

Review

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Review

# Cannabidiol (CBD) as Treatment for Anxiety, Depression, and Trauma: A Systematic Review of Clinical Evidence

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## Abstract

**Background:** Cannabidiol (CBD) is increasingly used as self-treatment for psychiatric symptoms despite limited evidence of efficacy. This systematic review examined clinical trials investigating effects of CBD on anxiety, mood, and trauma-related disorders and symptoms. **Methods:** Following PRISMA 2020 guidelines, MEDLINE, PsycINFO, and Embase were searched from inception to August 2026 for randomized controlled trials (RCTs) of CBD in adults with anxiety, mood, or trauma-related disorders or subthreshold anxiety, mood, or trauma-related symptoms. Risk of bias (RoB) was assessed using Cochrane RoB 2. **Results:** Of 733 publications identified, 12 reports from 10 RCTs met inclusion criteria: six examined anxiety, two mood / depressive, and four PTSD/trauma-related disorders or symptoms. In anxiety studies, CBD monotherapy reduced anxiety symptoms and negative self-evaluation in some populations, although effects varied across outcomes and dosing paradigms. Adjunctive CBD with exposure therapy for social anxiety disorder and panic disorder with agoraphobia provided no benefit over placebo. Trials in bipolar depression and depressive symptoms showed no CBD-specific effects. In trauma studies, CBD generally did not improve trauma-related, depressive, or anxiety symptoms. However, two reports from a single trial found that a single dose of CBD attenuated cognitive impairment induced by trauma-recall. One of these reports reported reduced anxiety among participants with nonsexual trauma. Two reports were low risk of bias, seven had some concerns, and three were high risk. **Limitations:** CBD adherence was objectively verified in three trials. The small, heterogeneous evidence base limited comparisons across diagnoses and outcomes. **Conclusions:** Evidence for CBD as treatment of anxiety, depressive, and trauma-related symptoms remains preliminary. Some anxiety trials found reductions in anxiety symptoms with CBD monotherapy, but findings were inconsistent across populations, outcomes, and dosing paradigms. Evidence was insufficient to determine CBD-specific effects on depressive or trauma-related symptoms. Future RCTs should standardize and objectively verify dosing and incorporate cognitive, physiological, and neurobiological outcomes.

**Keywords:** cannabidiol; systematic review; clinical trials; anxiety; depression; stress; trauma; mood

## Introduction

Cannabis consumption has been increasing recently, with global cannabis usage rates growing by over 20% from 2011 to 2021[1,2]. Canada has one of the highest rates of cannabis use, with surveys demonstrating that use has nearly doubled in the past decade, with over a fifth of Canadians (21–22%) reporting past-year use in 2019 and 2021, compared to 11–12% in 2012/2013 [3–5]. Since 2018, access

to cannabis has been facilitated by several regulatory changes, such as the legalization of recreational cannabis use in Canada and the Farm Bill legalizing hemp in the United States [6,7]. Similar trends are present in Europe, where past-month prevalence of cannabis use has increased by 27% among adults between 2010 and 2019, from 3.1% to 3.9% [8]. Products containing tetrahydrocannabinol (THC), the main psychoactive component of cannabis, have garnered the most interest in the recreational market; however, cannabidiol (CBD) products have also increased in popularity [5], particularly for medical purposes, such as for the treatment of anxiety and depression [5,9]. Currently, CBD is approved by the US Food and Drug Administration (FDA) and Health Canada as treatment or adjunctive treatment for certain seizure disorders [10]. Most consumers report using CBD for anxiety, depression, and sleep [8,9]. To date, there is little rigorous, high-quality research supporting the use of CBD for treatment of psychiatric disorders [13]. As the burden of mental disorders and the prevalence of self-medication with CBD continue to grow [14], it is imperative that we better understand current knowledge and evidence on CBD as treatment of psychiatric disorders and symptoms, and what role it may have as future therapeutic.

Although there is a large body of research linking cannabis use to psychiatric illness, the adverse psychiatric effects associated with cannabis are largely attributed to THC [15]. Preclinical and human studies have implicated long-term exposure to high-THC products with anxiety, depression, and psychotic disorders [15]. Conversely, evidence suggests CBD may positively affect these same disorders through its distinct mechanisms of action [15,16]. CBD has a low affinity for the cannabinoid 1 (CB1) and 2 (CB2) receptor [17], and potential inhibition of fatty acid amide hydrolase (FAAH), the enzyme responsible for degrading anandamide, by CBD has been reported [16,18,19]. By reducing anandamide degradation, FAAH inhibition may increase anandamide availability and prolong its signalling. However, evidence for direct FAAH inhibition by CBD is inconsistent, particularly in humans, where CBD may instead interfere with the intracellular transport of anandamide to FAAH via fatty acid-binding proteins (FABPs) [16,18]. Human studies have reported mixed effects of CBD on anandamide concentrations, with findings primarily based on peripheral blood measurements rather than direct assessments of the central nervous system (CNS) [20–22]. CBD also interacts with non-cannabinoid targets, such as transient receptor potential vanilloid 1 (TRPV1) and serotonin 5-HT<sub>1A</sub> receptors, which have been implicated in anxiety and stress regulation [18,23].

Preclinical models show that CBD may modulate emotional and stress-related responses, with reported effects including enhanced fear extinction, reduced conditioned freezing, and blunted stress-induced corticosterone release [27,28]. These findings have informed human experimental work in non-clinical and clinical populations, where single doses of CBD have been shown to reduce anxiety and cognitive impairment during simulated public-speaking tasks, with effects mostly observed on subjective anxiety and discomfort rather than physiological indices [25–27]. Conversely, some experimental fear-conditioning paradigms report CBD selectively reduces threat expectancy without altering skin conductance or startle response, suggesting effects may be specific to cognitive appraisal rather than global fear reactivity [28]. Neuroimaging studies also show that acute CBD administration reduces amygdala reactivity to fearful stimuli and modulates prefrontal-limbic connectivity [29].

Beyond anxiety and fear processing, preclinical studies have also reported antidepressant-like effects of CBD, including reductions in depressive-like behaviours and improvements in reward-related measures such as sucrose preference in animal models [30,31]. However, evidence for antidepressant effects in humans remains limited, and the broader clinical literature on CBD and psychiatric symptoms is mixed [32,33]. Studies outside the present review have reported both anxiolytic and null effects, with findings varying according to dose, administration schedule, and experimental context [34,35]. Similarly, preliminary evidence for effects on depressive symptoms remains limited and inconsistent, while trauma-related research has reported potential benefits in some clinical samples alongside limited and heterogeneous evidence overall [36,37]. Collectively,

these findings suggest that CBD may influence specific components of emotional, stress, and reward processing rather than producing a uniform reduction in psychiatric symptoms.

Existing systematic reviews have begun to synthesize this literature but with notable scope limitations. One recent review examined cannabinoid effects on anxiety broadly, aggregating CBD and THC-containing formulations without consistently isolating CBD-specific effects [33]. Another review focused narrowly on populations with PTSD, without extending to the broader anxiety and mood disorder spectrum or addressing whether effects differ across subclinical and clinical illness stages [37]. However, these reviews did not systematically examine whether CBD effects differ across symptom domains or across clinical and subclinical populations. To date, no review has comprehensively examined and evaluated evidence on CBD's effects across anxiety, mood, and trauma-related disorders and symptoms while considering differences across symptom domains and clinical versus subclinical populations. Thus, the aim of the present systematic review was to evaluate and synthesize findings from randomized controlled trials of CBD to characterize current evidence of CBD's effects across subjective, behavioural, physiological and biological outcomes, and across these psychiatric domains and populations.

## Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD420261488277).

### *Search Strategy*

A comprehensive search was conducted using Medline, PsycINFO, and Embase databases from inception to August 2026. The search strategy combined terms related to 1) cannabidiol (CBD) and 2) a broad range of psychiatric disorders to maximize the identification of potentially relevant studies. Although the search included a broad range of psychiatric conditions, the review focused on diagnosed disorders and subthreshold symptoms within the domains of anxiety, mood, and trauma- and stressor-related disorders. The full search strategy is available in the Supplementary Material. Retrieved articles were uploaded into Covidence for title/abstract and full-text screening [38]. Screening was conducted in two stages: title and abstract screening, followed by full-text screening. Three independent reviewers (AS, EL, SS), and any discrepancies were resolved through discussion with SK.

### *Eligibility Criteria*

Inclusion criteria were as follows: 1) randomized controlled trials of cannabidiol (CBD) involving human participants; 2) peer-reviewed original research; 3) studies examining CBD-specific interventions; and 4) studies assessing diagnosed psychiatric disorders or subthreshold psychiatric symptoms within the domains of anxiety, mood, and trauma- and stressor-related disorders. Eligible studies included clinical populations with a diagnosed disorder (e.g., social anxiety disorder, panic disorder, bipolar disorder, or PTSD), as well as non-clinical populations with elevated or subthreshold anxiety, depressive, stress- or trauma-related symptoms. Relevant assessments included validated self-report measures of anxiety, mood, PTSD, and related symptom severity; clinician-administered diagnostic and symptom-severity instruments; physiological and behavioral indices of fear and stress reactivity; and biological markers of stress response.

Studies were excluded if they met the following criteria: 1) studies examining general cannabis use, including THC-specific interventions with or without CBD; 2) studies that did not assess a relevant diagnosis or subthreshold symptoms within the domains of anxiety, mood, or trauma- and stressor-related disorders using validated tools (e.g., structured interviews or validated symptom scales); 3) reviews or meta-analyses, case series, case reports, commentaries, opinion papers,

unpublished studies, conference posters or published abstracts, dissertations, quasi-experimental studies, or other observational or uncontrolled study designs; 4) studies published in a language other than English; 5) studies examining neurodevelopmental, genetic, congenital, or physical health conditions (e.g., chronic pain, cancer therapy, epilepsy, or autism); 6) studies examining substance use and/or substance use disorders as a primary condition or outcome; 7) studies involving eating disorders; 8) studies involving pediatric or geriatric populations; and 9) studies involving animal models.

Data Extraction & Quality Assessment

Data extraction was completed independently by four reviewers (AS, EL, HI, SS). Extracted data included: author and year of publication; study design; sample characteristics (number of participants, mean age, percentage of women, country, and recruitment source); clinical diagnostic assessment and diagnostic system; psychiatric diagnosis; mood, anxiety, and other psychiatric symptom measure(s) and their designation (subjective/self-report, clinician-administered, or objective); CBD administration route and dose, control intervention, and concomitant medication use, including whether a medication washout period was reported; primary outcome; and key findings. Key findings also captured longitudinal effects, sex or gender differences, and other relevant results (e.g., moderator analyses, adverse events, and adherence), where reported.

