 %, Lethargy/lack of energy: 37.5 %, Memory impairment: 31.6 %, Palpitations: 15.4 %, Paranoia: 15.2 %, Confusion: 12.4 %<br>Severe/intolerable side effects were infrequent, mostly <2 %, except: Increased appetite: 6.1 %. | |
| (Martin et al., 2021) | USA | Observational longitudinal CO | 538 (Cannabis users 368, Female=286 Controls: 170, Female=141) | Adults (18+) with self-reported anxiety and/or depression. | **Compound(s):** Non-pharmaceutical products CBD-dominant (82 %), THC-dominant (23 %), balanced THC: CBD (7 %).<br>**Route**: Oral.<br>**Dose**: Mean oral CBD: 61 mg/day (range: 0.4–1050 mg), Mean THC: 2.1 mg/day (range: ≤0.01–40.3 mg).<br>**Regimen/Duration**: Self-administered; dosing frequency NR; duration NR. | Controls (non-users) and changes over time. | Anxiety (HADS), depression (HADS), sleep (PSQI), quality of life (WHOQOL-BREF). | Average follow-up: 14 months (up to 44 months) (long term) | **Anxiety Outcomes**<br>At baseline, medicinal cannabis users reported significantly lower depression scores (MD −1.85, $p < 0.001$) but not anxiety (MD −0.45, $p = 0.09$). Users also reported better sleep (PSQI MD −1.24, $p = 0.001$). Longitudinally, cannabis initiation reduced anxiety (MD −2.52, $p < 0.001$) scores, with sustained users also showing reductions in anxiety (MD −1.40, $p < 0.001$). Non-users showed no significant change.<br>**Quality of Life Outcomes**<br>Improved quality of life (WHOQOL-BREF MD 3.62, $p < 0.001$.<br>**Adverse Events**<br>Reported Adverse | 61.54 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Events (Cannabis Users, $n = 368$):<br>No perceived harms: 61 %<br>Reported harms:<br>Intoxication: 2 %,<br>Unpleasant inhalation effects (e.g., smoke smell, worsened asthma): 2 %,<br>Impaired cognition: 2 %, Fatigue: 2 %,<br>Gastrointestinal issues or nausea: 1 %,<br>Worsened anxiety/ paranoia: 3 %,<br>Worsened depression: <1 %.<br>Other (individual, unique reports): 5 %. | |
| (Meakin et al., 2020) | Canada | Observational, CS with retrospective data collection (Anonymous online survey) | 60<br>(From 150 prescribed Nabilone Completed survey: 60)<br>[Gender= NR] | Active Canadian Armed Forces (CAF) (18+) members diagnosed with PTSD. | **Compound(s):** Synthetic cannabinoid, pharmaceutical grade Nabilone.<br>**Route**: Oral.<br>**Dose**: Average 2.46 mg/day (range: 0.5–8 mg/day).<br>**Regimen/Duration**: Nightly use, duration ranged from <6 months to >24 months. Survey participants had used nabilone for up to 3 years. | Compared to own baseline measures, assessing changes in outcomes over time. | Nightmare suppression, side effects, additional benefits, Clinical Global Impression (CGI) ratings, and reasons for discontinuation. | Average 7 years of nightmare occurrence prior to treatment; treatment duration varied (<6 months to >24 months) (long term) | **Anxiety Outcomes**<br>73 % reported complete or near-complete remission of nightmares ($p <$ 0.001). Return of nightmares occurred within an average of one week after discontinuation. Dosages were effective upon restarting treatment.<br>**Adverse Events**<br>Out of 52 respondents who answered questions about side effects:<br>46 % ($n = 24$) reported mild and tolerable side effects<br>21 % ($n = 11$) reported moderate side effects, not interfering with functioning<br>8 % ($n = 4$) reported side effects that interfered with functioning. | 66.67 |
| (Moltke and Hindocha, 2021) | Denmark | CS | 387<br>(Female=237) | Adults (18+) who are current or past CBD users in an online setting with self-perceived | **Compound(s):** Non-pharmaceutical grade products CBD.<br>**Route**: 72.6 % sublingual (72.6 %), capsules, vaping, topical, edibles, spray, and | No comparison group. | Self-reported effects on anxiety, sleep, stress, and general health. | Not applicable | **Anxiety Outcomes**<br>42.6 % of participants reported using CBD for self-perceived anxiety. Among these participants, 86.5 % | 46.15 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | anxiety, stress and sleep problems. | drinks.<br>**Dose**: Self-reported majority <50 mg/day (54 % used <50 mg/day; 10.2 % did not know dosage).<br>**Regimen/Duration**: Most used CBD for <1 year; frequency ranged from once daily to multiple times per day. | | | | indicated that CBD reduced their anxiety levels, while 12.8 % reported no change in their anxiety symptoms, and 0.6 % experienced increased anxiety.<br>**Adverse Events**<br>Out of 388 responses to the side-effects question:<br>11 % ($n = 44$) reported dry mouth, 3 % ($n = 13$) reported fatigue<br>Others <2 %: Dizziness, Nausea, Upset stomach, Rapid heartbeat, Diarrhea, Headache, Anxiety, Psychotic symptoms, Sexual problems, Trouble concentrating. | |
| (Moreno-Sanz et al., 2022) | UK | Prospective Observational CO | 344 (Female=77) | Adults (18+) with diagnosed chronic pain (50.8 %), anxiety disorders (25.3 %), and other conditions like ADHD or PTSD. All patients had failed at least two prior treatments. | **Compound(s):** Pharmaceutical grade prescribed THC-predominant cannabis flower (KHIRON 20/1; 20 % THC, <1 % CBD).<br>**Route**: Inhalation.<br>**Dose**: Variable; individualised via titration protocol over 5-day initiation plan.<br>**Regimen/Duration**: Daily use; follow-up at 3 and 6 months. | Compared to own baseline measures, assessing changes in outcomes over time. | HRQoL via EQ-5D-5 L, mood (PHQ-9), sleep disturbances (Pittsburgh Sleep Quality Index), chronic pain (Brief Pain Inventory Short Form), anxiety (GAD-7). | 3 months and 6 months (medium term) | **Quality of Life Outcomes**<br>The inhalation of THC-predominant cannabis flos was associated with a significant improvement in health-related quality of life (HRQoL), with a mean improvement in EQ-5D VAS score of 12.4 points in the anxiety group.<br>**Anxiety Outcomes**<br>Anxiety symptoms measured with the GAD-7 questionnaire decreased by 50.7 % (mean score reduced from 12.7 to 6.28, $p < 0.001$). Quality of sleep improved significantly, with a mean reduction of approximately 3 points in the Pittsburgh Sleep Quality Index ($p < 0.001$). These improvements were sustained at 6 months, with no evidence of tolerance | 58.97 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | development.<br>**Adverse Events**<br>$N = 1$ mild headache that resolved within 1–2 h.<br>$N = 1$ transient memory loss, described "not relevant". | |
| (Nacasch et al., 2023) | Israel | Retrospective observational CO | 14 (Female=2) | Treatment-resistant combat PTSD patients, mostly male (18+) (86 %), mean age 49.5, diagnosed for ≥3 years, treatment-resistant to ≥2 medications and ≥2 psychotherapies. | **Compound(s):** Pharmaceutical grade cannabis specific compound NR.<br>**Route:** Inhalation or sublingual oil.<br>**Dose**: ≤20 g/month (initial dose), exact dose per patient NR.<br>**Regimen/Duration:** Night-time use only, follow-up 0.5–3 years. | Baseline measures prior to initiating cannabis treatment. | PTSD symptom severity (Posttraumatic Diagnostic Scale, PDS), sleep quality and duration (Pittsburgh Sleep Quality Index, PSQI), nightmare frequency. | 6 months–3 years (mean 1.1 years) (long term) | **Anxiety Outcomes**<br>Significantly improvement in PTSD symptom severity scores by 24.4 % ($p < 0.01$), including intrusiveness (MR 2.0, $p < 0.05$), avoidance (MR 2.6, $p < 0.05$), and alertness (MR: 3.1, $p < 0.01$). Sleep improved significantly (MR PSQI 4.5, $p < 0.01$), subjective sleep quality improvement (MR 1.5 points, $p < 0.01$), and sleep duration increased (0.9 h, $p < 0.01$). No significant change in nightmare frequency ($p = 0.27$). Improvements were observed across genders, with women showing marginally greater benefits.<br>**Adverse Events**<br>NR. | 56.41 |
| (Rapin et al., 2021) | Canada | Retrospective Observational CO | 279 (Female =190) | Adults (18+) prescribed CBD-rich products for clinically diagnosed chronic pain or other conditions. | **Compound(s):** Prescription use not pharmaceutical-grade CBD CBD:THC ratio >10:1.<br>**Route:** Oral (oils, extracts) and inhaled (dried flower).<br>**Dose:** Mean CBD dose 11.5 mg/day (range 2–156 mg); mean THC dose 0.5 mg/day (range 0–6 mg) for CBD-rich products.<br>For patients switching to THC: CBD-balanced or THC-rich products: up to 60 mg THC/day.<br>**Regimen/Duration:** Retrospective observational | Compared to own baseline measures, assessing changes in outcomes over time. | ESAS-r scores for pain, anxiety, depression, and wellbeing. | 6 months (medium term) | **Anxiety Outcomes**<br>Moderate/severe symptoms: Anxiety: Scores reduced from 6.61±1.78 to 4.15 ±3.09 at 3 months ($p < 0.001$) and to 3.96 ±3.19 at 6 months ($p = 0.38$). Wellbeing: Scores improved from 6.47±1.83 to 4.72 ±2.5 at 3 months ($p < 0.001$) and to 4.93 ±2.23 at 6 months ($p = 0.89$). Mild symptoms: No significant improvement; some | 71.79 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | follow-up at 3 months (FUP1) and 6 months (FUP2). | | | | scores worsened (e.g., anxiety MD −0.63, $p <$ 0.05). THC addition showed no significant additional effects ($p >$ 0.2).<br>**Adverse Events**<br>NR. | |
