Clinical and Research Perspectives of the Use of Cannabinoids In the Treatment of Mental Disorders: Systematic Review

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Abstract. Mental disorders such as posttraumatic stress disorder (PTSD), psychosis, anxiety, and attention-deficit/hyperactivity disorder (ADHD) are significant global health burdens. While conventional pharmacotherapies and psychotherapies offer symptom relief, up to one-third of patients exhibit inadequate response or intolerable side effects, prompting the exploration of alternative or adjunctive treatments.

The researchers conducted a comprehensive literature search in January 2024 across PubMed, Scopus, and EBSCOhost. They screened peer-reviewed studies published in English between 2014 and 2023, using predefined eligibility criteria. The team extracted data using Cochrane-based templates and performed quality assessments with the RoB 2 tool for randomised trials and the Newcastle-Ottawa Scale for observational studies. Finally, they conducted a narrative synthesis based on diagnostic categories.

The researchers included ten studies—nine randomised controlled trials and one observational study—that examined cannabinoid interventions in PTSD, psychosis-spectrum disorders, ADHD, and social anxiety. Cannabidiol (CBD) was the most commonly studied compound. Neurobiological improvements were consistently observed in psychosis and PTSD, while clinical symptom reduction was more evident in social anxiety and ADHD. Although findings were heterogeneous, CBD demonstrated favourable safety across all studies, with mild or no adverse effects reported.

CBD appears to be safe and shows therapeutic promise in certain psychiatric conditions, particularly for neurobiological modulation in psychosis and PTSD, symptom reduction in social anxiety, and behavioural improvements in adult ADHD. However, evidence remains preliminary. Standardised, large-scale trials are needed to confirm efficacy, refine dosing, and guide clinical use.

Keywords: Cannabinoids; Cannabidiol; Delta-9-tetrahydrocannabinol; CBD; THC; PTSD; Psychosis; ADHD; Anxiety; Mental disorders; Psychiatry.

INTRODUCTION

Mental disorders, including depression, anxiety, posttraumatic stress disorder (PTSD), and schizophrenia, rank among the leading causes of disability worldwide, imposing a significant burden on individuals and society [1, 2]. While conventional pharmacotherapies and psychotherapies offer symptom relief, up to one-third of patients exhibit inadequate response or intolerable side effects, prompting the exploration of alternative or adjunctive treatments [1].

Cannabinoid-based interventions have emerged as promising candidates due to their interaction with the endocannabinoid system (ECS), a neuromodulatory system that regulates mood, stress response, memory, and emotion. The two principal phytocannabinoids – delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) – exert distinct neuropharmacological profiles. THC acts primarily as a partial agonist at CB1 receptors, with psychoactive effects that may exacerbate psychosis or anxiety in vulnerable individuals. In contrast, CBD appears to modulate the ECS via indirect mechanisms, including allosteric modulation of CB1 receptors and enhancement of anandamide signalling, and has been associated with anxiolytic, antipsychotic, and neuroprotective effects without intoxicating properties [2–4].

Despite growing interest, existing evidence on the psychiatric efficacy of cannabinoids remains limited and heterogeneous. Authors [1] concluded that there is "low-quality evidence" for cannabinoids improving symptoms in anxiety and PTSD, with no compelling support for their use in depression or psychosis. Similarly, a 2019 Lancet Psychiatry review analysing 80 studies found insufficient evidence to endorse cannabinoids for anxiety, depression, PTSD, ADHD, or psychosis, citing high variability in study quality, outcome measurement, and sample size [5].

Among the most promising findings are those related to schizophrenia. Several studies suggest that high-dose CBD (800–1,000 mg/day) may reduce positive and cognitive symptoms with comparable efficacy to amisulpride, a standard antipsychotic, but with fewer side effects [6–8]. However, these trials are often constrained by short durations, modest sample sizes, the inclusion of patients on antipsychotics, and inconsistent use of placebo controls, which limit their generalizability.

Similarly, there is encouraging but conflicting evidence about CBD's effects on anxiety disorders. At moderate dosages (such as 300 mg), some studies have shown that CBD has acute anxiolytic effects; these effects frequently follow an inverted U-shaped dose-response curve. However, different stress-induction models, dosing strategies, and illness subtypes yield varying therapeutic outcomes [9–11].