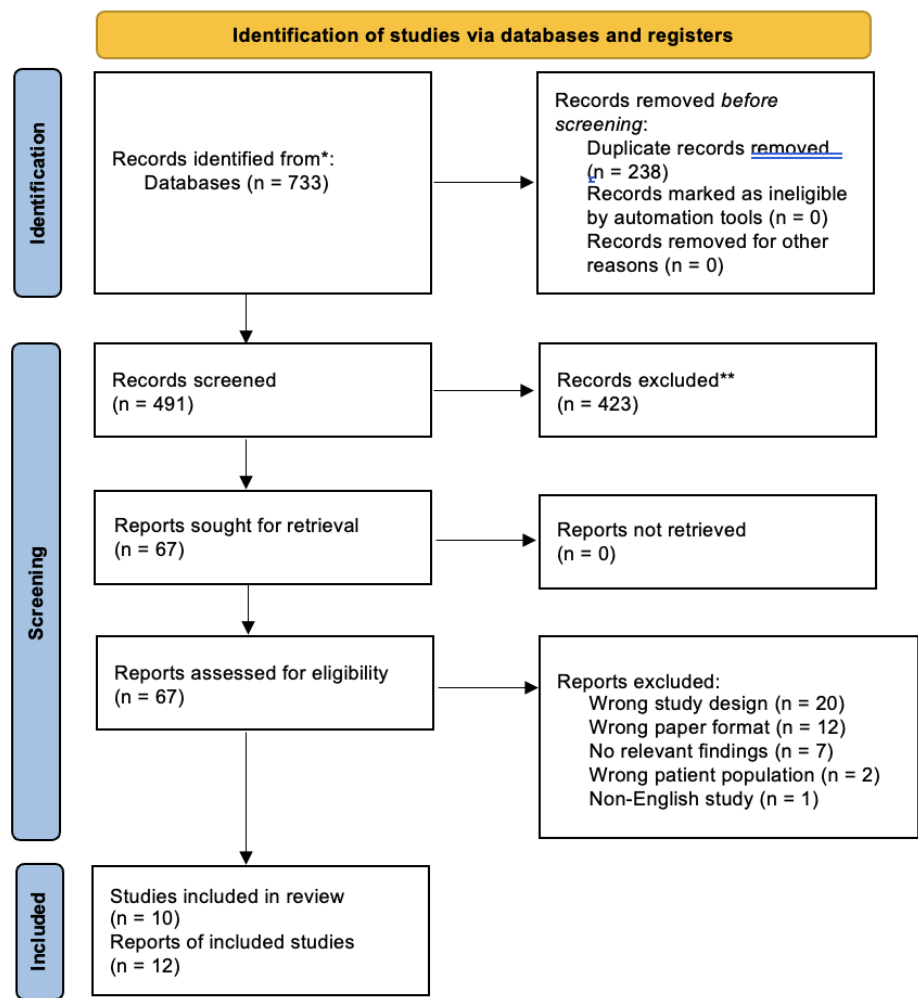


Figure 1. PRISMA Flow Diagram.

Sample designation was classified as clinical when participants met criteria for a psychiatric diagnosis established through a structured or clinician-administered diagnostic assessment (e.g., SCID, MINI, CAPS-5). It was classified as non-clinical when participants had no formal psychiatric diagnosis, including those recruited for elevated symptoms on a self-report measure (e.g., PSWQ, PSS-10) or subthreshold trauma symptoms. Healthy control groups were included only as comparators.

All included studies were randomized controlled trials, thus methodological quality was evaluated using the Cochrane Collaboration Risk of Bias Tool 2.0 (RoB 2)[39]. Studies were designated as either low risk, some concerns, high risk, or critical risk (no study met this designation). Because multiple reports could arise from the same underlying trial and different outcomes could have different methodological characteristics, risk-of-bias ratings could differ across reports or outcomes from the same trial. The quality ratings were used to inform the interpretation of individual findings (Tables 1-3).

Results

Study Characteristics

Our search identified 733 articles, of which 12 reports from 10 unique trials met the inclusion criteria. Seven trials characterized participants using structured or clinician-administered diagnostic interviews, while three recruited non-clinical samples selected based on elevated trait anxiety, worry, or perceived stress [28,40–50]. Three trials investigated social anxiety disorder; three investigated PTSD or subthreshold PTSD symptoms; one investigated mixed mild-to-moderate anxiety disorders; one investigated bipolar depression; and two investigated elevated worry or perceived stress. All trials administered quantified oral or sublingual CBD, with doses ranging from 25–600 mg/day for 2–12 weeks or 300–600 mg as a single acute dose [28,40–50]. Three trials objectively verified CBD administration [41,43,46]. Anxiety-related outcomes were assessed in all trials, while five also included depressive or mood measures. Eight reports used rating scales (self-report or clinician-administered) for outcomes, whereas four included objective physiological measures alongside rating scales [28,40–50].

All trials randomized participants to parallel groups and blinded the CBD-versus-placebo comparison. Sample sizes ranged from 29 to 180 participants, with seven of ten trials enrolling fewer than 65. Mean ages ranged from approximately 23 to 44 years (one trial restricted enrolment to 18–19-year-olds), and women made up between 30% and 81% of samples [47]. Trials were conducted in Brazil (n = 3), the USA (n = 3), and the Netherlands, Japan, India, and Germany (n = 1 each).

Every trial included a placebo comparator matched to the CBD formulation (e.g., oil-filled capsules or softgels, lactose capsules, or a matching oral solution). One trial additionally included an unblinded no-treatment control [50], and one included a healthy control group that completed the task without medication [40]. Only one trial compared multiple fixed CBD doses in parallel arms [50 vs. 300 mg/day] [46], six administered a single fixed dose, and three titrated doses within a single CBD arm [41,42,50]. Two trials tested CBD as an adjunct, to exposure therapy [28,45] or to mood stabilizers [42]. Concomitant medication use varied: two trials enrolled treatment-naïve participants [40,47], one prohibited regular medications [50], and the remaining seven did not require participants to be medication-free, four of which excluded CBD-interacting agents [41,43,46,49]. No trial reported a medication washout period.

Among the six reports on anxiety disorders or elevated trait worry, two were rated as having low risk of bias [45,46], three as having some concerns [40,41,47], and one as having high risk (Kwee et al., 2024). Among the four reports on trauma/PTSD outcomes, two were rated as having some concerns [43,48] and two as having high risk [44,49]; none were rated as low risk. For the two reports on mood-related outcomes, one in bipolar depression [42] and one in highly stressed individuals at risk for depression [50], both were rated as having some concerns. Overall, two of 12 reports were rated as low risk, seven as having some concerns, and three as high risk. Study-level details, including control interventions and concomitant medication use, are provided in Table 1.

**Table 1.** Findings for CBD use across mood, anxiety, PTSD, and trauma-related populations and symptoms (N = 713).

| Author & Year              | Study Design                                                                                                                                                                                                                                               | Sample                                                                                                                                                     | Clinical Diagnosis Assessment & Diagnostic System                 | Psychiatric Diagnosis | Mood/ Anxiety Symptom Measure               | Control Intervention & Concomitant Medication Use                                                                                                                                                                                    | Primary Outcome                                                                                                                                                                                                       | Key Findings                                                                                                                                                                                                                                                                                                                                                       | RoB Score     |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|-----------------------|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Anxiety / Anxiety Disorder |                                                                                                                                                                                                                                                            |                                                                                                                                                            |                                                                   |                       |                                             |                                                                                                                                                                                                                                      |                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                    |               |
| Bergamaschi, 2011          | Double-blind, randomized, placebo-controlled parallel-group experimental trial. Treatment-naïve adults with generalized SAD received a single 600 mg dose of CBD or placebo 90 min before a simulated public speaking test (SPST); a healthy control group | 36 young adults (mean age = 23.6 years, 50% women) in Brazil; 24 treatment-naïve SAD patients and 12 HC, recruited from undergraduate university students. | Self-report (MINI-SPIN); clinician-administered (SCID-CV); DSM-IV | SAD                   | Subjective/ self-report (VAMS, SSPS-N, BSS) | Oral CBD capsules (600 mg single dose), containing ≥99.9% pure CBD dissolved in corn oil, administered 90 min before SPST; placebo = identical capsules containing corn oil. Participants were treatment-naïve and had not taken any | VAMS anxiety factor during the SPST; primary analysis compared changes across experimental phases between SAD-CBD, SAD-placebo, and healthy control groups using repeated-measures ANOVA, with post-hoc between-group | - Anxiety: A single 600 mg dose of CBD significantly attenuated SPST-induced anxiety in patients with SAD compared with placebo (phase × group interaction, $p < .001$ ); anxiety was significantly lower in the CBD group during speech performance ( $p = .012$ ).<br>- Social-evaluative & subjective symptoms: CBD significantly reduced SPST-induced negative | Some concerns |

|               |                                                                                                                                                                                                 |                                                                                                                                                 |                    |                      |                                                        |                                                                                                                                                                                                            |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                    |          |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|----------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
|               | completed the SPST without medication.                                                                                                                                                          |                                                                                                                                                 |                    |                      |                                                        | medication for ≥3 months; no medication washout period reported.                                                                                                                                           | comparisons following significant phase × group interactions.                                                                                                                                                      | self-evaluation (SSPS-N; phase × group interaction, $p = .006$ ), cognitive impairment ( $p < .001$ ), and discomfort ( $p = .036$ ) compared with placebo. BSS scores increased during the SPST, but the CBD group did not differ significantly from placebo or healthy controls. |          |
| Gournay, 2023 | Double-blind, randomized, placebo-controlled parallel-group trial. Adults with elevated trait worry were randomized to 300 mg CBD, 50 mg CBD, or placebo twice daily for 2 weeks; acute effects | 63 adults (mean age = 29.27 years, 50.8% women) from the local community in the USA; participants had elevated trait worry and were predominant | Self-report (PSWQ) | Elevated trait worry | Subjective/self-report (BMWS, DASS-A anxiety subscale) | Oral hemp-derived CBD isolate in MCT-oil softgels; 300 mg/day (150 mg twice daily) or 50 mg/day (25 mg twice daily) for 2 weeks; placebo = MCT-oil softgels. Participants were required to maintain stable | Mixed linear models examined the effects of treatment condition (300 mg CBD, 50 mg CBD, placebo) and time on BMWS across Day 1 and Week 2, including treatment × time interactions. Acute effects were assessed by | - Worry: CBD did not significantly reduce worry symptoms (BMWS) compared with placebo or 50 mg CBD, either acutely or after 2 weeks of treatment.<br>- Anxiety symptoms: Repeated administration of 300 mg CBD/day resulted in a significantly greater reduction in physiological  | Low risk |

|                  |                                                          |                                                    |                                        |                                    |                                              |                                                                                                                                                                                                                       |                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |               |
|------------------|----------------------------------------------------------|----------------------------------------------------|----------------------------------------|------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
|                  | were assessed on Day 1 and repeated effects at Day 14.   | ly white, highly educated, and single.             |                                        |                                    |                                              | medication use, but prescription anxiety medications and specified CBD-interacting medications were excluded; no medication washout period reported. High-fat snack consumed before dosing to standardize absorption. | comparing treatment conditions on Day 1; repeated effects were assessed through treatment × time comparisons, particularly 300 mg CBD vs placebo. | hyperarousal symptoms of anxiety (DASS-A) over the 2-week treatment period compared with placebo (time × treatment interaction: $\beta = -2.61$ , $t = 3.02$ , $p < .01$ , $d = 1.37$ ). No significant acute treatment effect was observed.<br>- Within-group changes: DASS-A scores decreased significantly from Day 1 to Week 2 in the 300 mg CBD ( $\beta = -3.54$ , 95% CI [-4.79, -2.28]) and 50 mg CBD groups ( $\beta = -1.57$ , 95% CI [-2.82, -0.32]), but not placebo. The 300 mg vs 50 mg CBD difference in slopes was not statistically significant. |               |
| Gundugurti, 2024 | Phase III, double-blind, randomized, placebo-controlled, | 178 adults (mean age = 37.4 years, 36.5% women) in | Clinician-administered (ICD-11); self- | Mild to moderate anxiety disorders | Subjective/self-report (GAD-7, PHQ-9, PSQI); | Nanodispersible oral CBD solution (150 mg/mL), titrated between 300–600                                                                                                                                               | Change in GAD-7 and HAM-A scores from baseline to end of treatment (visit 9),                                                                     | - Anxiety: CBD significantly reduced anxiety symptoms compared with placebo, with greater reductions in                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Some concerns |