| (Rifkin-Zybutz et al., 2023) | UK | Prospective CO | 302<br>(Female =95) | Patients (18+) with generalised anxiety disorder (GAD). | **Compound(s):** Prescription use cannabis products THC and/or CBD.<br>**Route:** Oral (oil), Sublingual (oil), Inhaled (dry flower via vaporisation).<br>**Dose:** Median daily CBD dose at baseline: 2.0 mg (IQR: 0.1 to 20 mg). Median daily THC dose at baseline: 21.0 mg (IQR: 19.0 to 40.0 mg).<br>**Regimen/Duration:** Continuous use for up to 6 months. Treatment adjusted over time, some switched product type. | Compared to own baseline measures, assessing changes in outcomes over time. | GAD-7, Sleep Quality Scale (SQS), EQ-5D-5 L (Quality of Life). | 1, 3, and 6 months (medium term) | **Anxiety Outcomes**<br>GAD-7 improved significantly: MD: −5.3 (1 month), −5.5 (3 months), −4.5 (6 months); $p < 0.001$ for all timepoints. Sleep Quality improved: MD: 1.8 (1 month), 1.9 (3 months), 1.5 (6 months); $p < 0.001$ for all timepoints. Quality of Life (EQ-5D-5 L) improved: MD: 0.15 (1 month), 0.15 (3 months), 0.11 (6 months); $p < 0.001$ for all timepoints.<br>**Adverse Events**<br>$N = 39$ AE, total AEs=269, Severe AE $n = 11$<br>Types: Dry mouth (8.3 %), Fatigue (7.3 %). Insomnia (6.3 %), Somnolence (5.3 %). Lethargy (5.3 %), Nausea (5.3 %)<br>Most common severe AE $n = 6$ insomnia. | 74.36 |
| (Roitman et al., 2014) | Israel | Open-label, single-arm, interventional pilot study. | 10<br>(Female =3) | Adults (18+) (mean age 52.3) with clinically diagnosed chronic PTSD, trauma exposure ≥3 years prior, on stable psychotropic medication for ≥4 weeks before the study. | **Compound(s):** Pharmaceutical-grade, prescription use THC.<br>**Route**: Sublingual (administered as THC dissolved in olive oil).<br>**Dose**: Titrated from 2.5 mg twice daily to 5 mg twice daily (10 mg total per day). All participants reached maximum dose.<br>**Regimen/Duration**: 3 weeks of continuous treatment.<br>**Product details**: 5 mg/0.2 mL THC oil prepared by dissolving 100 mg THC in 4 | Baseline measures before THC initiation. | PTSD symptoms (CAPS), global improvement (CGI), sleep quality (PSQI), nightmare frequency (NFQ), nightmare effects (NES), adverse effects. | 3 weeks (short term) | **Anxiety Outcomes**<br>Statistically significant reduction in PTSD hyperarousal symptoms (MD −8.0, $p = 0.02$). Global improvement: CGI-S decreased from 6.0 ± 0.47 to 4.9 ± 0.99 ($p = 0.02$); CGI-I improved significantly (MD −0.8, $p = 0.03$). Sleep Quality: PSQI improved from 17.2 ± 2.65 to 13.9 ± 4.48 ($p$<???0.05).<br>Nightmare frequency: | 53.85 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | mL olive oil; delivered via no-needle syringe. | | | | NFQ decreased significantly (MD −0.37, $p = 0.04$); 20 % (2 patients) achieved complete remission of nightmares. Nightmare effects: NES scores improved significantly (MD −9.3, $p = 0.002$). Clinically significant decrease in symptoms severity with the use of cannabis. **Adverse Events** $N = 4$ AEs all mild Types: dry mouth $n = 2$, headache $n = 1$, dizziness =1. | |
| (Rosenthal and Pipitone, 2021) | USA | CS | 157 (Female =93) | Self-diagnosed and registered medical marijuana (MMJ) patients (18+) in Florida. | **Compound(s):** Marijuana Mixed THC/CBD cannabis strains (most commonly high THC/low CBD; some high THC only, some high CBD only). **Route**: Inhalation (vape oil 81.5 %, smoked flower 69.4 %, vaporised flower 29.9 %), oral (tinctures 56.7 %, edibles 47.1 %, capsules 24.2 %, tablets 4.5 %, soft gels 5.7 %), topical (lotions 34.4 %, patches 19.7 %). **Dose**: NR. **Regimen/Duration**: Daily use was common; duration of use and dosing frequency not consistently reported. | No comparison group. | Patient demographics, use patterns, symptoms treated, perceived symptom relief, changes in medication use, and adequacy of information from physicians and dispensaries. | Not applicable | **Anxiety Outcomes** Most patients used MMJ daily, primarily for anxiety (82 %), pain (78 %), and stress (73 %), reporting good or complete relief (87–91 %). 65 % reduced or discontinued at least one prescription or OTC drug, including opioids (18–20 %), anxiolytics (18–20 %), and NSAIDs (28 %). Adequate guidance was provided by dispensaries (79 %) and physicians (75 %), but gaps in MMJ education among physicians were noted. **Adverse Events** Dry mouth, Drowsiness, Increased anxiety, Increased heart rate. Confusion/ mental fog, Memory loss, Paranoia, Blurred vision, GI distress, Insomnia, Headache, Depression. | 51.28 |
| (Sagar et al., 2021) | USA | Observational, longitudinal CO | 54 (Completed all timepoints: 27) [Female =34] | Adults (21+) initiating medical cannabis (MC). | **Compound(s):** Non-pharmaceutical cannabis (dispensary-acquired) cannabis products THC and | Compared to own baseline measures, assessing | Stroop Colour Word Test, Trail Making Test (Trails B), WCST, LNS, RAVLT, | 3, 6, and 12 months (long term) | **Anxiety Outcomes** Improved executive function; faster Stroop interference times at | 74.36 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CBD.<br>**Route**: Oromucosal (61.1 %), oral (40.7 %), smoked (55.6 %), vaped (50.0 %), cutaneous (9.3 %); no use of transdermal or suppository forms.<br>**Dose**: Self-reported Mean CBD: 153.9 mg/week, 201.6 mg/week, 113.5 mg/week.<br>**Regimen/Duration**: Mean frequency of use was 9–11 times/week. | changes in outcomes over time. | POMS, BDI, BAI, STAI, PSQI. | | all follow-ups (e.g., baseline 105.44 s vs 12 months 90.59 s, $p < 0.01$); fewer perseverative errors on WCST after 12 months (8.21 vs 6.55, $p < 0.01$).<br>Verbal learning and memory were stable, though slight reductions in long-delay memory were statistically significant but not clinically meaningful (RAVLT: 11.38 vs 10.66, $p = 0.04$).<br>Clinical improvements in anxiety (BAI: 10.61 vs 6.09, $p = 0.02$), and improved sleep quality (PSQI: 8.96 vs 6.24, $p < 0.01$).<br>**Adverse Events**<br>NR. | |
| (Smith et al., 2017) | Canada | Retrospective observational CO (chart review) | 100 (Female =3) | Military and police veterans with PTSD (18+) (97 % male, mean age 43). | **Compound(s):** Prescription not pharmaceutical grade THC and CBD from various cannabis strains.<br>**Route**: NR.<br>**Dose**: Self-reported average of 9.4 g/day at follow-up (range: <5 g to >10 g/day); self-titrated from 1 g/day, with physician-advised ceiling of 10 g/day.<br>**Regimen/Duration**: Duration of use ranged from <3 months to 18 months; most commonly <3 months or 11–12 months. | Compared to own baseline measures, assessing changes in outcomes over time. | PTSD symptom severity (scale 0–10), social/family impact, pain severity, PTSD-related medication use. | 3 to 18 months (most < 12 months) (long term) | **Anxiety Outcomes**<br>PTSD Symptoms: Aggregate PTSD symptom scores reduced from 7.0 to 2.9 (59 % reduction, ES 1.5, $p < 0.001$). Suicidal thoughts decreased by 77 % (ES 1.0, $p < 0.001$). Anxiety decreased by 59 % (ES 9.0, $p < 0.001$). Social/Family Impact: Aggregate score reduced from 6.5 to 2.7 (59 % reduction, ES 1.2, $p < 0.001$). Medication Use: 50 % reduction in PTSD-related medications; 36 % discontinued all PTSD medications. Medical cannabis demonstrated significant improvement in PTSD symptoms, pain, and social/family impact. | 69.23 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | **Adverse Events** NR. | |
| (Stack et al., 2023) | Australia | Observational CO | 198 (effectiveness analysis, Female =105)568 (adverse events analysis Female =304) | Participants with diagnosed anxiety disorders (18+) including PTSD ($n$ = 57 for PTSD subset). | **Compound(s):** Prescription medicinal cannabis use CBD and THC in varying ratios (CBD-only, THC-only, CBD-dominant, THC-dominant, or balanced). **Route**: Oral (capsules or liquid). **Dose**: Median 50 mg/day CBD (IQR 85 mg); median 4.4 mg/day THC (IQR 20 mg). PTSD subgroup CBD-only: median 95 mg/day (IQR 117.6 mg); THC-dominant: median 33.8 mg/day. **Regimen/Duration**: Dose and regimen determined by treating physician; observational period median 154.4 days (IQR 246.6). | Compared to own baseline measures, assessing changes in outcomes over time. | Anxiety, depression, fatigue, social activity participation, PROMIS-29 and adverse events. | Not specified | **Anxiety Outcomes** Significant mean improvement from baseline to follow-up was observed in anxiety [PROMIS-29] (64.6 vs 59.6, $p < 0.001$), fatigue (62.9 vs 56.9, $p < 0.001$), and social participation (36.5 vs 41.5, $p < 0.001$). In the PTSD subset ($n$ = 57), anxiety improved (64.9 vs 60.8, $p < 0.001$), fatigue (63.9 vs 57.6, $p < 0.001$), and social activity (36.8 vs 42.1, $p < 0.001$). **Adverse Events** AEs: 60 % ($n$ = 341/568) reported at least one adverse event (AE). Types Dry mouth: 32.6 % Somnolence (drowsiness): 31.3 % Fatigue: 18.5 %, Dizziness: 10.9 % Anxiety (increased): 9.5 %. THC-specific tolerability findings: Dry mouth (OR = 1.010, $p = 0.005$), Nausea (OR = 1.008, $p = 0.008$). | 61.54 |