|             |                                                                                                                                                                                                                        |                                                                                                        |                                          |                                                    |                                                                                         |                                                                                                                                                                                                                                                    |                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                        |          |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------|----------------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
|             | parallel-group, multicenter trial. Adults with mild to moderate anxiety disorders were randomized 1:1 to nanodispersible CBD oral solution or placebo for 12 weeks, followed by dose tapering and 1 week of follow-up. | India; participants had mild to moderate anxiety disorders and were recruited across 10 clinical sites | report (DASS-21)                         |                                                    | clinician-administered (HAM-A, CGI-S, CGI-I)                                            | mg/day for 12 weeks, followed by reduction to 150 mg/day during Week 12 and discontinuation at Week 13; placebo = matching oral solution. Concomitant medications known to interact with CBD were excluded; no medication washout period reported. | CBD vs. placebo, compared using ANCOVA with treatment arm, visit, and baseline score as covariates.                            | GAD-7 (treatment difference = -7.02, 95% CI [-7.52, -6.52], p < .0001) and HAM-A scores (-11.9, 95% CI [-12.6, -11.3], p < .0001).<br>- Secondary outcomes: CBD significantly improved clinician-rated global improvement and severity (CGI-I and CGI-S), depressive symptoms (PHQ-9), and sleep quality (PSQI) compared with placebo (all p < .0001). |          |
| Kwee, 2022* | Double-blind, randomized, placebo-controlled, parallel-group multicenter trial. Treatment-refractory adults                                                                                                            | 80 adults (mean age = 36.7 years, 40.0% women) in the Netherlands; treatment-                          | Clinician-administered (SCID-IV); DSM-IV | SAD (n=37), panic disorder with agoraphobia (n=43) | Subjective/self-report (FQ, BAI, BDI-II, BSQ, SPAI-18, MI, ACQ); clinician-administered | Oral synthetic CBD capsules (300 mg single dose ~2 h before each of 8 weekly exposure sessions); CBD purity >99.9%;                                                                                                                                | Fear memory expression and re-extinction, assessed using subjective fear, shock expectancy, fear-potentiated startle, and skin | - Primary outcome: FQ scores significantly decreased over time, but CBD did not significantly improve FQ scores compared with placebo.                                                                                                                                                                                                                 | Low risk |

|             |                                                                                                                                                                     |                                                                                                                                    |              |                                 |                                                                    |                                                                                                                                                                                                                                                |                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |           |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------|---------------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
|             | with social anxiety disorder (SAD) or panic disorder with agoraphobia received 8 weekly therapist-assisted exposure in vivo sessions augmented with CBD or placebo. | refractory patients with SAD (n = 37) or panic disorder with agoraphobia (n = 43), recruited from three mental health care centres |              |                                 | (CGI, LSAS, PDSS)                                                  | placebo = identical lactose capsules. Antipsychotics and regular daytime benzodiazepines were excluded; stable serotonergic antidepressant use was permitted (42.5% overall; 46.2% CBD, 39.0% placebo). No medication washout period reported. | conductance response; CBD vs placebo effects were assessed using multilevel models across fear-conditioning blocks during retention and re-extinction. | - Secondary clinical outcomes: CBD did not produce significantly greater, faster, or more enduring improvement than placebo on measures of anxiety, depression, social anxiety, panic symptoms, agoraphobic cognitions, or bodily sensations. Both groups improved over time.<br>- Fear extinction & treatment response: CBD did not significantly enhance within-session fear extinction, accelerate early treatment response, increase the probability of response, or enhance consolidation of extinction learning. |           |
| Kwee, 2024* | Double-blind, randomized, placebo-controlled parallel-group trial. Adults with                                                                                      | 80 adults (mean age = 33.8 years, 41.2% women) in the                                                                              | Not reported | SAD (n=24), panic disorder with | Subjective/self-report (VAS fear, VAS shock expectancy); objective | Oral CBD capsules (300 mg single dose) or identical placebo, administered ~2                                                                                                                                                                   | Fear memory expression and re-extinction (i.e., reduction of previously conditioned fear                                                               | - Fear retention: CBD significantly reduced shock expectancy compared with placebo for both the conditioned stimulus (CS+) ( $\beta =$                                                                                                                                                                                                                                                                                                                                                                                 | High risk |

|                |                                                                                                                                                                                                                                              |                                                                                                                                         |                                                    |                                                 |                                                       |                                                                                                                                                                                                                                                                                                           |                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |               |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|-------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
|                | social anxiety disorder or panic disorder with agoraphobia received CBD or placebo before 8 weekly exposure-therapy sessions; fear conditioning was assessed before treatment (time 0) and 80 min after the first CBD/placebo dose (time 1). | Netherlands; treatment-refractory patients with SAD or panic disorder with agoraphobia, recruited from three mental health care centres |                                                    | agoraphobia (n=27)                              | (SCR, fear-potentiated startle/EMG eyeblink response) | h before weekly exposure-therapy sessions; fear-conditioning outcomes at T1 were assessed 80 min after the first dose. Serotonergic antidepressants were permitted if stable for ≥4 weeks; regular daytime benzodiazepines and recreational drugs were prohibited. No medication washout period reported. | following prior extinction), assessed using subjective fear, shock expectancy, fear-potentiated startle, and skin conductance response. | -20.86, p = .004, ES = -1.37) and safety stimulus (CS-) (β = -14.80, p = .03, ES = -1.20).<br>- Fear re-extinction: No overall CBD effect on re-extinction was observed. However, in exploratory moderator analyses, CBD was associated with greater subjective fear during re-extinction among antidepressant users (β = 20.88, p = .03) and interfered with safety learning measured by fear-potentiated startle in antidepressant users (β = 0.05, p = .01) and women (β = 0.05, p = .006). |               |
| Masataka, 2019 | Double-blind, randomized, placebo-controlled parallel-group trial. Japanese                                                                                                                                                                  | 37 participants from Japan aged 18-19 years (29.7% women)                                                                               | Clinician-administered (SCID-I/P, SCID-II); DSM-IV | SAD with comorbid avoidant personality disorder | Subjective/self-report (FNE, LSAS)                    | Oral CBD oil (300 mg/day) administered as a single afternoon dose for 4 weeks;                                                                                                                                                                                                                            | Change in FNE score from preintervention to postintervention; LSAS was assessed as an                                                   | - Social anxiety: CBD significantly reduced social anxiety symptoms over time compared with placebo, as indicated by significant group × time                                                                                                                                                                                                                                                                                                                                                  | Some concerns |

|                             |                                                                                                                                                   |                                                                                                                                                                                 |                                                   |                                                                      |                                                                                   |                                                                                                                                                                                                                                        |                                                                                                                                                                                                          |                                                                                                                                                                          |               |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
|                             | adults aged 18–19 years with diagnosed social anxiety disorder (SAD) and avoidant personality disorder received daily CBD or placebo for 4 weeks. | with SAD and avoidant personality disorder, recruited from several hospitals near Osaka Prefecture, Japan; all participants were treatment-naïve and had symptoms for ≥6 months |                                                   |                                                                      |                                                                                   | CBD was THC-free and contained no other cannabinoids or terpenes; placebo = matching olive oil. Participants were treatment-naïve, with no previous or concurrent psychological/drug treatment; no medication washout period reported. | additional measure of social anxiety symptoms. CBD vs placebo effects were assessed by comparing pre- to post-intervention scores using a 2 × 2 repeated-measures ANOVA (measurement × treatment group). | interactions for both FNE and LSAS (both p < 0.001), reflecting greater symptom reduction in the CBD group.                                                              |               |
| Depression / Mood Disorders |                                                                                                                                                   |                                                                                                                                                                                 |                                                   |                                                                      |                                                                                   |                                                                                                                                                                                                                                        |                                                                                                                                                                                                          |                                                                                                                                                                          |               |
| Pinto, 2024                 | Single-site, randomized, double-blind, placebo-controlled pilot trial. Adults with bipolar I/II disorder and a                                    | 35 adults (M age = 43.9 years, 68.6% women) in Brazil; outpatients with bipolar I or II                                                                                         | Clinician-administered (MINI, MADRS, YMRS); DSM-5 | Current major depressive episode in patients with bipolar I disorder | Subjective/self-report (PHQ-9); clinician-administered (MADRS, YMRS, CGI-S, HAMD, | Oral CBD capsules (99.6% purity, THC-free); 150 mg/day initially, increased to 300 mg/day at week 2 for participants                                                                                                                   | Change in MADRS scores from baseline to week 8 between CBD and placebo using generalized estimating equations,                                                                                           | -Primary analysis: MADRS scores significantly decreased from baseline to week 8 in both groups, but there was no significant difference between CBD and placebo in MADRS | Some concerns |

|               |                                                                                                                            |                                                                                        |                      |                                           |                                          |                                                                                                                                                                                                                                                                                                                      |                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |               |
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|               | current major depressive episode received adjunctive CBD vs placebo for 12 weeks; primary efficacy was assessed at week 8. | disorder experiencing a current MDE, recruited at Hospital de Clínicas de Porto Alegre |                      | (n=24) or bipolar II disorder (n=11)      | HAM-A, BPRS, FAST)                       | not achieving ≥50% MADRS reduction; placebo = identical corn-oil capsules. Adjunctive to stable lithium, valproate, or atypical antipsychotic treatment at therapeutic levels for ≥4 weeks; antidepressants were also used by 68.4% of CBD and 50.0% of placebo participants. No medication washout period reported. | adjusting for age, gender, years of education, and baseline MADRS. | change or in any other clinical rating scale.<br>- Exploratory analysis: Among participants who did not meet response criteria at week 2 (11 per group), 300 mg/day CBD produced a significantly greater reduction from week 2 to week 8 in MADRS scores compared with placebo(estimated mean change difference = -7.09, 95% CI [-12.50, -1.69], p = .010) and HAMD scores (-6.18, 95% CI [-9.58, -2.77], p = .0004). Reductions in PHQ-9 and BPRS scores were not significant. |               |
| Winkler, 2025 | 3-arm randomized parallel-group trial; 30-day CBD                                                                          | 180 highly stressed university students at                                             | Self-report (PSS-10) | At risk for depression; "highly stressed" | Subjective/self-report (PSS-10, DASS-21, | Sublingual full-spectrum CBD oil; titrated from 0.02 mg/kg/day                                                                                                                                                                                                                                                       | PSS-10 and DASS-21 depressive symptoms                             | - Stress: CBD and placebo produced significantly greater reductions in perceived stress than no                                                                                                                                                                                                                                                                                                                                                                                 | Some concerns |

|                      |                                                                                                                                                                                                                |                                                                                                                                                                                                                                           |  |                                                           |                       |                                                                                                                         |                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                        |  |
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|                      | oil vs placebo oil vs no-treatment control; participants randomized to CBD (n=59), placebo (n=61), or no treatment (n=60). Experimenters were blinded to CBD vs placebo but not to the no-treatment condition. | risk for depression (M age = 24.1 years, 81.1% women) in Germany; participants had depressive symptoms and perceived stress (PSS-10 ≥23) but no diagnosed acute or chronic physical or mental illness, recruited from a German university |  | participant s according to a PSS-10 score of 23 or higher | PHQ-15, PSQI, WEMWBS) | to 1 mg/kg/day (~1.7–85 mg/day); placebo = hemp seed oil. No regular medications permitted; no washout period reported. | subscale compared pre- to post-intervention change across CBD-oil, placebo-oil, and no-treatment control groups using 3 × 2 mixed ANOVA, with planned CBD vs placebo, placebo vs no-treatment, and CBD vs no-treatment contrasts. | treatment, but CBD did not differ significantly from placebo.<br>- Depressive symptoms: CBD and placebo produced significantly greater reductions in depressive symptoms than no treatment, but CBD did not differ significantly from placebo.<br>- Anxiety: No significant CBD-related effect compared with placebo; the group × time interaction was nonsignificant. |  |
| PTSD symptoms / PTSD |                                                                                                                                                                                                                |                                                                                                                                                                                                                                           |  |                                                           |                       |                                                                                                                         |                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                        |  |

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| Bogenschutz, 2026 (Study 2) | Double-blind, randomized, placebo-controlled proof-of-concept trial. Study 2: AUD + PTSD/subthreshold PTSD, CBD vs placebo, 5:3 randomization, 6 weeks. Participants and study team members were blinded to treatment assignment; medication was dispensed by an unblinded team member with no participant interaction. | 29 adults (Mean age = 38.6 years, 62.1% women) in the USA; participants had moderate to severe AUD with DSM-5 PTSD (66.7%) or subthreshold PTSD, and were recruited at New York University | Clinician-administered (SCID, CAPS-5); DSM-5 | AUD + PTSD (n=20) or AUD + subthreshold PTSD (n=10) | Subjective/self-report (BAI, BDI-II, PCL-5) | Oral CBD capsules (200 mg/capsule); 600 mg/day divided into morning/evening doses for 6 weeks, with dose reduction permitted for intolerance; placebo = identical capsules without CBD. No AUD pharmacotherapy or medications with potentially significant pharmacokinetic interactions with CBD permitted; no washout period reported. | Average number of standard drinks per day (DPD) during treatment; CBD vs placebo comparison using MMRM, with time, treatment, treatment × time, and baseline DPD as fixed effects. | - Depression/anxiety: No significant CBD vs placebo treatment effects on BDI-II or BAI scores.<br>- PTSD: No significant CBD vs placebo treatment effect on PCL-5 scores.<br>- Exploratory: Significant time × treatment interaction for BDI-II ( $F(2,42.3) = 4.884, p = .012$ ), with lower BDI-II scores in the CBD vs placebo group at week 1 only ( $p = .007$ ); this difference was not sustained at later time points. | Some concerns |
| Bolsoni, 2022a*             | Double-blind, randomized, placebo-                                                                                                                                                                                                                                                                                      | 33 adults (Mean age = 33.2 years, 75.8%                                                                                                                                                    | Clinician-administer                         | PTSD with (n=22) or without                         | Subjective/self-report (STAI,               | Oral CBD capsules (300 mg single dose);                                                                                                                                                                                                                                                                                                 | VAMS scores assessing subjective                                                                                                                                                   | - Anxiety: Trauma recall increased VAMS anxiety and STAI-state scores in                                                                                                                                                                                                                                                                                                                                                       | Some concerns |

|                 |                                                                                                                                                                                                                        |                                                                                                                                                                                                                            |                      |                                                  |                                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |           |
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|                 | controlled trial. CBD vs placebo, parallel groups, single-dose administration 90 min before traumatic-memory recall; participants underwent a second recall session 1 week later without pharmacological intervention. | women) in Brazil; patients diagnosed with PTSD according to DSM-5 criteria, with depressive and/or anxiety disorder comorbidities permitted, recruited through a university hospital, outpatient clinics, and social media | ed (SCID); DSM-5     | (n=11) comorbid depressive and anxiety disorders | VAMS); objective (blood pressure, heart rate, salivary cortisol) | CBD dissolved in corn oil (200 mg/mL) and administered 90 min before trauma recall; placebo = identical capsules containing corn oil only. Psychiatric medication use was permitted (47% CBD; 56.25% placebo); no medication washout period reported. | symptoms induced by traumatic-memory recall; CBD vs placebo effects were compared across pre- and post-recall phases using repeated-measures ANOVA. | both groups, but CBD did not significantly attenuate anxiety versus placebo.<br>- Cognitive impairment: CBD attenuated the recall-induced increase in VAMS cognitive impairment versus placebo (group × phase: $F_{1,31} = 5.14$ , $p = 0.03$ ), with the effect persisting at 1 week ( $F_{1,31} = 4.59$ , $p = 0.04$ ).<br>- Physiological measures: No significant CBD–placebo differences were observed in BP, HR, or salivary cortisol. Systolic BP increased after trauma recall on Day 2 ( $F_{1,31} = 7.94$ , $p = 0.008$ ), but there was no significant group × phase interaction. |           |
| Bolsoni, 2022b* | Randomized, parallel-group,                                                                                                                                                                                            | 33 adults (M age = 33.2                                                                                                                                                                                                    | Clinician-administer | PTSD with or without                             | Subjective/self-report                                           | Oral CBD capsules (300 mg                                                                                                                                                                                                                             | VAMS scores, comparing CBD                                                                                                                          | - Cognitive impairment: Increased                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | High risk |

|  |                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                      |                  |                                           |                                                                   |                                                                                                                                                                                                                                   |                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |
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|  | double-blind, placebo-controlled trial. CBD vs placebo, 1:1 randomization, single-dose administration 90 min before traumatic-memory recall; exploratory post-hoc analysis stratified participants by sexual vs nonsexual trauma. | years, 75.8% women) in Brazil; patients diagnosed with PTSD according to DSM-5 criteria, including 14 with sexual trauma and 19 with nonsexual trauma, recruited through a university hospital, outpatient clinics, and social media | ed (SCID); DSM-5 | comorbid depressive and anxiety disorders | (VAMS); objective (blood pressure, heart rate, salivary cortisol) | single dose); CBD powder (99.6% purity) dissolved in corn oil; placebo = identical capsules containing corn oil only. Psychiatric medication use was permitted (52.9% CBD; 43.8% placebo); no medication washout period reported. | vs placebo on changes in subjective anxiety and other trauma-recall-induced symptoms before vs after recall using three-way repeated-measures ANOVA (group × trauma type × phase). | significantly after trauma recall, with a greater increase in placebo than CBD (phase × group: $F_{1,29} = 4.28$ , $p = 0.048$ ).<br>- Anxiety: In the exploratory nonsexual-trauma subgroup, CBD significantly attenuated the recall-induced increase versus placebo (mean difference = $-9.82$ , $p = 0.033$ ); no significant difference was observed in the sexual-trauma subgroup.<br>- Cognitive impairment by trauma type: In the nonsexual-trauma subgroup, CBD significantly attenuated the recall-induced increase versus placebo (mean difference = $-8.21$ , $p = 0.008$ ); no significant difference was observed in the sexual-trauma subgroup. |  |
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|               |                                                                                                                                                                                                                                              |                                                                                                                                                                      |                                                                    |                                                                                                           |                                                                     |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                              | - Physiological measures: Systolic BP and HR increased significantly after trauma recall, but CBD did not significantly attenuate these responses versus placebo; the HR response also varied by trauma type (phase × trauma interaction).                                                                                                                               |           |
| Gournay, 2024 | Double-blind, randomized, placebo-controlled trial. Trauma-exposed adults with elevated stress and subthreshold PTSD symptoms, but no full PTSD diagnosis, were randomized to CBD vs placebo; acute effects were assessed after a single 300 | 42 trauma-exposed adults (M age = 23.12 years, 57.1% female biological sex) in the USA; elevated perceived stress, lifetime trauma exposure, and ≥1 PTSD Criterion B | Self-report (PSS-10); clinician-administered (DIAMOND-PTSD); DSM-5 | Subthreshold PTSD symptoms: trauma-exposed individuals with elevated stress and ≥1 PTSD intrusion symptom | Subjective/self-report (VAMS-A, VAMS-D); objective (heart rate/ECG) | Oral CBD softgels (50 mg/softgel); 300 mg single dose acutely, followed by 300 mg/day for 1 week with food; placebo = identical MCT softgels without CBD. Participants were required to maintain stable medication use; prescription anxiety | Trauma-script-elicited emotional reactivity, assessed using state anxiety (VAMS-A), distress (VAMS-D), and heart rate, comparing 300 mg CBD vs placebo for acute (Phase I) and repeated (Phase III) administration using a repeated-measures | - Anxiety & distress: Trauma-script presentation significantly increased anxiety and distress, but CBD did not significantly attenuate these responses compared with placebo following either the initial 300-mg dose or 1 week of daily 300-mg dosing.<br><br>- Heart rate: No significant differences between CBD and placebo were observed in heart-rate responses to | High risk |

|  |                                                            |                                               |  |  |  |                                                                                                         |                                                                                          |                                                                        |  |
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|  | mg dose and repeated effects after 1 week of daily dosing. | symptom, but did not meet full PTSD criteria. |  |  |  | medications and specified interacting medications were excluded. No medication washout period reported. | ANOVA testing the condition × script type × script reactivity × study phase interaction. | trauma-script presentation following acute or repeated administration. |  |
|--|------------------------------------------------------------|-----------------------------------------------|--|--|--|---------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------|--|

Note. ACQ = Agoraphobic Cognitions Questionnaire; ANOVA = analysis of variance; AUD = alcohol use disorder; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; BMWS = Brief Measure of Worry Severity; BP = blood pressure; BPRS = Brief Psychiatric Rating Scale; BSQ = Body Sensations Questionnaire; BSS = Bodily Symptoms Scale; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CBD = cannabidiol; CGI = Clinical Global Impression; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; CI = confidence interval; CS+ = conditioned stimulus; CS- = safety stimulus; DASS-21 = Depression Anxiety Stress Scales-21; DASS-A = Depression Anxiety Stress Scales, anxiety subscale; DIAMOND-PTSD = Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders, PTSD module; DPD = drinks per day; DSM-IV/DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 4th/5th edition; ECG = electrocardiogram; EMG = electromyography; ES = effect size; FAST = Functioning Assessment Short Test; FNE = Fear of Negative Evaluation Scale; FQ = Fear Questionnaire; GAD-7 = Generalized Anxiety Disorder-7; HAM-A = Hamilton Anxiety Rating Scale; HAMD = Hamilton Depression Rating Scale; HC = healthy controls; HR = heart rate; ICD-11 = International Classification of Diseases, 11th Revision; LSAS = Liebowitz Social Anxiety Scale; M = mean; MADRS = Montgomery-Åsberg Depression Rating Scale; MCT = medium-chain triglyceride; MDE = major depressive episode; MI = Mobility Inventory for Agoraphobia; MINI = Mini-International Neuropsychiatric Interview; MINI-SPIN = Mini-Social Phobia Inventory; MMRM = mixed model for repeated measures; n = number of participants; PCL-5 = PTSD Checklist for DSM-5; PDSS = Panic Disorder Severity Scale; PHQ-9/PHQ-15 = Patient Health Questionnaire-9/-15; PSQI = Pittsburgh Sleep Quality Index; PSS-10 = Perceived Stress Scale-10; PSWQ = Penn State Worry Questionnaire; PTSD = posttraumatic stress disorder; RoB = risk of bias; SAD = social anxiety disorder; SCID-CV/-I/P/-II/-IV = Structured Clinical Interview for DSM (Clinician Version / Axis I Disorders, Patient Edition / Axis II Personality Disorders / DSM-IV); SCR = skin conductance response; SPAI-18 = Social Phobia and Anxiety Inventory-18; SPST = Simulated Public Speaking Test; SSPS-N = Self-Statements during Public Speaking Scale, negative self-statement subscale; STAI = State-Trait Anxiety Inventory; THC = Δ9-tetrahydrocannabinol; VAMS = Visual Analogue Mood Scale (VAMS-A = anxiety; VAMS-D = distress); VAS = Visual Analogue Scale; WEMWBS = Warwick-Edinburgh Mental Well-being Scale; YMRS = Young Mania Rating Scale.