| (Sznitman et al., 2022) | Israel | Daily diary-based prospective CO | 77 (Female =34) | Diagnosed PTSD patients (18–70) using licensed medical cannabis. | **Compound(s):** Prescription cannabis THC and CBD. **Route:** Inhalation. **Dose:** Self-titrated, ad libitum use; individual THC: mean 17.84 % (SD 3.80), CBD: mean 4.35 % (SD 4.35). **Regimen/Duration:** Nightly use reported over a 14-day period via electronic daily diary. | Within-person and between-person variations in time gap between cannabis use and sleep start time. | Number of awakenings, nightmares, early awakenings. | 2 weeks (short term) | **Anxiety Outcomes** Shorter time gaps between cannabis use and sleep onset were associated with lower likelihood of nightmares (OR 1.004, $p = 0.012$). Higher CBD concentrations were associated with reduced early awakenings (OR 0.772, $p = 0.048$). No association was found | 46.15 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | with nightly awakenings. **Adverse Events** NR. | |
| (Tait et al., 2023) | Australia | Prospective Multicentre Observational CO | 2327 (Female=1462) | Adults (18–97; mean age 51) prescribed medicinal cannabis (MC) for diagnosed chronic health conditions. | **Compounds**: Prescription pharmaceutical- grade THC and CBD (various ratios). **Route**: Oral (oil formulation). **Dose**: LGP Classic 1:20 (1 mg THC / 20 mg CBD per ml): median 1.0ml/day LGP Classic 10:10 (10 mg THC / 10 mg CBD per ml): median 0.75ml/day LGP Classic 20:5 (20 mg THC / 5 mg CBD per ml): median 0.57ml/day L GP Classic CBD 50 (50 mg CBD per ml): median 1.0ml/ day. (**Regimen/Duration**: Daily administration; titrated over ~2 weeks to optimal dose; follow-up for 3 months. | No comparison group; within-subject longitudinal tracking. | HRQL (EQ-5D-5 L, QLQ-C30), pain, fatigue, sleep (PROMIS), anxiety, depression (DASS-21). | 3 months (medium term) | **Quality of Life Outcomes** Statistically and clinically meaningful improvements observed in HRQL (EQ-5D-5 L, $d = 0.54$; QLQ-C30, $d = 0.64$), fatigue ($d = 0.54$), anxiety ($d = 0.45$). No significant changes in sleep disturbance. Short-term findings suggest MC improves quality of life and specific symptoms, but further long-term analyses are required. **Adverse Events** Withdrawals due to tolerability issues 3 months $n = 127$. Reasons unwanted side effects n-30. | 71.79 |
| (Turna et al., 2019) | Canada | CS | 2032 (Female=41.5 %) | Canadian medicinal cannabis (CMP) users (16–84) in an online setting self-reported based on validating screening tools. | **Compounds**: Pharmaceutical grade cannabinoids: dried cannabis plant high THC (over 18 %), low CBD (1 %), -Nabilone: 5.9 % of sample, Dronabinol: 1.0 %, Sativex: 1.6 %. **Dose**: Ranged from <1 g/day (35 %), 1–2 g/day (42 %), ≥3 g/day (23 %) OR NR. **Regimen/Duration:** Ongoing daily use NR for each product. | Self-reported outcomes, no external comparison. | Prevalence of psychiatric disorders, symptom severity (GAD-7, PHQ-9, Mini-SPIN, PAS), cannabis use patterns, medication substitution, perceived symptom improvement, and strain preferences. | Not applicable | **Anxiety Outcomes** 43.7 % ($n = 888$) used CMP for anxiety. 63.4 % met criteria for ≥1 disorder (GAD, SAD, depression, or panic disorder). CMP was perceived as improving symptoms (92 %) but most still reported moderate severity. Nearly half (49 %) replaced prescribed medications (e.g., antidepressants 23.8 %, benzodiazepines 15.8 %, opioids 19.2 %). From the following categories there was a reduction in "anxiety, worry, fears" (92.0 %), "irritability" (75.5 %), "difficulty falling to sleep" (72.4 %), "anxiety attacks" (58.8 %) and "low mood" | 48.72 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | (56.9 %).<br>**Adverse Events**<br>NR. | |
| (Vaddiparti et al., 2023) | USA | Prospective, single-arm, interventional (pilot) study | 15<br>(Female =9) | Adults (18+) with clinically diagnosed PTSD. | **Compound(s):** Prescription use cannabis specific compound NR.<br>**Route:** Inhalation (74.1 % of products), oral (7.4 %), sublingual (18.5 %).<br>**Dose:** NR dosing frequency ranged from 1 to 6 times/day.<br>**Regimen/duration:** 70-day follow-up. | (Single arm) Changes over time. | PTSD Checklist for DSM-5 (PCL-5), PSQI, Positive and Negative Affect Schedule (PANAS), PROMIS Global Health V1.2. | 30 and 70 days (medium term) | **Anxiety Outcomes**<br>PTSD symptom severity improved significantly at 30 days (PCL-5: 49.60 vs 30.33, $p = 0.001$) and 70 days (PCL-5: 49.60 vs 29.0, $p = 0.001$); nightmares decreased significantly at 70 days (PCL-5 nightmares: 2.00 vs 0.87, $p = 0.023$); sleep duration increased (5.03 vs 6.83 h, $p = 0.002$), sleep quality improved (PSQI sleep quality: 2.27 vs 1.07, $p < 0.001$), and total PSQI score decreased (13.79 vs 9.13, $p < 0.001$); negative affect reduced (31.64 vs 22.93, $p < 0.001$); global mental health improved significantly (8.73 vs 12.13, $p < 0.001$); the most significant changes occurred by 30 days except for nightmares, which improved significantly by 70 days.<br>**Adverse Events**<br>NR. | 74.36 |
| (Vickery et al., 2022) | Australia | Longitudinal Registry Cohort Study | 3961<br>(Female =2020) | Cannabis-naïve patients diagnosed with chronic, complex conditions and polypharmacy (2–96). | **Compound(s):** Prescription, pharmaceutical grade THC: CBD<br>Ratios used: Balanced (50.3 %), CBD-only (31.1 %), THC-dominant (13.8 %), CBD-dominant (4.4 %), THC-only (0.4 %).<br>**Route**: Oral (oil or capsules only.<br>**Dose**: Median THC = 10 mg/day; CBD = 22.5 mg/day.<br>**Regimen/duration**: Dose titrated over first two weeks; monitored at least every 8 weeks for 12 months, then | No comparison group; within-subject longitudinal tracking. | Pain (BPI), mental health (DASS-21), sleep (ISI), quality of life (SF-36), adverse events (TRAEs). | 2 years (long term) | **Anxiety Outcomes**<br>Oral MC significantly improved pain (25 % reduction), mental health (DASS-21: anxiety −25.5 %, stress −27.7 %), sleep (ISI −35 %), and quality of life (SF-36: physical function +34.4 %, emotional well-being +37.3 %) ($p < 0.001$).<br>**Adverse Events**<br>AE: 1477 37.3 %<br>Severity: mild 67 %, | 71.79 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | every 12 weeks for up to 24 months. | | | | moderate 31 %, severe <2 %, serious 0.05 % Types: sedation 68.2 %, dry mouth 79.9 %. | |
| (Walsh et al., 2023) | Canada | RCT Randomised, Blinded, Placebo-Controlled Crossover Study | 6 (Female =1) Retention 83.3 % 5/6 | Adults (35–65) with diagnosed PTSD. | **Compound(s):** Prescription, pharmaceutical grade cannabis:<br>1. THC 10 % ± 2 % / CBD 10 % ± 2 % (balanced).<br>2. THC 10 % ± 2 % / CBD <1 % (THC-dominant).<br>3. Placebo: THC <1 % / CBD <1 %.<br>**Route:** Vaporised.<br>**Dose:**2 g per day, ad libitum.<br>**Regimen/Duration:** 3 weeks with 2 week wash out periods. | Placebo cannabis (<1 % THC and <1 % CBD). | CAPS-5 and PCL-5 scores pre- and post-treatment. | 3 weeks per condition (short term) | **Anxiety Outcomes** CAPS-5 scores: Reduction from baseline (39.00±5.90) to post-treatment (30.67±11.17) ($p$ = 0.11, $d$ = 0.80). PCL-5 scores: Reduction from baseline (63.93 ±10.91) to post-treatment (50.61 ±19.84) ($p$ = 0.05, $d$ = 1.02). Results indicate medium to large within-subject effect sizes for PTSD symptom reduction with active cannabis conditions.<br>**Adverse Events** NR. | 74.36 |
| (Zaki et al., 2017) | Canada | Prospective Observational CO | 2588 (Male=69.2 %) | Adults with non-cancer medical conditions clinically diagnosed. | **Compound(s):** NR prescription use.<br>**Route**: NR.<br>**Dose**: NR.<br>**Regimen/Duration**: Tracked 4–10 months. | Baseline versus 4-month and 10-month follow-ups. | Symptom severity, quality of life (QOL), pain, and side effects. | 10 months (long term) | **Anxiety Outcomes** 4-month follow-up, 77.5 % of patients ($n$ = 162) showed significant anxiety improvement, with a MR of 2.4 points ($p$ = 0.0006). By 10 months, 74.8 % ($n$ = 77) reported sustained improvement, though without statistical significance ($p$ = 0.4). Anxiety severity decreased from moderate to mild in 49 % of cases at 4 months.<br>**Quality of Life Outcomes** Quality of life measures, including mood and sleep, showed significant improvement throughout the study ($p$ < 0.001).<br>**Adverse Events** 4-month FU ($n$ = 23) : Dry mouth (69.6 %) - Psychoactive effects | 41.02 |