\* Indicates separate reports from the same trial (Kwee 2022a and 2024b; Bolsoni 2022a and 2022b).

*CBD and Mood Disorders / Symptoms*

Pinto et al. conducted a 12-week pilot RCT in 35 adults with a diagnosed current major depressive episode in bipolar I or II disorder, randomized to adjunctive CBD (150 mg/day; n=19) or placebo [42]. The primary aim was to assess the efficacy of adjunctive CBD for bipolar depression, with change in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline to week 8 as the primary outcome. Participants who did not meet response criteria ( $\geq 50\%$  reduction in MADRS scores) at week 2 had their CBD dose increased to 300 mg/day, and were included in an exploratory analysis. The primary outcome was change in MADRS score from baseline to week 8. MADRS scores improved significantly in both the CBD and placebo groups, but the between-group difference was not significant. Response rates at week 8 were also not significantly different between the CBD and placebo groups, nor were remission rates. Similarly, no significant between-group differences were observed across other measures of depression, anxiety, or functioning. These additional clinical measures were secondary outcomes and likewise showed no significant CBD-versus-placebo differences. In the exploratory analysis of participants who did not respond by week 2, reductions in MADRS scores from weeks 2 to 8 were significantly greater in the CBD group than the placebo group, with a similar between-group difference in Hamilton Depression Rating Scale (HAMD) scores. PHQ-9 and BPRS scores showed similar though non-significant trends. These findings were from an exploratory analysis restricted to week-2 nonresponders and therefore should be distinguished from the null primary analysis of the full randomized sample. A statistically significant between-group difference in BMI was also observed from baseline to week 12, reflecting a small decrease in BMI in the CBD group and an increase in the placebo group. However, the study did not report this change as clinically meaningful. The trial was terminated early because of the COVID-19 pandemic [42].

Winkler et al. conducted a 30-day RCT in 180 highly stressed university students without a diagnosed psychiatric disorder who were selected for subthreshold depressive symptoms and elevated risk for depression [50]. Participants received sublingual 10% full-spectrum CBD oil, gradually increased from 0.02 mg CBD/kg/day to 1 mg CBD/kg/day by day 30, or placebo oil; CBD was self-administered without formal verification of intake. Depressive symptoms, perceived stress, somatic symptoms, sleep, and well-being were assessed using self-report measures (Depression Anxiety Stress Scale; DASS-21, Perceived Stress Scale-10; PSS-10, Patient Health Questionnaire-15; PHQ-15, Pittsburgh Sleep Quality Index; PSQI, and Warwick-Edinburgh Mental Well-being Scale; WEMWBS). The primary analysis examined pre- to post-intervention changes in perceived stress and depressive symptoms across the CBD, placebo, and no-treatment groups, with planned CBD-versus-placebo contrasts used to determine whether changes were specific to CBD. Significant group-by-time interactions were observed for depressive symptoms and perceived stress. However, planned contrasts indicated that these effects reflected improvements in both oil groups relative to the no-treatment condition rather than a specific CBD effect. Both CBD and placebo showed greater reductions in depressive symptoms than no treatment, whereas the change in depressive symptoms did not differ between CBD and placebo. Thus, the primary CBD-versus-placebo comparisons did not demonstrate a CBD-specific effect on either perceived stress or depressive symptoms. No significant CBD-specific effects were observed for the other outcome measures [50]. Somatic symptoms, sleep, and well-being were assessed as additional outcomes and likewise did not show significant CBD-specific effects.

*CBD and Anxiety Disorders / Symptoms*

Six reports from five trials focused on anxiety disorders or elevated anxiety/worry. Four reports investigated social anxiety disorder (SAD) [28,40,45,47], one of which included comorbid avoidant personality disorder (Masataka, 2019) and two of which, from the same trial, also included panic disorder with agoraphobia [28,45]. Of the remaining two, one investigated mild-to-moderate anxiety disorders [41] and the other elevated trait worry [46]. Diagnoses were established with clinician-

administered measures in four reports [40,41,45,47], with a self-report measure in one [46], and were not reported in one [28]. Five reports used clinical cohorts and one used a non-clinical cohort [46].

Four studies investigated CBD as a standalone treatment for anxiety symptoms [40,41,46,47]. A single 600 mg oral dose of CBD in individuals with SAD produced significantly lower anxiety, cognitive impairment, and discomfort on the Visual Analogue Mood Scale (VAMS) during the speech phase of the Simulated Public Speaking Test (SPST), lower sedation during the anticipatory phase, and significantly lower negative self-evaluation on the Self-Statements during Public Speaking Scale Negative Self-Statement Subscale (SSPS-N) during the speech phase, compared to placebo. No significant differences were observed on the Bodily Symptoms Scale (BSS) [40]. The primary aim of Bergamaschi et al. (2011) was to examine the acute anxiolytic effect of CBD during simulated public speaking, with the VAMS anxiety factor during the SPST serving as the primary outcome [40]. The effects on negative self-evaluation, cognitive impairment, discomfort, and bodily symptoms represented additional outcomes. Additionally, 300 mg/day of oral CBD oil administered over four weeks to individuals with SAD and comorbid avoidant personality disorder significantly reduced Fear of Negative Evaluation Scale (FNE) and Liebowitz Social Anxiety Scale (LSAS) scores from baseline to end of treatment compared to placebo [47]. Masataka et al. (2019) primarily evaluated change in FNE scores, with LSAS scores providing an additional measure of social anxiety symptoms. Furthermore, in a larger sample of individuals with mild-to-moderate anxiety disorders, Gundugurti et al. administered a titrated regimen increasing from 150 mg/day to 450 mg/day and then 600 mg/day at weekly intervals over 12 weeks. There were significant reductions in the primary outcome measures (Generalized Anxiety Disorder-7, GAD-7; Hamilton Anxiety Rating Scale, HAM-A) and in the secondary outcome measures (Clinical Global Impression-Improvement, CGI-I; Clinical Global Impression-Severity, CGI-S; Patient Health Questionnaire-9, PHQ-9; Pittsburgh Sleep Quality Index, PSQI), compared to placebo [41]. The primary analysis therefore focused on change in GAD-7 and HAM-A scores from baseline to the end of treatment, whereas CGI-I, CGI-S, PHQ-9, and PSQI were secondary outcomes (Gundugurti et al., 2024).

In contrast, one RCT investigated 300 mg of oral CBD as an adjunct to exposure therapy sessions in individuals with SAD or panic disorder with agoraphobia [28,45]. No significant differences were found in the primary outcome (Fear Questionnaire; FQ) or in the secondary outcomes (Beck Anxiety Inventory; BAI; Beck Depression Inventory-II; BDI-II; Body Sensations Questionnaire; BSQ; or Social Phobia and Anxiety Inventory-18; SPAI-18), compared to placebo (Kwee et al., 2022). The primary aim of Kwee et al. (2022) was to determine whether CBD enhanced the clinical effects of exposure therapy, with FQ scores serving as the primary clinical outcome. The BAI, BDI-II, BSQ, SPAI-18, and other clinician-rated measures were secondary clinical outcomes. A secondary experimental report from the same RCT found that CBD selectively reduced shock expectancy during fear retention but produced no significant differences in subjective fear, skin conductance, or fear-potentiated startle, compared to placebo. Kwee et al. (2024) was a separate report from the same trial that examined fear-conditioning and extinction as experimental/mechanistic outcomes rather than the primary clinical treatment outcome. Exploratory analyses further indicated impaired re-extinction of subjective fear in participants taking serotonergic medication, although these findings were not consistently supported [28]. These moderator analyses were exploratory and should therefore be distinguished from the overall CBD-versus-placebo analysis of fear re-extinction.

The single study in a non-clinical sample of individuals with elevated trait worry administered 50 mg/day or 300 mg/day of oral CBD acutely and over two weeks. It found no significant differences in Brief Measure of Worry Severity (BMWS) scores, either acutely or with repeated administration, in either dosing condition compared to placebo [46]. The primary aim of Gournay et al. (2023) was to determine whether acute or repeated CBD administration reduced worry severity, with BMWS scores as the primary outcome. However, Depression Anxiety Stress Scales-Anxiety subscale (DASS-A) scores decreased significantly more with repeated 300 mg/day CBD than with placebo over the two-week treatment period, with no significant acute effect [46]. DASS-A was a secondary anxiety outcome; therefore, the significant repeated-dose DASS-A finding should be interpreted separately

from the null primary BMWS finding. Within-group DASS-A scores also decreased significantly from Day 1 to Week 2 in the 300 mg and 50 mg CBD groups but not placebo, while the difference in slopes between the two CBD doses was not statistically significant [46].

#### *CBD and PTSD / Trauma-Related Symptoms:*

Four reports examined PTSD diagnoses and trauma-related symptoms: three studies examined CBD effects in clinically diagnosed populations with PTSD, while one included a sub-clinical sample of trauma-exposed individuals [43,44,48,49]. Three reports utilized structured clinical interviews to confirm diagnoses [43,44,48], while one used both a clinician-rated and a self-report scale to assess PTSD symptoms [49]. Across the studies, a variety of outcome measures were used to assess changes in psychiatric symptoms including PTSD symptoms [43], depression [43,44,48,49], anxiety [43,44,48,49], and cognitive impairment [44,48]. Psychiatric symptoms were assessed using subjective self-report measures including the BAI, BDI-II, PTSD Checklist for DSM-5 (PCL-5), State-Trait Anxiety Inventory (STAI), and VAMS [43,44,48,49].

All four reports, from three trials, used an oral CBD formulation (capsules or softgels). Schedules differed: Bolsoni et al. from the same trial, gave a single 300 mg dose 90 minutes before a laboratory trauma-recall task, with a second recall session one week later without drug [44,48]. The primary aim of the Bolsoni et al. trial was to examine the effects of acute CBD on subjective and physiological responses to traumatic-memory recall. Bolsoni et al. (2022a) reported the primary overall treatment comparison, whereas Bolsoni et al. (2022b) represented a subsequent exploratory analysis examining whether responses differed according to sexual versus non-sexual trauma [44,48]. Gournay et al. gave a single 300 mg dose, followed by 300 mg/day for one week, to assess acute and repeated effects [49]. The primary aim of Gournay et al. (2024) was to determine whether acute and repeated CBD administration altered trauma-script-elicited emotional reactivity, assessed through state anxiety, distress, and heart-rate responses. Bogenschutz et al. gave 600 mg/day in two divided doses for six weeks, i.e., regular daily administration [43]. The parent trial primarily investigated CBD effects in individuals with AUD; however, Study 2 included participants with AUD and PTSD or subthreshold PTSD and prospectively assessed PTSD symptoms, making these outcomes eligible for the present review. The primary outcome of the parent trial was alcohol consumption, whereas PTSD symptoms, depression, and anxiety were additional outcomes in Study 2. None combined CBD with psychotherapy or exposure sessions. One RCT reported improved trauma-related cognitive impairment across two reports [44,48], whereas neither of the two studies with repeated dosing [43,49] found significant benefits on trauma-related symptoms. Both longitudinal studies tracked compliance by asking participants to record each drug administration [43,49]. Overall, CBD was well-tolerated by individuals with PTSD, with few reports of adverse events.

Across the four reports examining PTSD or subthreshold PTSD symptoms, outcomes primarily focused on trauma-related symptoms or emotional reactivity. Bogenschutz et al. [43] assessed changes in overall PTSD symptoms using the PCL-5 following six weeks of daily CBD administration and found no significant treatment effect. This PTSD analysis represented an additional outcome within the AUD-focused trial rather than the primary trial outcome. Similarly, the two reports by Bolsoni et al. (2022) examined subjective and physiological responses to traumatic-event recall following a single 300 mg dose of CBD [44,48]. Neither found an overall reduction in anxiety compared with placebo, although one report found reduced anxiety during trauma recall among participants with non-sexual trauma [37]. The overall CBD-versus-placebo comparison was the principal analysis, whereas the difference observed in the non-sexual trauma subgroup arose from an exploratory trauma-type analysis and should not be interpreted as evidence of a general anxiolytic effect in PTSD. Gournay et al. (2024) examined trauma-script-elicited emotional reactivity in trauma-exposed individuals with subthreshold PTSD symptoms and found no effects of acute or repeated CBD administration on anxiety, distress, or heart rate [49]. These outcomes constituted the primary trauma-reactivity analysis for this study and therefore directly addressed its prespecified experimental question. Thus, across reports, CBD did not demonstrate consistent improvements in

PTSD-related outcomes or anxiety symptoms. Three reports also examined objective measures of anxiety-related physiological arousal, including heart rate and blood pressure, and found no consistent effects of CBD compared to placebo conditions [44,48,49].

All four reports measured changes in depressive symptoms following CBD intervention [43,44,48,49]. Across all studies, there were no significant effects of CBD on depressive symptoms, both acutely and following repeated dosing. These outcomes constituted the primary trauma-reactivity analysis for this study and therefore directly addressed its prespecified experimental question. Two reports found significant improvements in cognitive impairment following a single CBD exposure during a trauma recall task, with improvements lasting one week after drug administration, an effect still present at a follow-up recall session 1 week later without further dosing; no later time points were assessed [44,48]. These cognitive findings were additional experimental outcomes of the Bolsoni trial and should therefore be distinguished from the primary anxiety/trauma-recall analysis.

## Discussion

This systematic review summarized findings from 10 randomized controlled trials (12 reports) examining effects of CBD effects on anxiety, mood, and trauma-related disorders and symptoms across the clinical - subclinical spectrum. Overall, findings varied across psychiatric domains and populations, with the most consistent pattern emerging for anxiety disorders and symptoms. Across studies of treatment-naïve individuals with social anxiety disorder and mild-to-moderate anxiety, CBD monotherapy resulted in reductions in anxiety symptoms and/or negative self-evaluation [40,41,47] compared to placebo, whereas adjunctive CBD administered alongside exposure therapy did not demonstrate benefit over placebo [28,45]. Evidence from non-clinical populations was more limited and mixed. In contrast, studies examining mood and PTSD outcomes did not demonstrate clinical effects of CBD in their primary outcomes. The available evidence suggests a potentially domain- and context-dependent effect of CBD, with greater consistency for subjective or cognitive-evaluative anxiety outcomes than for peripheral physiological measures. However, the small number of independent trials and heterogeneity in populations, treatment contexts, and outcome measures limit potential conclusions and do not inform or allow specific clinical recommendations.

### *CBD and Mood Disorders / Symptoms:*

Controlled studies examining the efficacy of CBD for mood disorders remain limited, with much of the available evidence derived from secondary outcomes in heterogenous clinical populations. This review identified only one controlled trial in a diagnosed mood disorder population, involving bipolar depression, and one trial examining subclinical depressive symptoms. Neither demonstrated a significant effect of CBD over placebo. For both trials, substantial improvement was observed in the placebo groups, which may have reduced the ability to detect between-group effects. Pinto et al. reported marked improvements in depressive symptoms in both treatment groups, while Winkler et al. found that both CBD and placebo improved stress and depressive symptoms relative to a no-treatment control [42,50]. Expectancy effects may also contribute to perceived benefits of CBD, as experimental studies have shown that CBD-related expectancies can influence subjective and physiological responses, including anxiety and stress responses [34,51–53]. For example, a randomized expectancy study found that participants who believed that they had received CBD demonstrated changes in sedation and heart-rate variability, while individuals with stronger pre-existing beliefs about CBD's anxiolytic effects reported greater reductions in anxiety under the CBD-expectancy condition [34].

The available evidence also does not establish whether CBD has a dose-dependent effect on mood symptoms. In Winkler et al. a relatively low, weight-adjusted dose of CBD did not produce greater improvements than placebo [50]. In Pinto et al., participants with bipolar depression who did not respond after two weeks of 150 mg/day experienced greater reductions in depressive symptoms during the subsequent period when the dose was increased to 300 mg/day [42]. It is of note that this

analysis was exploratory, involving a small subgroup of participants, and did not directly compare randomized CBD doses. It therefore, cannot establish a dose-response relationship in bipolar depression [42,50]. Evidence from anxiety studies further suggests that CBD effects may not follow a simple linear dose-response relationship. Linares et al. found that an acute 300 mg dose reduced anxiety during simulated public speaking, whereas 150 and 600 mg doses did not differ significantly from placebo, consistent with an inverted U-shaped dose-response pattern [35]. However, these findings concern an acute experimental anxiety paradigm rather than depressive symptoms and should not be extrapolated to antidepressant effects. Studies specifically designed to compare CBD doses in mood disorders are needed to determine whether dose influences therapeutic response.

Several factors limit interpretation of these findings. The two trials differed substantially in population, CBD formulation, dosing regimen, and clinical context, limiting direct comparison [42,50]. Both were also rated as having some concerns regarding risk of bias. In Winkler et al., recruitment was terminated prematurely because of the COVID-19 pandemic, further limiting statistical power. Importantly, the limited evidence should not be interpreted as evidence that CBD is ineffective across depressive disorders. The only trial conducted in a diagnosed mood disorder population examined bipolar depression rather than unipolar depression/major depressive disorder, while the other trial involved individuals with subclinical depressive symptoms. Thus, the available evidence from controlled is insufficient to draw any conclusions about the efficacy of CBD for mood disorders, ie., bipolar depression, major depressive disorder, or depressive disorders more broadly.

#### *CBD and Anxiety*

Findings from clinical populations suggest that acute and repeated CBD administration may reduce anxiety symptoms, although effects have not been consistent across studies or outcome measures [40,41,47]. In contrast, repeated adjunctive CBD administration alongside exposure therapy did not improve clinical anxiety outcomes compared to placebo [28,45]. Differences in treatment context, exposure procedures, participant characteristics, dosing, and outcome measurement may contribute to these findings. In the fear-conditioning paradigm, CBD selectively reduced threat expectancy without altering skin conductance or fear-potentiated startle, suggesting that CBD may influence some cognitive or evaluative components of threat response without producing corresponding changes in peripheral physiological arousal [28].

Findings from non-clinical samples further complicate this interpretation. In the non-clinical anxiety study, neither acute nor repeated CBD administration attenuated worry severity, although repeated 300 mg administration was associated with reductions in anxiety symptoms [46]. Given that worry represents a core cognitive feature of anxiety, the absence of an effect on worry suggests that CBD may not consistently influence all cognitive components of anxiety [46]. However, this was the only included anxiety trial involving a non-clinical sample, making it difficult to determine whether the null findings reflect differences in baseline symptom severity, diagnostic status, or other sample characteristics. Dose may also contribute to variability in response. In individuals with social anxiety disorder, an acute 600 mg dose reduced anxiety, whereas in healthy individuals anxiolytic effects were observed at 300 mg but not at 150 or 600 mg [34,53]. Together, these findings raise the possibility of a non-linear dose-response relationship, although the available studies were not designed to systematically test dose-response effects.

The contrast between clinical and non-clinical samples therefore warrants further investigation, but the current evidence is insufficient to conclude that diagnostic status or baseline symptom severity moderates response to CBD. Overall, acute and repeated CBD administration may reduce anxiety-related symptoms, particularly in clinical populations, but effects have varied across outcomes and dosing paradigms [41,44,45,48]. The evidence should therefore be interpreted cautiously given the limited number of studies and variation in methodological quality and current findings and evidence from controlled studies does not allow any clinical recommendations.

#### *CBD and PTSD*

Overall, the available evidence from controlled, randomized studies does not demonstrate consistent benefits of CBD for PTSD-related symptoms or anxiety. Across the four relevant reports, outcomes primarily focused on trauma-related emotional or physiological responses rather than longitudinal changes in overall PTSD symptom severity. Bogenschutz et al. (2026) was the only report to assess overall PTSD symptom severity during treatment using the PCL-5, and found no significant effect of six weeks of daily CBD administration [43]. The two Bolsoni et al. (2022) reports examined subjective and physiological responses to traumatic-event recall following a single 300 mg dose of CBD [44,48]. Neither report found an overall reduction in anxiety compared with placebo, although one identified reduced anxiety during trauma recall among participants with non-sexual trauma [44]. Gournay et al. (2024) similarly found no acute or repeated effects of CBD on trauma-script-elicited anxiety, distress, or heart rate in trauma-exposed individuals with subthreshold PTSD symptoms [49].

The two Bolsoni et al. reports, which were based on the same underlying sample, did identify reductions in trauma-related cognitive impairment following acute CBD administration [44,48]. In one report, reductions in anxiety and cognitive impairment were observed among participants with non-sexual trauma histories but not among those with sexual trauma histories [44]. These findings are consistent with preclinical and experimental human research suggesting that CBD may influence aspects of fear memory, threat expectancy, and cognitive appraisal [23,28]. However, because the trauma-type analysis was exploratory and based on a small subgroup, these findings should be considered preliminary. They may nevertheless indicate that CBD effects in trauma-related conditions depend on the specific component of the stress response being assessed and on characteristics of the trauma-exposed population.

Importantly, none of the four reports provided evidence of improvement in overall PTSD symptom severity following CBD exposure, and only one directly assessed longitudinal change in PTSD symptoms [43,44,48,49]. This distinction is important when interpreting the apparent benefits observed for anxiety or cognitive impairment during trauma recall, as improvements in these acute experimental responses do not necessarily translate into reductions in core PTSD symptoms and associated functional impairment. Previous observational and non-randomized research has suggested potential benefits of CBD in PTSD populations, but methodological limitations in these studies do not allow any causal interpretation [36]. The present randomized evidence remains insufficient to determine whether CBD may improve core PTSD symptoms.