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**Table 1** (*continued*)

| Author (year) | Location | Study Type | Study Size (N) | Setting/Population | Intervention/Exposure | Comparison | Outcome Measures | Follow-up Duration | Main Findings | MASTER Scale |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | (65.2 %)<br>- Decreased memory (35.3 %)<br>- Decreased concentration (35.3 %)<br>- Sleepiness (32.4 %).<br>At 10-month FU ($n$ = 23)<br>: Side effect frequency generally decreased except for increased sleepiness and memory complaints.<br>Severity (4-month FU)<br>: Most effects were mild to moderate.<br>- Example: 45.9 % reported mild dry mouth, 45.5 % mild psychoactive effects, 46.8 % moderate sleepiness. | |

MASTER Scale ranges from (0–100 Relative Risk of Bias). Studies which scored 75 and above in the MASTER Scale were classified as low relative risk of bias. For qualitative studies the QualSyst tool was used, and a score of 19* was classified as low relative risk of bias. Results presented as mean ± standard deviation unless otherwise stated. Abbreviations: ADHD: attention-deficit/hyperactivity disorder, AE Adverse Events, Anx Anxiety, β beta, BPI: Brief Pain Inventory, BMWS: A Brief Measure of Worry Severity, CBD: cannabidiol, CGI-C: Clinical Global Impression Change, CGI-I: Clinical Global Impression Improvement, CO: cohort, CS: cross sectional, DASS-A: Depression, Anxiety and Stress Scale Anxiety, d: effect size, ESAS: Edmonton Symptom Assessment Scale, EQ-SD-5L: five-level EuroQol five-dimensional questionnaire, FACIT-PAI: The Functional Assessment of Chronic Illness Therapy Palliative Care, GAD-7: General Anxiety Disorder −7, HADS: Hospital Anxiety and Depression Scale, HR: hazard ratio, IPAQ: International Physical Activity Questionnaire, ISI: Insomnia Severity Index, MD: mean difference, MR: mean reduction, NR: not reported, OCD: Obsessive Compulsive Disorder, OCD-VAS: Obsessive Compulsive Disorder Visual Analogue Scale, OR: odds ratio, PCL-C: Post-traumatic Stress Disorder Checklist: Civilian Scale, PROMS: Patient Reported Outcome Measures, PTSD: Post-Traumatic Stress Disorder, RCT: randomised controlled trial, SF-MPQ-2: Short-form McGill Pain Questionnaire-2, SPRINT: The Short Post-Traumatic Stress Disorder Rating Interview, SQS: Sleep Quality Scale, STAI-E: State Trait Anxiety Inventory (English Version), STAI-S: State Anxiety, STAI-T: Trait Anxiety, THC: tetrahydrocannabinol, UK: United Kingdom, USA: United States of America, VAS: Visual Analogue Scale, WBQ: Walking Behaviour Questionnaire, WHOQOL-BREF: World Health Organization Quality of Life-BREF, Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

### 2.3. Search strategy

The main concepts considered included terms covering medicinal cannabis/marijuana, anxiety disorders and treatments/therapies. The full search terms are included in Supplementary Table 1.

### 2.4. Selection and data collection process

A two-stage process was conducted in Covidence that included screening title and abstract, followed by full-text review conducted by two independent reviewers (LR, ES) with a third reviewer (CC) resolving any conflicts. If additional unpublished information was needed to determine a study's eligibility for inclusion, we attempted to contact the corresponding author via email and followed up with a second email if we had no response to the first**.** We contacted two authors via email with no response, so these studies were excluded. We also excluded studies ($n$ = 37) that did not report sufficient usable data.

We designed a data extraction form following a consultation with the research team and a pilot with coauthor ES, which two review authors (LR and ES) used to extract data from eligible studies. Extracted data were compared and any discrepancies being resolved through discussion and (if required) consultation with CC.

### 2.5. Data items

The following is an abridged version of data items, the full list is presented in supplementary materials. Data items included author, year of publication, geographic location, population group, method of recruitment, medicinal cannabis exposures (preparation, type, dose), outcomes, covariates, loss-to-follow-up, statistical methods used, measure of association used, main result, and conflicts of interest declared.

### 2.6. Risk of bias assessment

Risk of bias tools used to evaluate the included studies comprised the MethodologicAL Standard for Epidemiological Research (MASTER) scale (Stone et al., 2019), as it assesses the relative risk of bias across all included study designs, and the QualSyst Tool for qualitative studies (Kmet, 2004) consistent with previous reviews (Black et al., 2019; Ohan et al., 2023;). The MASTER scale assesses study quality across eight methodological standards and encompasses a total of 40 items. These standards and corresponding biases include equal recruitment, equal retention (both under selection bias), equal ascertainment (information bias and design-related bias), equal implementation (information bias), equal prognosis (analytic bias, confounding and design-related bias), sufficient analysis (analytic bias), temporal precedence (design-related bias) and equal recruitment (external validity). Each item is assigned a 1 (criteria met) or 0 (not met), yielding a scoring range from 0 to 40. To standardise scores across studies, a relative risk of bias score is calculated by dividing each study's total score by the highest score achieved among all studies, using the highest scoring study as a benchmark. Higher scores reflect lower risk of bias and greater methodological rigor, whereas lower scores indicate a greater risk of bias.

Two reviewers (LR, ES) independently applied the tool to each included study. Any discrepancies in judgement of risk of bias were resolved through discussion between the two authors with a third author (CC) acting as a moderator if necessary. The MASTER scale works with the highest-scoring study serving as the benchmark; all other studies are scored relative to this benchmark, where lower scores indicate a greater risk of bias.