#### *General Considerations: Dosing, Placebo Effects, and Adjunctive Treatment:*

Across anxiety, mood, and trauma studies, differences in CBD dose and administration schedule represent an important source of heterogeneity. The included studies used acute oral CBD doses ranging from acute doses of 150 mg to 600 mg to repeated regimens extending from approximately 25 to 600 mg per day, making it difficult to identify a dose associated with consistent therapeutic effects [35,41,42,44,45,49,50]. Some findings suggest that CBD effects may be non-linear, with beneficial effects observed at intermediate rather than higher doses in some experimental paradigms [27,35]. However, these findings were generally derived from anxiety or experimental outcomes rather than studies in mood disorders, and most included trials were not designed as dose-ranging studies. Consequently, the current evidence cannot establish an optimal dose for psychiatric symptoms in general. Future trials should directly compare multiple CBD doses within the same clinical population and should consider both absolute and weight-adjusted dosing.

Placebo response and expectancy represent another important consideration. The substantial improvement observed in placebo groups in the mood studies, together with experimental evidence that expectations can influence responses to CBD, highlights the importance of adequately controlled designs when evaluating subjective psychiatric outcomes [34,42,50]. This may be particularly relevant for CBD because participants may have pre-existing expectations regarding its therapeutic effects. Future trials should therefore incorporate rigorous placebo controls and, where possible, assess

treatment expectancy so that expectancy-related effects can be distinguished from pharmacological effects.

The effects of CBD may also differ when administered as an adjunct to existing psychological or pharmacological treatment. In the included anxiety literature, Kwee et al. (2022) examined CBD as an adjunct to therapist-assisted exposure therapy in individuals with social anxiety disorder or panic disorder with agoraphobia and found no additional clinical benefit over placebo [45]. Although this does not demonstrate an interaction between CBD and exposure therapy, it highlights the difficulty of isolating the incremental effects of CBD when administered alongside an established psychological intervention. Pharmacological interactions are also relevant when CBD is administered alongside concomitant medications. CBD can affect drug-metabolizing pathways, including CYP2C19, although the magnitude and clinical relevance of these interactions vary across medications; notably, controlled human studies did not identify a clinically relevant effect of CBD on CYP3A4 activity [54]. A clinically demonstrated example comes from epilepsy treatment: among children with refractory epilepsy receiving concomitant clobazam, CBD administration was associated with a mean 60% increase in clobazam concentrations and a 500% increase in its active metabolite, N-desmethyloclobazam, with adverse effects reported in 77% of participants and alleviated following clobazam dose reduction [55]. Subsequent pharmacokinetic trials similarly identified the CBD–clobazam combination as the principal clinically important drug–drug interaction among commonly used antiseizure medications evaluated, whereas interactions with valproate and several other agents were comparatively limited [54]. These findings are particularly relevant to psychiatric populations, in which CBD may be used alongside antidepressants, antipsychotics, mood stabilizers, or other psychotropic medications. Future studies should therefore evaluate CBD both as monotherapy and as an adjunct to established psychological and pharmacological treatments, with systematic assessment of concomitant medications, pharmacokinetic interactions, and adverse effects.

### *Strengths and Limitations*

All the conclusions drawn from this review must be reconciled with the limitations in the literature and study methodology. To begin, there is significant variability in CBD dose quantity and administration frequency and duration; this is particularly pronounced when exploring diagnosis-specific outcomes and does not allow any causal inferences, particularly regarding longer-term implications. Relatedly, dosing timelines varied considerably both within and across diagnostic categories, and studies using acute versus repeated dosing paradigms often produced divergent findings, making it difficult to disentangle whether observed effects (or lack thereof) reflect true pharmacological action or simply insufficient duration of exposure. Additionally, only three studies quantitatively assessed CBD use, and self-administration without formal verification of intake was common across trials, further limiting confidence in compliance and dose-response conclusions. Risk of bias was also a persistent concern: across the included diagnostic categories, most studies were rated as having some concerns, with two PTSD studies rated as high risk, further constraining the strength of conclusions that can be drawn. This search strategy also produced a small pool of eligible studies, limited to 12 total, and diagnostic heterogeneity within categories (e.g., comorbidities, subclinical versus clinical samples) limited direct comparability even among studies targeting the same disorder. This considerable heterogeneity and variability across studies included in this review did not allow for the conducting of a meta-analysis.

An additional limitation is that some reports originated from the same underlying trials, meaning that findings from multiple reports should not be interpreted as additional evidence or independent replications. This is particularly relevant to the PTSD literature, where the two reports demonstrating improvements in trauma-related cognitive impairment were derived from the same RCT. The small number of independent trials additionally precluded formal quantitative synthesis and limited the ability to evaluate potential moderators such as dose, treatment duration, baseline symptom severity, or clinical status.

The outcome measures also varied substantially across studies. Although this allowed the review to capture effects across subjective and physiological domains, it limited direct comparison between studies and makes it difficult to determine whether apparent differences across domains reflect true differences in CBD effects or differences in measurement approaches.

Finally, the absence of neuroimaging and neurobiological measures among the included trials limits conclusions related to neurobiological mechanisms underlying observed clinical or behavioural effects. Thus, the findings do not provide direct evidence for CBD effects on the underlying neural systems represented by these domains.

It is also valuable to consider the strengths of this review. First, data extraction was completed independently by 2 reviewers per psychiatric diagnosis, with a third reviewer to address discrepancies between reviewers. Furthermore, included reports were constrained to RCTS, allowing conclusions to be based on experimental evidence while avoiding confounding inherent in observational research. The review also included of both clinical and subclinical populations and considered outcomes across subjective and physiological domains, allowing patterns of CBD response to be explored beyond individual diagnostic categories. Finally, risk of bias was assessed for each respective report's outcomes, acknowledging variances in methodological quality across outcomes from the same trial.

## Conclusions

Overall, the current randomized controlled evidence does not establish CBD as an effective treatment for mood disorders or core PTSD symptoms, while findings for anxiety symptoms are suggestive of potential benefit but remain preliminary. The limited number of independent trials, variability in CBD dose and formulation, inconsistent verification of treatment adherence, and heterogeneity in outcome measures constrain interpretation across psychiatric populations and further analysis. Future research should prioritize adequately powered randomized controlled trials in well-characterized clinical populations, with standardized CBD formulations and objectively verified dosing and adherence. Studies should also distinguish acute from repeated administration and directly examine whether treatment effects vary according to baseline symptom severity, diagnostic status, dose, treatment duration, and concomitant pharmacological treatment. Given that several included studies assessed subjective and physiological outcomes that did not always converge, future trials would benefit from harmonized assessment of clinical symptoms alongside behavioural and physiological measures. In particular, trials should directly assess core symptoms of the specific target disorder as primary outcomes rather than relying primarily on secondary symptom measures. Research examining CBD as an adjunctive treatment should also account for potential pharmacokinetic interactions with concomitant medications. Collectively, these approaches would help determine whether the domain-specific effects observed in the current literature are reproducible, identify populations most likely to benefit, and clarify whether observed effects extend beyond nonspecific or expectancy-related treatment effects.

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## References

1. World drug report 2023 [Internet]. Vienna: UN, Office on Drugs and Crime; 2023 [cited 2026 Aug 31]. Available from: <https://digitallibrary.un.org/record/4013736>
2. World drug report 2013 [Internet]. Vienna: UN, Office on Drugs and Crime; 2013 [cited 2026 Aug 31]. Available from: <https://digitallibrary.un.org/record/4039065>
3. Health Canada. Canadian tobacco alcohol and drugs (CTADS): 2015 summary. 2017.
4. Tobacco C. Alcohol and Drugs Survey (CTADS): summary of results for 2017. Health Canada. 2019.
5. Canada H. Canadian Cannabis Survey 2024: Summary [surveys] [Internet]. 2024 [cited 2026 Aug 31]. Available from: <https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/canadian-cannabis-survey-2024-summary.html>
6. Government of Canada. Justice Laws Website [Internet]. 2018 [cited 2026 Aug 31]. Cannabis Regulations. Available from: <https://laws-lois.justice.gc.ca/eng/regulations/SOR-2018-144/FullText.html>
7. Dorothy C. Kafka. Congress.gov [legislation] [Internet]. 2025 [cited 2026 Aug 31]. The 2018 Farm Bill's Hemp Definition and Legal Challenges to State Laws Restricting Certain THC Products. Available from: <https://www.congress.gov/crs-product/R48637>
8. Manthey J, Freeman TP, Kilian C, López-Pelayo H, Rehm J. Public health monitoring of cannabis use in Europe: prevalence of use, cannabis potency, and treatment rates. *The Lancet Regional Health – Europe*. 2021 Nov 1;10. doi:10.1016/j.lanepe.2021.100227
9. Goodman S, Wadsworth E, Schauer G, Hammond D. Use and Perceptions of Cannabidiol Products in Canada and in the United States. *Cannabis & Cannabinoid Research*. 2022 Jun 1;7(3):355–64. doi:10.1089/can.2020.0093
10. Canadian Agency for Drugs and Technologies in Health. Cannabidiol (Epidiolex): CADTH Reimbursement Recommendation: Indication: As adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2024 [cited 2026 Sep 28]. (CADTH Reimbursement Reviews and Recommendations). Available from: <http://www.ncbi.nlm.nih.gov/books/NBK604815/> PubMed PMID: 38985911.
11. Goodman S, Wadsworth E, Schauer G, Hammond D. Use and Perceptions of Cannabidiol Products in Canada and in the United States. *Cannabis & Cannabinoid Research*. 2022 Jun 1;7(3):355–64. doi:10.1089/can.2020.0093
12. Commissioner O of the. FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD). FDA [Internet]. 2026 Jun 1 [cited 2026 Aug 31]. Available from: <https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd>
13. Dammann I, Rohleder C, Leweke FM. Cannabidiol and its Potential Evidence-Based Psychiatric Benefits – A Critical Review. *Pharmacopsychiatry*. 2024 May;57(03):115–32. doi:10.1055/a-2228-6118
14. Gkitakou A, Have MT, Batelaan NM, Luik AI, Penninx BWJH. Anxiety and mood disorders on the rise: exploring clinical profiles and risk factors. *The British Journal of Psychiatry*. 2026 Jun;228(6):513–20. doi:10.1192/bjp.2025.10454
15. Stella N. THC and CBD: Similarities and differences between siblings. *Neuron*. 2023 Feb 1;111(3):302–27. doi:10.1016/j.neuron.2022.12.022 PubMed PMID: 36638804.
16. Tham M, Yilmaz O, Alaverdashvili M, Kelly MEM, Denovan-Wright EM, Laprairie RB. Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. *British Journal of Pharmacology*. 2019;176(10):1455–69. doi:10.1111/bph.14440
17. Martinez Naya N, Kelly J, Corna G, Golino M, Abbate A, Toldo S. Molecular and Cellular Mechanisms of Action of Cannabidiol. *Molecules*. 2023 Jan;28(16):5980. doi:10.3390/molecules28165980