### 2.7. Synthesis method

We extracted data on the characteristics (including study type, study size, setting/population, follow-up duration,) of included studies using a data extraction template we created and performed a narrative synthesis. For the purpose of this review, follow-up duration was categorised as immediate (single session), short term (<1 month), medium term (1 – 6 months), and long term (>6 months). A meta-analysis was considered, however was not feasible due to the substantial heterogeneity in study designs and measures used across included studies.

### 2.8. Reporting and certainty assessment

No certainty assessment was used for this review due to the heterogeneity of study designs.

## 3. Results

### 3.1. Study characteristics

The initial search identified 11,031 published studies. After screening titles and abstracts, this number was reduced to 8756 studies. Full-text screening further narrowed it down to 326 studies. Among these, 94 studies were deemed eligible; however, 37 studies were excluded due to insufficient usable data, resulting in 57 studies included in the review (PRISMA flow chart, Fig. 1).

#### 3.1.1. Study country, setting and design

Studies were primarily conducted in the US ($n$ = 22, 39 %), followed by Canada ($n$ = 13, 23 %), the United Kingdom ($n$ = 6, 11 %), Australia ($n$ = 4, 7 %), Brazil ($n$ = 4, 7 %), The Netherlands ($n$ = 3, 5 %), Israel ($n$ = 3, 5 %), Denmark ($n$ = 1, 2 %) and Japan ($n$ = 1, 2 %).

The studies spanned from 1981 to 2023, with most ($n$ = 54, 95 %) being published after 2014. The large range is due to restrictions on medicinal cannabis research through the 1980s to early 2000s (Baron, 2015). However synthetic cannabinoids like Nabilone were not initially subjected to the same legal constraints, with some research conducted in the early 1980s (Baron, 2015).

Setting types included in this review were clinical settings (including registry data and RCTs) and community settings (including online surveys). As per Table 1, many different study designs were included in the review: 40 % cohort ($n$ = 23), 21 % RCTs ($n$ = 12), 18 % cross-sectional ($n$ = 10), 9 % single arm intervention ($n$ = 5), 5 % cross over trials ($n$ = 3), 4 % qualitative ($n$ = 2) and 4 % other study designs ($n$ = 2).

As indicated in Table 1 and illustrated in Fig. 2, a wide variety of study designs, with a broad range of study sizes (6–37,303 participants) were included in this review. The distribution and varying bubble sizes in Fig. 2 highlight the considerable heterogeneity across study designs, anxiety diagnosis type and study sizes.

#### 3.1.2. Anxiety outcome type

Of the outcomes investigated by studies included in this review, 39 % ($n$ = 22) examined GAD, 28 % ($n$ = 16) PTSD, 19 % ($n$ = 11) GAD and PTSD, with the remainder investigating other anxiety-related disorders, including 9 % ($n$ = 5) SAD and 7 % ($n$ = 4) OCD and other phobias.

#### 3.1.3. Cannabis treatment type

Twenty-four studies (42 %) investigated a combination of CBD, THC, and/or synthetic based preparations, 14 investigated only CBD (25 %), four (7 %) investigated synthetic compound Nabilone, and five (9 %) investigated THC only. Ten studies (18 %) did not specify or report what cannabinoid was used. The most common route of administration investigated was oral (45 studies, 79 %), and a high proportion of studies investigated non-pharmaceutical, self-reported dispensary grade cannabis (25 studies, 44 %).

#### 3.1.4. Symptom measurements used

>30 different outcome measures were used throughout the 57 studies in this review to investigate symptoms of anxiety. The most commonly used validated measure was the Generalised Anxiety Disorder 7-item (GAD-7) which assesses GAD scored from 0–21 (Spitzer et al.,

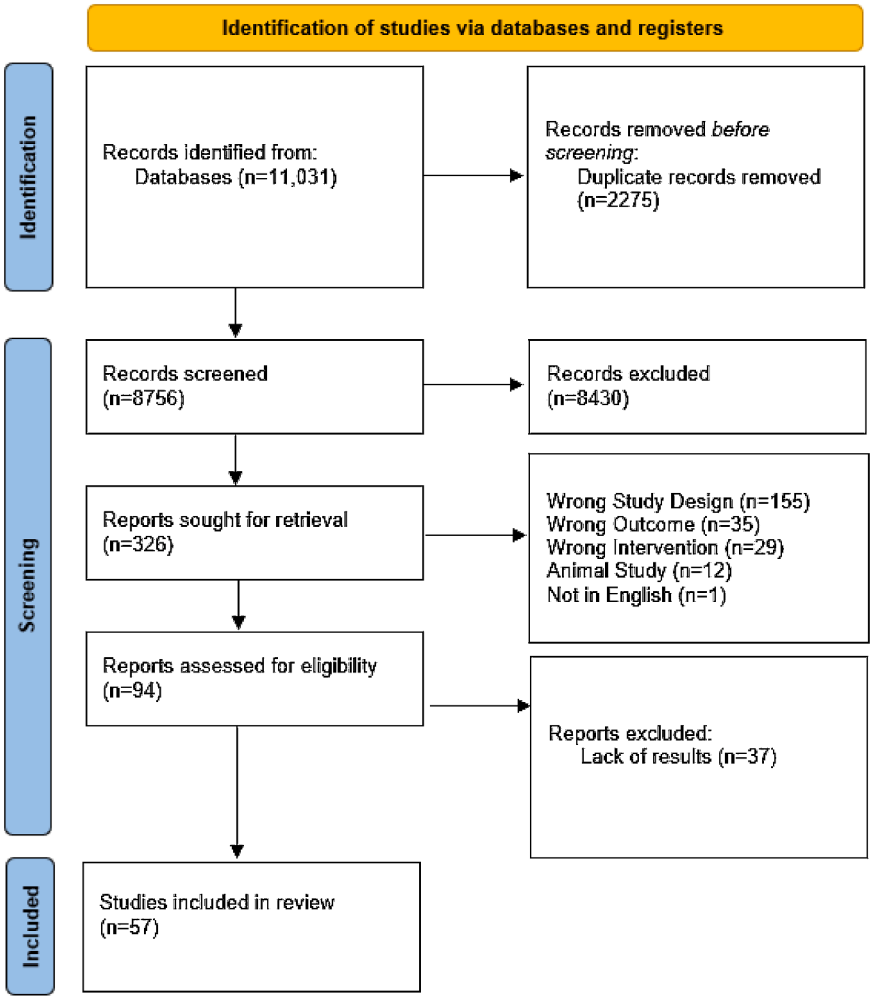


**Fig. 1.** PRISMA Flow Chart for study selection.

2006); and was used in eight (14 %) studies (Bapir et al., 2023; Dugosh et al., 2023; Erridge et al., 2023; Lee et al., 2022; Moreno-Sanz et al., 2022; Rifkin-Zybutz et al., 2023; Sachedina et al., 2022; Turna et al., 2019). Other commonly used scales included the 40-item State Trait Anxiety Inventory (STAI), used to measure trait and state anxiety (score range: 20–80)(Julian, 2011; Spielberger et al., 1971) and the Depression Anxiety and Stress Scale 21 (DASS-21) which assesses symptom severity across three domains: depression, anxiety and stress (score range: 0–21) (Lovibond, 1995). Additional tools included the Visual Analogue Mood Scale (VAMS) which measures mood states in populations with cognitive and communication impairments (score range: 0–100), and the 30-item Clinician-Administered PTSD Scale for DSM-V (CAPS-5) used to assess PTSD symptom severity and establish a formal diagnosis (American Psychiatric Association, 2013; Weathers et al., 2018).

#### 3.1.5. Adverse events

Thirty studies (53 %) reported adverse events. The most common adverse events reported across the studies were dry mouth ($n = 19$, 33 %), fatigue ($n = 10$, 18 %), somnolence/drowsiness/sleepiness ($n = 14$, 25 %), nausea ($n = 11$, 19 %) and headaches ($n = 11$, 19 %). The adverse events were reported as mild to moderate in 28 of these studies, with the remaining two studies reporting serious adverse events, including elevated liver enzymes (Souza et al., 2022) and psychosis (Erridge et al., 2023). In studies focusing on GAD: dry mouth, fatigue, drowsiness was most frequently reported (Bapir et al., 2023; Cahill et al., 2021; Dahlgren et al., 2022; Erridge et al., 2023; Rifkin-Zybutz et al., 2023; Souza et al., 2022; Stack et al., 2023; Vickery et al., 2022). Studies investigating PTSD reported similar types of adverse events, however, patients also experienced mild to moderate adverse psychoactive effects (Chan et al., 2017; Zaki et al., 2017). For CBD formulations, the most common adverse events reported included dry mouth, fatigue, drowsiness, and headaches. In contrast, THC and Nabilone formulations were more frequently associated with mild to moderate psychoactive effects, sedation and restlessness.

### 3.2. Risk of bias assessment

The relative risk of bias varied across the included studies, reflecting the heterogeneity with respect to study design and robustness. On average, the relative risk of bias score for the quantitative studies based on the MASTER scale (Stone et al., 2019) was 62.9 % (ranging scores from 17.9 % (Altman et al., 2023) to 100 % (Masataka, 2019). The median relative risk of bias was 66.6 %, and the interquartile range was 28.2. Thirteen (23 %) studies scored in the top quartile and are classified as high quality studies, according to Stone et al., (Stone et al., 2019), with the remaining 44 studies (77 %) in the low-to-moderate quality range.

Thirteen studies (23 %) implemented participant blinding, and three (5 %) studies blinded caregivers but not patients. Over half of the studies ($n = 36$) addressed how they managed loss-to-follow-up or missing data. In addition, 14 studies had follow-up periods that were possibly insufficient to observe a meaningful effect. Furthermore, 26 studies had financial or personal conflicts of interests, or omitted a conflict of interested declaration statement.

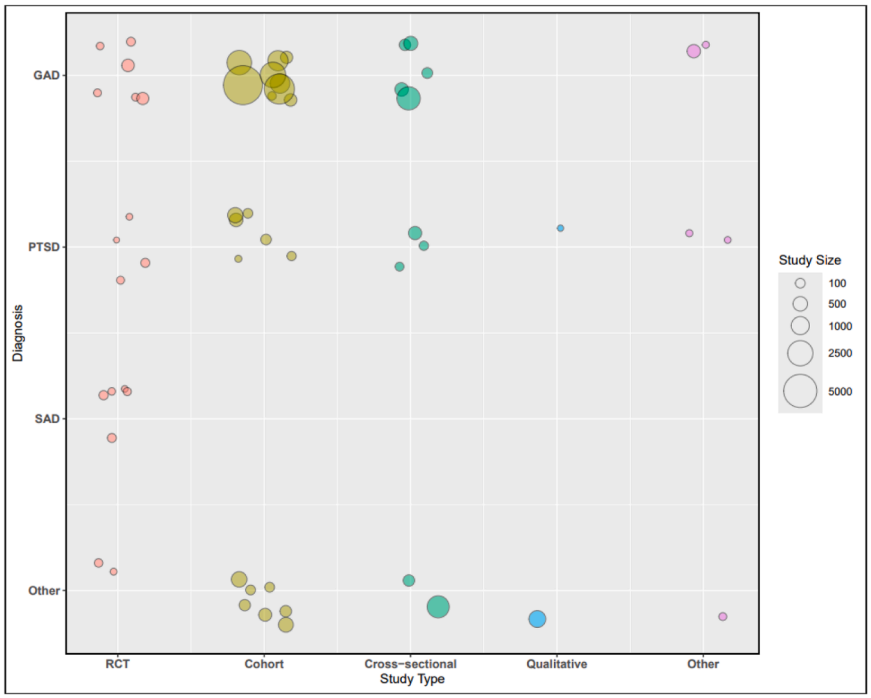


**Fig. 2.** Bubble Chart of study designs by diagnosis and study size.

Both qualitative studies (Garcia-Romeu et al., 2022; Krediet et al., 2020) were evaluated using the QualSyst Tool and received an overall bias score of 19 out of a possible 20; classifying them as having high methodological quality. Maximum scores were reported across 10 items including: questions sufficiently described, appropriate study design, sufficient context for conducting the study, sampling strategies, appropriate data collection, analysis, verification procedures used, conclusions supported by results and reflexivity in the account (Kmet, 2004). The only section that received a partial score in both studies related to the description of the theoretical framework, with each study scoring 1 point for this criterion.

### 3.3. *Efficacy and effectiveness of medicinal cannabis*

Of the 13 studies identified as having a low risk of bias and high methodological quality using the MASTER scale (Stone et al., 2019), 69 % ($n = 9$) reported that medicinal cannabis was effective in treating a range of anxiety-related disorders, in terms of symptom reduction and/or quality of life (Bapir et al., 2023; Gournay et al., 2023; Jetly et al., 2015; Kwee et al., 2023; Masataka, 2019; Sachedina et al., 2022; Souza et al., 2022; Weiss et al., 2023; Zabik et al., 2023). Among these, three studies (Gournay et al., 2023; Kwee et al., 2023; Weiss et al., 2023) reported non-statistically significant symptom improvement. Conversely, 31 % ($n = 4$) of the high-quality studies (Grant et al., 2022; Kayser et al., 2020; Kwee et al., 2022; Stanley et al., 2023) found no significant differences in the reduction of anxiety symptoms compared to placebo, with two specifically focusing on conditions including OCD and Trichotillomania (Grant et al., 2022; Kayser et al., 2020). Additionally, the two qualitative studies (Garcia-Romeu et al., 2022; Krediet et al., 2020), which scored highly on the QualSyst tool (Kmet, 2004), reported improvements in both symptoms and quality of life among participants using medicinal cannabis.

In contrast to the studies with a higher relative risk of bias, the majority (39 out of 42) reported that medicinal cannabis was effective in reducing anxiety symptoms and/or enhancing quality of life.

#### 3.3.1. *Generalised anxiety disorder (GAD)*

A total of 22 studies investigated the use of medicinal cannabis for treating people with GAD. Twenty one (95 %) reported that medicinal cannabis reduced anxiety symptoms and showed improvement in quality of life by the end of the observation period (0 - 24 months) (Altman et al., 2023; Bapir et al., 2023; Dahlgren et al., 2022; Erridge et al., 2023; Fabre and McLendon, 1981; Faraj et al., 2023; Gournay et al., 2023; Hundal et al., 2018; Kimless et al., 2022; Moltke and Hindocha, 2021; Rapin et al., 2021; Rifkin-Zybutz et al., 2023; Rosenthal and Pipitone, 2021; Sachedina et al., 2022; Sagar et al., 2021; Souza et al., 2022; Tait et al., 2023; Turna et al., 2019; Vickery et al., 2022; Weiss et al., 2023; Zaki et al., 2017). One study, however, found that CBD specifically had no significant effect on test anxiety, general anxiety or test performance (Stanley et al., 2023). There was variability in the follow up durations in these studies, five (23 %) did not report a follow up or was not applicable, two (9 %) were immediate single sessions, three (14 %) were short term, six (27 %) were medium term, and six (27 %) were long term. Of the studies, nine investigated a combination of cannabinoid compounds and did not delineate the difference in results via compound, while three did not report any information on the compound or dosage examined. Six studies investigated CBD and one study Nabilone. Among these studies, one study reported that neither the 50 mg nor the 300 mg CBD doses resulted in a significant difference in outcomes (Gournay et al., 2023) or the ratio of CBD and THC products (Rapin et al., 2021); one study reported a positive treatment response at a lower CBD dose of 30 mg/day, compared to previous trials where a response was only observed at 300 mg/day (Dahlgren et al., 2022). However, studies which only examined a single therapeutic dose, rather than ongoing therapy, showed no improvement in anxiety symptoms (Hundal et al., 2018; Stanley et al., 2023).

Of the 13 highest quality studies, six studies investigated GAD, and five reported that medicinal cannabis was effective in reducing anxiety symptoms and improved quality of life by the end of the observation period (0 - 24 months) (Bapir et al., 2023; Gournay et al., 2023; Sachedina et al., 2022; Souza et al., 2022; Weiss et al., 2023). One study, however, found that CBD had no significant effect on test anxiety, general anxiety or test performance (Stanley et al., 2023). The authors noted that the study lacked statistical power and the observed effects was not statistically significant (Stanley et al., 2023).

Among the high-quality studies reporting symptom reduction, there

was some variability in the results. Souza et al. reported a significant reduction in anxiety scores using the GAD-7, with scores decreasing significantly ($p < 0.001$) (Souza et al., 2022). Similarly, Sachedina et al. observed a reduction in GAD-7 scores from a baseline score of 11.1 to 6.0 after >24 months ($p < 0.001$) (Sachedina et al., 2022). Gournay et al. who used the Brief Measure of Worry Severity (BMWS) also reported a reduction in mean scores from 16.86 (±standard deviation (SD) 5.02) to 11.45 (±6.11) by week 2; however this reduction was not statistically significant (Gournay et al., 2023).

#### 3.3.2. Post traumatic stress disorder (PTSD)

A total of 16 studies (28 %) evaluated the effectiveness of medicinal cannabis for treating participants with PTSD, with 88 % ($n = 14$) reporting an improvement in PTSD symptoms including in sleep scores and general wellbeing (Bolsoni et al., 2022; Bonn-Miller et al., 2022; Bruce et al., 2021; Chan et al., 2017; Greer et al., 2014; Krediet et al., 2020; LaFrance et al., 2020; Meakin et al., 2020; Nacasch et al., 2023; Roitman et al., 2014; Smith et al., 2017; Sznitman et al., 2022; Vaddiparti et al., 2023; Walsh et al., 2023). Of the included studies, six did not specify the cannabinoid compound administered, four investigated THC dominant formulations, three examined combined CBD and THC preparations, and two evaluated the synthetic cannabinoid Nabilone. One study found that a single CBD dose did not reduce PTSD symptoms (Bolsoni et al., 2022). The remainder of the different compounds were reported to be associated with an improvement in symptoms. Consistent with studies examining GAD, there was heterogeneity across designs, measures of outcomes, study populations, and cannabis types examined. Some studies indicated prolonged relief from PTSD symptoms, with one reporting that participants with PTSD using cannabis were 2.57-times ($p = 0.03$) more likely to no longer meet the DSM-IV (American Psychiatric Association, 1994) criteria for PTSD by year one (Bonn-Miller et al., 2022). Comparable with the GAD studies, there was variability in follow up time four (25 %) did not report a follow up or was not applicable, five (31 %) short term, two (13 %) medium term, and five (31 %) were long term. Less than half of the studies (44 %) reported information regarding dosages or types of cannabis used.