18. Peng J, Fan M, An C, Ni F, Huang W, Luo J. A narrative review of molecular mechanism and therapeutic effect of cannabidiol (CBD). *Basic & Clinical Pharmacology & Toxicology*. 2022;130(4):439–56. doi:10.1111/bcpt.13710
19. Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *British Journal of Pharmacology*. 2007;150(5):613–23. doi:10.1038/sj.bjp.0707133
20. Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl. Psychiatry* 2:e94. *Translational psychiatry*. 2012 Feb 21;2:e94. doi:10.1038/tp.2012.15
21. Hua DYH, Hindocha C, Baio G, Lees R, Shaban N, Morgan CJ, et al. Effects of cannabidiol on anandamide levels in individuals with cannabis use disorder: findings from a randomised clinical trial for the treatment of cannabis use disorder. *Translational Psychiatry*. 2023 Apr 21;13(1):131. doi:10.1038/s41398-023-02410-9
22. Chester LA, Englund A, Chesney E, Oliver D, Wilson J, Sovi S, et al. Effects of Cannabidiol and Delta-9-Tetrahydrocannabinol on Plasma Endocannabinoid Levels in Healthy Volunteers: A Randomized Double-Blind Four-Arm Crossover Study. *Cannabis & Cannabinoid Research*. 2024 Feb 1;9(1):188–98. doi:10.1089/can.2022.0174
23. Lisboa SF, Stern CAJ, Gazarini L, Bertoglio LJ. Chapter Ten - Cannabidiol effects on fear processing and implications for PTSD: Evidence from rodent and human studies. In: Del-Bel E, Gomes FV, Lisboa SF, editors. *Cannabidiol in Neurology and Psychiatry* [Internet]. Academic Press; 2024 [cited 2026 Aug 31]. p. 235–50. (International Review of Neurobiology). Available from: <https://www.sciencedirect.com/science/article/pii/S0074774224000503> doi:10.1016/bs.irm.2024.03.007
24. Brancato A, Castelli V, Lavanco G, D'Amico C, Feo S, Pizzolanti G, et al. Social stress under binge-like alcohol withdrawal in adolescence: evidence of cannabidiol effect on maladaptive plasticity in rats. *Psychological Medicine*. 2023 Sep;53(12):5538–50. doi:10.1017/S0033291722002744
25. de Faria SM, de Moraes Fabrício D, Tumas V, Castro PC, Ponti MA, Hallak JE, et al. Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease. *J Psychopharmacol*. 2020 Feb 1;34(2):189–96. doi:10.1177/0269881119895536
26. Linares IM, Zuardi AW, Pereira LC, Queiroz RH, Mechoulam R, Guimarães FS, et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. *Braz J Psychiatry*. 2019 Feb;41(1):9–14. doi:10.1590/1516-4446-2017-0015
27. Zuardi AW, Rodrigues NP, Silva AL, Bernardo SA, Hallak JEC, Guimarães FS, et al. Inverted U-Shaped Dose-Response Curve of the Anxiolytic Effect of Cannabidiol during Public Speaking in Real Life. *Front Pharmacol*. 2017 May 11;8. doi:10.3389/fphar.2017.00259
28. Kwee CMB, Van Der Flier FE, Duits P, Van Balkom AJLM, Cath DC, Baas JMP. Effects of cannabidiol on fear conditioning in anxiety disorders: decreased threat expectation during retention, but no enhanced fear re-extinction. *Psychopharmacology*. 2024 Apr;241(4):833–47. doi:10.1007/s00213-023-06512-6
29. Fusar-Poli P, Allen P, Bhattacharyya S, Crippa JA, Mechelli A, Borgwardt S, et al. Modulation of effective connectivity during emotional processing by  $\Delta^9$ -tetrahydrocannabinol and cannabidiol. *Int J Neuropsychopharmacol*. 2010 May 1;13(4):421–32. doi:10.1017/S1461145709990617
30. Jantsch J, Wickert F, Fraga G de F, de Fraga LS, Durán-Carabali LE, Guedes RP. Effects of cannabidiol on anxiety- and depressive-like behaviors and cognition: a systematic review and meta-analysis of preclinical studies. *Molecular Psychiatry*. 2026 Jun 30. doi:10.1038/s41380-026-03733-x
31. Shoval G, Shbiro L, HersHKovitz L, Hazut N, Zalsman G, Mechoulam R, et al. Prohedonic Effect of Cannabidiol in a Rat Model of Depression. *Neuropsychobiology*. 2016 Mar 25;73(2):123–9. doi:10.1159/000443890
32. Calapai G, Mannucci C, Chinou I, Cardia L, Calapai F, Sorbara EE, et al. Preclinical and Clinical Evidence Supporting Use of Cannabidiol in Psychiatry. *Evidence-Based Complementary and Alternative Medicine*. 2019 Jan 1;2019(1):2509129. doi:10.1155/2019/2509129
33. Bahji A, Meyyappan AC, Hawken ER. Efficacy and acceptability of cannabinoids for anxiety disorders in adults: A systematic review & meta-analysis. *Journal of Psychiatric Research*. 2020 Oct 1;129:257–64. doi:10.1016/j.jpsychires.2020.07.030

34. Spinella TC, Stewart SH, Naugler J, Yakovenko I, Barrett SP. Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: a randomized crossover study. *Psychopharmacology*. 2021 Jul;238(7):1965–77. doi:10.1007/s00213-021-05823-w

35. Linares IM, Zuardi AW, Pereira LC, Queiroz RH, Mechoulam R, Guimarães FS, et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. *Braz J Psychiatry*. 2019;41:9–14. doi:https://doi.org/10.1590/1516-4446-2017-0015

36. Elms L, Shannon S, Hughes S, Lewis N. Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series. *The Journal of Alternative and Complementary Medicine*. 2019 Apr 1;25(4):392–7. doi:10.1089/acm.2018.0437

37. Rodas JD, George TP, Hassan AN. A Systematic Review of the Clinical Effects of Cannabis and Cannabinoids in Posttraumatic Stress Disorder Symptoms and Symptom Clusters. *J Clin Psychiatry*. 2024 Feb 14;85(1):23r14862. doi:10.4088/JCP.23r14862 PubMed PMID: 38353645.

38. Veritas Health Innovation. Covidence systematic review software [Internet]. Melbourne, Australia. Available from: <https://www.covidence.org>

39. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ*. 2011 Oct 18;343:d5928. doi:10.1136/bmj.d5928 PubMed PMID: 22008217.

40. Bergamaschi MM, Queiroz RHC, Chagas MHN, de Oliveira DCG, De Martinis BS, Kapczinski F, et al. Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients. *Neuropsychopharmacol*. 2011 May;36(6):1219–26. doi:10.1038/npp.2011.6

41. Gundugurti PR, Banda N, Yadlapalli SSR, Narala A, Thatikonda R, Kocherlakota C, et al. Evaluation of the efficacy, safety, and pharmacokinetics of nanodispersible cannabidiol oral solution (150 mg/mL) versus placebo in mild to moderate anxiety subjects: A double blind multicenter randomized clinical trial. *Asian Journal of Psychiatry*. 2024 Jul;97:104073. doi:10.1016/j.ajp.2024.104073

42. Pinto JV, Crippa JAS, Ceresér KM, Vianna-Sulzbach MF, Silveira Júnior EDM, Santana Da Rosa G, et al. Cannabidiol as an Adjunctive Treatment for Acute Bipolar Depression: A Pilot Study: Le cannabidiol comme traitement d’appoint de la dépression bipolaire aiguë : une étude pilote. *Can J Psychiatry*. 2024 Apr;69(4):242–51. doi:10.1177/07067437231209650

43. Bogenschutz MP, Blessing E, Dgheim D, Cho D, Zhang J, Laska EM, et al. Effects of cannabidiol in alcohol use disorder patients with and without co-occurring post-traumatic stress disorder: Tolerability but no evidence for efficacy in two randomized proof-of-concept trials. *Alcohol, Clinical and Experimental Research*. 2026;50(1):e70212. doi:10.1111/acer.70212

44. Bolsoni LM, Crippa JAS, Hallak JEC, Guimarães FS, Zuardi AW. The anxiolytic effect of cannabidiol depends on the nature of the trauma when patients with post-traumatic stress disorder recall their trigger event. *Braz J Psychiatry*. 2022;44:298–307. doi:https://doi.org/10.1590/1516-4446-2021-2317

45. Kwee CM, Baas JM, Van Der Flier FE, Groenink L, Duits P, Eikelenboom M, et al. Cannabidiol enhancement of exposure therapy in treatment refractory patients with social anxiety disorder and panic disorder with agoraphobia: A randomised controlled trial. *European Neuropsychopharmacology*. 2022 Jun;59:58–67. doi:10.1016/j.euroneuro.2022.04.003

46. Gournay LR, Ferretti ML, Bilsky S, Vance E, Nguyen AM, Mann E, et al. The effects of cannabidiol on worry and anxiety among high trait worriers: a double-blind, randomized placebo controlled trial. *Psychopharmacology*. 2023 Oct;240(10):2147–61. doi:10.1007/s00213-023-06437-0

47. Masataka N. Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers With Social Anxiety Disorders. *Front Psychol*. 2019 Nov 8;10:2466. doi:10.3389/fpsyg.2019.02466

48. Bolsoni LM, Crippa JAS, Hallak JEC, Guimarães FS, Zuardi AW. Effects of cannabidiol on symptoms induced by the recall of traumatic events in patients with posttraumatic stress disorder. *Psychopharmacology*. 2022 May 1;239(5):1499–507. doi:10.1007/s00213-021-06043-y

49. Gournay LR, Ferretti ML, Nguyen AM, Bilsky S, Shields GS, Mann E, et al. The effects of acute versus repeated cannabidiol administration on trauma-relevant emotional reactivity: A double-blind, randomized, placebo-controlled trial. *Journal of Traumatic Stress*. 2024;37(6):946–58. doi:10.1002/jts.23072

50. Winkler A, Meis AC, Hermann C. Placebo effects in a RCT assessing 30 days of low dose Cannabidiol (CBD) treatment for psychological distress in stressed students at risk for depression. *J Cannabis Res.* 2025 Nov 28;7(1):98. doi:10.1186/s42238-025-00366-9
51. Perry RN, Ethier-Gagnon MA, Helmick C, Spinella TC, Tibbo PG, Stewart SH, et al. The impact of cannabidiol placebo on amygdala-based neural responses to an acute stressor. *J Psychopharmacol.* 2024 Nov;38(11):935–48. doi:10.1177/02698811241287557
52. Zhekova RM, Perry RN, Spinella TC, Dockrill K, Stewart SH, Barrett SP. The impact of cannabidiol placebo on responses to an acute stressor: A replication and proof of concept study. *J Psychopharmacol.* 2024 Jan;38(1):116–24. doi:10.1177/02698811231219060
53. De Vita MJ, Maisto SA, Gilmour CE, McGuire L, Tarvin E, Moskal D. The effects of cannabidiol and analgesic expectancies on experimental pain reactivity in healthy adults: A balanced placebo design trial. *Experimental and Clinical Psychopharmacology.* 2022 Oct;30(5):536–46. doi:10.1037/pha0000465
54. Patsalos PN, Szaflarski JP, Gidal B, VanLandingham K, Critchley D, Morrison G. Clinical implications of trials investigating drug-drug interactions between cannabidiol and enzyme inducers or inhibitors or common antiseizure drugs. *Epilepsia.* 2020 Sep 1;61(9):1854–68. doi:10.1111/epi.16674
55. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia.* 2015 Aug 1;56(8):1246–51. doi:10.1111/epi.13060

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