Of the 13 highest quality studies, two investigated PTSD and found medicinal cannabis an effective treatment option. One study investigated trauma exposed adults with PTSD and non-PTSD controls, and found that the use of medicinal cannabis can influence brain activity related to fear learning and memory in adults with trauma which could help to improve the process of overcoming fear (Zabik et al., 2023). The other study focused on military personnel and reported that treatment with the synthetic cannabinoid Nabilone significantly reduced the frequency of nightmares ($p = 0.03$) (Jetly et al., 2015). Additionally, a high-quality qualitative study found that veterans experienced improved sleep quality, and greater relaxation in addition to partners of participants highlighting improvement in patient-wellbeing (Krediet et al., 2020).

Several studies reported significant improvements in various sleep measures following treatment with medicinal cannabis. Jetley et al. reported a greater mean reduction in recurring and distressing dreams between the cannabis group (3.6 ± 2.4) compared to the non-cannabis group of (1.0 ± 2.1) ($p = 0.03$) (Jetly et al., 2015). Another study reported a significant increase in sleep quality between week one and four following treatment initiation ($p < 0.01$) (Roitman et al., 2014), while a further study reported an increase in sleep hours from 5.03 to 6.83 h across 70 days (SD 1.9)(Vaddiparti et al., 2023). These results were echoed by a qualitative study where veterans discussed a wide range of therapeutic effects experienced from medicinal cannabis, particularly in improved sleep quality and a reduction in nightmares (Krediet et al., 2020). However, not all studies included in the review reported improvements in sleep parameters, with one finding no statistically significant improvement in the frequency of nightmares ($p = 0.27$) (Nacasch et al., 2023).

#### 3.3.3. Social anxiety disorder (SAD)

A total of five studies investigated the use of medicinal cannabis in those with SAD, four studies reported reductions in anxiety symptoms (Bergamaschi et al., 2011; Crippa et al., 2011; Kwee et al., 2023; Masataka, 2019). All studies examining SAD used CBD, however only three reported dosages (range 300–600 mg) (Bergamaschi et al., 2011; Crippa et al., 2011; Kwee et al., 2022). All studies had follow-up periods (Bergamaschi et al., 2011; Crippa et al., 2011; Kwee et al., 2022, 2023; Masataka, 2019) ranging from a single session to 6 months.

Of the 13 highest quality studies, three investigated SAD yielding a range of findings. The highest quality study in the review, Masataka et al. found the use of CBD improved social anxiety scores in Japanese adolescents new to treatment (mean±SD 74.2 ± 7.5 v 62.1 ± 8.7 for CBD, and 69.9 ± 10.3 v 66.8 ± 11.2 for placebo; $p < 0.001$) (Masataka, 2019). Another study reported that CBD reduced shock expectancy, suggesting benefits in alleviating fear anticipation ($p = 0.004$) (Kwee et al., 2023). However, a third study found that CBD did not significantly enhance early treatment response, within session fear extinction nor extinction learning ($p = 0.089$)(Kwee et al., 2022).

#### 3.3.4. Other anxiety studies

Of the remaining studies ($n = 14$, 25 %), a combination of anxiety-related disorders was investigated including GAD, PTSD, OCD and/or phobias but results were not disaggregated by anxiety sub-type. Seven studies investigated a combination of CBD and THC cannabinoids, three studies did not report any cannabinoid information, while the remaining four investigated CBD, THC and Nabilone. Half ($n = 7$) of the studies provided detailed dosage information. Twelve studies reported improvement in symptom severity of the condition(s) examined (Ashare et al., 2022; Berger et al., 2022a; Cahill et al., 2021; Cameron et al., 2014; Dugosh et al., 2023; Garcia-Romeu et al., 2022; Kalaba and Ware, 2022; Lee et al., 2022; Lintzeris et al., 2018; Martin et al., 2021; Moreno-Sanz et al., 2022; Stack et al., 2023). Only one study investigated the use of medicinal cannabis for treatment-resistant anxiety, which reported a 50 % reduction in symptom scores within 12 weeks in under half (40 %, $n = 12$) of the participants (Berger et al., 2022b). Another study reported a 32 % reduction in the use of anti-anxiety medication within the first three months of beginning medicinal cannabis treatment (Dugosh et al., 2023). Another study investigating multiple anxiety-related disorders reported no significant changes in participants with GAD after six weeks of treatment, however, 81 % of patients with PTSD reported improvements between weeks one and six (Cahill et al., 2021).

Of these 14 studies, only two were of high quality (low relative risk of bias) with each investigating a specific condition of OCD (Kayser et al., 2020) or Trichotillomania (Grant et al., 2022). Kayser et al. reported both THC and CBD reduced self-reported OCD symptoms but showed no significant differences from placebo ($p = 0.577$) (Kayser et al., 2020). Grant et al. was the only study in the review which investigated skin Trichotillomania (a skin picking disorder) and found participants on placebo improved significantly compared to the CBD group, thus the authors did not recommend CBD as a suitable medication for this condition (Grant et al., 2022).

## 4. Discussion

The majority of studies included in this review reported that medicinal cannabis reduced anxiety symptoms; however, these findings should be interpreted with caution due to substantial heterogeneity and a moderate to high risk of bias in many studies. Among studies with a low relative risk of bias studies included in this review, 69 % reported improvements in anxiety symptoms and quality of life following medicinal cannabis use. Among high-quality trials that investigated GAD, there were consistent reductions in anxiety scores reported. Similarly, qualitative findings highlighted improvements in both symptom relief and sleep quality, especially for participants with PTSD. Despite the

reported benefits, the heterogeneity of study designs, cannabinoid formulations investigated, dosing regimens, and the lack of standardised protocols—alongside generally low study quality—limits the ability to draw definitive conclusions regarding the efficacy of medicinal cannabis for the treatment of anxiety-related disorders.

Our review predominantly included studies investigating GAD or PTSD, which likely reflects that these are the most common anxiety-related conditions being treated with medicinal cannabis in real-world clinical practice. Furthermore, 25 % of studies investigated a combination of GAD and PTSD, highlighting the overlap between conditions that can complicate treatment for these disorders. The lack of studies investigating OCD and phobias suggests that there is a gap in the literature that warrants further investigation. The findings from this review reinforce the need for more rigorous, standardised and long-term research to better determine the role of medicinal cannabis in the treatment of anxiety-related disorders. Additionally, this review adds to the growing body of literature in this area, while underscoring need for further high-quality research.

Previous systematic reviews on medicinal cannabis have largely focused on a broad spectrum of health conditions including chronic pain, cancer, chemotherapy-induced nausea, and childhood epilepsy (National Academies of Sciences and Medicine, 2017). This was alongside reviews of psychiatric and other mental health conditions such as depression, ADHD, bipolar disorder, schizophrenia, psychoses and personality disorders (Botsford et al., 2020; Hoch et al., 2019; Sarris et al., 2020), with mixed results and consistent calls for further research in these areas. Reviews conducted on anxiety and depressive disorders reported that CBD could be effective in reducing symptoms of anxiety, however concluded there was a need for well-designed RCTs to determine efficacy (Black et al., 2019; Chadwick et al., 2020; Hasbi et al., 2023; Khan et al., 2020; Sarris et al., 2020). Similarly, Han et al. (2024) and Bonaccorso et al. (2019), reported that CBD could be effective in the treatment of GAD and PTSD; however both studies were limited in sample size, highlighting the need for additional trials (Bonaccorso et al., 2019; Han et al., 2024). A review focused on PTSD found potential benefits particularly in improving the quality of sleep for participants, but was limited by a high relative risk of bias (Hindocha et al., 2020). Our review builds on this foundation of knowledge in the area by exclusively focusing on anxiety-related disorders, and addresses a critical gap by examining specific cannabinoid compound and types of interventions.

### 4.1. *Efficacy and effectiveness of medicinal cannabis*

Among the highest-quality studies evaluated using the MASTER scale (Stone et al., 2019), medicinal cannabis was shown to improve anxiety symptoms in disorders such as GAD, PTSD, and SAD (Bapir et al., 2023; Gournay et al., 2023; Jetly et al., 2015; Kwee et al., 2023; Masataka, 2019; Sachedina et al., 2022; Souza et al., 2022; Weiss et al., 2023; Zabik et al., 2023). One high-quality study highlighted its potential for future therapeutic interventions aimed at enhancing fear extinction learning and memory in patients with PTSD (Zabik et al., 2023). However, for specific conditions like test anxiety, OCD, and Trichotillomania, results indicated that medicinal cannabis would not be recommended as a treatment option (Grant et al., 2022; Kayser et al., 2020; Stanley et al., 2023). A low-quality study on treatment resistant anxiety, suggested that medicinal cannabis may be a treatment option (Berger et al., 2022b). However, further rigorous research is needed to substantiate these findings (Berger et al., 2022b). Overall, the majority of high-quality studies provided evidence suggesting that medicinal cannabis may be an effective treatment for a range of anxiety-related disorders. While lower-quality studies also reported symptom improvements, more rigorous research is necessary to confirm these outcomes.

Among the lower-quality studies, three reported null or negative findings. Stanley et al., 2023 found that CBD had no significant impact on test anxiety, general anxiety or test performance (Stanley et al., 2023). Bolsoni et al., 2022 reported CBD had a limited overall impact on PTSD symptoms (Bolsoni et al., 2022), while Hundal et al., 2018 concluded that CBD did not exhibit anxiolytic effects (Hundal et al., 2018).

Across disorders, there were limited data on the long-term effectiveness of treatment beyond six months. While these findings suggest that medicinal cannabis may provide short-term symptom relief (within 4–6 weeks of treatment initiation) and improvements in quality of life, further research is needed to determine whether these effects are sustained in the long term. Given that anxiety-related disorders often persist across the lifespan (Kessler et al., 2012), it is crucial to determine whether medicinal cannabis can reduce the duration and severity of symptoms.

Previous research has indicated a link between sleep—particularly sleep disturbances and poor sleep quality— and cognitive, emotional, and interpersonal functioning which all contribute to poorer mental health (Baglioni et al., 2016; Kahn et al., 2013). Additionally, studies have shown significant associations between poor sleep quality and anxiety-related disorders beyond PTSD, underscoring the critical role of addressing sleep disturbances in effectively managing anxiety disorders (Alvaro et al., 2013; Chellappa and Aeschbach, 2022). In this review, several studies reported improvement in sleep parameters, including sleep duration, reduction in nightmares and fewer nighttime interruptions, particularly among participants with PTSD (Jetly et al., 2015; Krediet et al., 2020; Meakin et al., 2020; Nacasch et al., 2023; Roitman et al., 2014; Sznitman et al., 2022; Vaddiparti et al., 2023). This is reflected in existing literature that reported THC may improve sleep quality and reduce dreaming, which is a key source of distress in patients with PTSD (Belleville et al., 2009). Notably, only two of the studies were rated as high quality (Jetly et al., 2015; Krediet et al., 2020). Thus, more robust research is needed to determine whether medicinal cannabis has clinically meaningful effects on sleep and, in turn, symptom severity in PTSD. Future studies should also explore which cannabis formulations are most effective for improving sleep, and whether such benefits extend to individuals with anxiety disorders beyond PTSD.

There was a large range of cannabinoids used, with limited information available regarding dosages and results were often not delineated with the different combinations of cannabinoid compounds. As such, it is unclear from the included literature if there are differences between types of cannabinoids and therapeutic dosages in terms of efficacy or effectiveness in treating anxiety-related disorders. Furthermore, comprehensive research is needed regarding the specific varieties of cannabinoids, as some research suggests that growing location and cannabis strain can affect the levels of CBD and THC within the plant, and thus have different effects on participants using this medicinally (Szejko et al., 2024).

Across the studies, medicinal cannabis was generally well tolerated, with adverse events generally being mild to moderate in severity. In studies using CBD formulations, the most frequently reported adverse events in participants with GAD were dry mouth, fatigue, and drowsiness (Bapir et al., 2023; Erridge et al., 2023; Gournay et al., 2023; Rifkin-Zybutz et al., 2023; Souza et al., 2022). In contrast, studies involving THC or Nabilone formulations, primarily used for participants with PTSD, commonly reported psychoactive effects such as sedation and in some cases agitation. As adverse events associated with cannabinoid products have been examined in detail elsewhere (Pratt et al., 2019; Wang et al., 2008), an in-depth analysis of adverse events was beyond the scope of the review.

Given the high proportion of studies (77 %) scored as having moderate to high risk of bias, the findings of the review should be interpreted with caution. Possible biases included selection bias, information bias and design-related limitations. Sampling bias was evident in three studies that included participants with prior cannabis use or were from cohorts that are seeking to legitimise therapeutic use of cannabis (Chan et al., 2017; Erridge et al., 2023; LaFrance et al., 2020). Furthermore, the

widespread reliance on self-reported outcomes may have introduced recall, reporting or social desirability bias (Van de Mortel, 2008). There were high rates of declared or potential conflicts of interest in 26 studies (47 %) included in the review, raising the possibility of sponsorship bias and the overstatement of cannabis-related benefits. These sources of bias highlight the need for more rigorous and transparent research. They also warrant caution in drawing definitive conclusions about the efficacy of medicinal cannabis for anxiety-related disorders, given the low-moderate quality of many studies included in this review.

As the demand for medicinal cannabis to treat anxiety-related disorders continues to grow, it is crucial to conduct more research on these interventions to ensure that vulnerable individuals receive the most appropriate treatment for their condition.

### 4.2. Future research

There are several gaps in the current literature that future research could address. Longitudinal studies with extended follow-up periods (exceeding one year) are needed to investigate long-term effectiveness and safety of medicinal cannabis in managing anxiety symptoms. This would provide important evidence on whether medicinal cannabis could be a viable option for the long-term management of anxiety disorders, which can persist throughout the lifespan for some individuals (Michael et al., 2007). Additionally, future studies should explore the influence of cannabinoid dose and type on the sustained management of anxiety symptoms over time.

High quality study designs with greater standardisation in measurement tools and outcomes are essential to enable meaningful comparisons across studies. In addition to standardisation, research on specific cannabis strains and dosage amounts across all anxiety disorders remains limited and should be considered. This reflects a broader challenge within the field of medicinal cannabis research, and the findings of this review contribute to the growing calls for standardisation (Jugl et al., 2021; National Academies of Sciences and Medicine, 2017).

The overrepresentation of studies from high-income countries particularly the United States, Canada, and the United Kingdom highlights a need for more diverse research. Studies conducted in lower-to-middle-income countries would help improve the generalisability of findings and ensure a broader range of populations are represented.

Future studies should also investigate how medicinal cannabis can be integrated with standard treatments, such as Selective Serotonin Reuptake Inhibitors (SSRIs), traditional anxiolytics and cognitive therapy for anxiety-related disorders (Bystritsky, 2006). Additionally, research into the potential for cannabinoid tolerance and dependence over extended periods of use would be valuable.

### 4.3. Strengths and limitations

A key strength of the review is the use of a rigorous and comprehensive search strategy, with two independent reviewers. Furthermore, the use of the MASTER scale and QualSyst risk of bias assessment tools allowed the researchers to objectively assess the quality and risk of bias of the studies.

A notable limitation of this review was the inability to conduct a meta-analysis due to substantial heterogeneity in study designs and outcome measures. The high level of heterogeneity also made it challenging to draw definitive conclusions or assess the generalisability of the results. Furthermore, the exclusion or limited reporting of cannabinoid regimes, doses and formulations within the studies hindered synthesis of the findings. However, this issue is common across the broader field of cannabis research, where there have been increasing calls for standardisation of dosing that accounts for the intended therapeutic use and subjective effects to determine the efficacy of medicinal cannabis (Jugl et al., 2021; National Academies of Sciences and Medicine, 2017). Furthermore, the majority of studies were assessed to be low to medium quality which raises issues in terms of multiple forms of bias, including selection bias, information bias, and sponsorship bias. Additionally, the reliance on self-reported symptom changes in most studies may have introduced recall, reporting and social desirability biases (Van de Mortel, 2008).

## 5. Conclusion

Across a range of anxiety-related disorders, most high-quality studies found that medicinal cannabis reduced anxiety symptoms in individuals with GAD, PTSD and SAD. Studies investigating OCD and Trichotillomania found medicinal cannabis had little to no effect on improving anxiety-related symptoms. The remaining low-to-moderate quality studies included in the review found similar findings of positive effects. However, due to the heterogeneity in the study designs, outcomes, lack of information provided on cannabinoid regime and dosage the results are less compelling. As the study quality in the existing literature was generally low, future research with higher-quality study designs and more robust methodologies are needed. Clear gaps remain in the evidence regarding the effects of dosage and type of medicinal cannabis on anxiety treatment outcomes. Given the increase in prescribing medicinal cannabis to treat anxiety, more research is urgently needed to address these gaps in the knowledge.

## Abbreviations

GAD: General Anxiety Disorder
OCD: Obsessive Compulsive Disorder
PTSD: Post-Traumatic Stress Disorder
SAD: Social Anxiety Disorder

## CRediT authorship contribution statement

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Supplementary materials

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