Despite growing academic interest in cannabinoid psychiatric applications, there are numerous methodological and clinical gaps in the existing literature. One significant limitation is the variation in dosage regimens and formulations employed between trials. The types and ratios of cannabinoids administered in trials vary greatly, including cannabidiol (CBD), delta-9-tetrahydrocannabinol (THC), or combination formulations, as well as administration routes and dosages. This diversity makes it difficult to draw consistent conclusions or do reliable meta-analyses across studies [1].

Another ongoing challenge is the composition of study participants. Many clinical trials disproportionately target people with chronic or treatment-resistant mental health disorders who are already receiving pharmacological interventions. Furthermore, several researchers only consider mental health outcomes as secondary endpoints or within larger assessments of cannabis use, reducing the generalizability and specificity of their findings [4].

Collectively, these limitations underscore the need for a rigorous and methodologically comprehensive synthesis of current research. This review fills this gap by thoroughly investigating both randomised and observational studies on cannabinoid application in managing mental health conditions. It intends to stratify findings by diagnosis, cannabinoid type, and outcome domain, while critically evaluating efficacy and safety.

METHOD

Development of the Research Question. The research question was developed using the PICO framework [12], a recognised tool for structuring clinical research questions:

1) Population (P): Individuals diagnosed with mental disorders (e.g., depression, anxiety, PTSD, schizophrenia).

2) Intervention (I): Use of cannabinoids (e.g., THC, CBD, full-spectrum cannabis).

3) Comparator (C): Placebo, standard care, or no intervention.

4) Outcomes (O): Clinical outcomes including symptom severity, functional improvement, adverse effects, relapse, and cognitive effects.

Primary research question: What is the effectiveness and safety of cannabinoid-based interventions in the treatment of mental disorders in human populations?

Eligibility Criteria. The inclusion and exclusion criteria were informed by the PICOS framework (Population, Intervention, Comparator, Outcomes, Study Design).

Inclusion Criteria:

a) Peer-reviewed randomised controlled trials (RCTs), quasi-experimental studies, cohort studies, and case-control studies.

b) Studies involving human participants diagnosed with mental disorders.

c) Interventions including any form of cannabinoid-based treatment (CBD, THC, synthetic cannabinoids, etc.).

d) Studies reporting on at least one clinical outcome (efficacy or adverse effects).

e) Publications in English from 2014 to 2023.

Exclusion Criteria:

a) Animal studies or preclinical trials.

b) Non-peer-reviewed articles, conference abstracts, and commentaries.

c) Studies where mental health outcomes are not primary or secondary outcomes.

d) Studies focusing solely on substance use disorders or recreational cannabis use.

Information Sources and Search Strategy

The researchers conducted a comprehensive literature search in January 2024 across PubMed, EBSCOhost PsycINFO, and Scopus. They included both MeSH terms and Title and Abstract keywords in the search strategy.

The search term for databases that do not make use of the MeSH term is as follows:

("cannabinoids" OR "CBD" OR "THC" OR "medical cannabis" OR "phytocannabinoids") AND ("mental disorders" OR "psychiatric disorders" OR "depression" OR "anxiety" OR "PTSD" OR "schizophrenia") AND ("treatment" OR "therapy")

The compiled search term for PubMed is as follows:

("Cannabinoids"[Mesh] OR "Cannabidiol"[Mesh] OR "Tetrahydrocannabinol"[Mesh] OR "Cannabis"[Mesh] OR "Medical Marijuana"[Mesh] OR cannabinoids[tiab] OR CBD[tiab] OR THC[tiab] OR "medical cannabis"[tiab] OR phytocannabinoids[tiab]) AND ("Mental Disorders"[Mesh] OR "Depressive Disorder"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Post-Traumatic Stress Disorders"[Mesh] OR "Schizophrenia"[Mesh] OR "Bipolar Disorder"[Mesh] OR "Obsessive-Compulsive Disorder"[Mesh] OR "Attention Deficit Disorder with Hyperactivity"[Mesh] OR "psych*"[tiab] OR "mental disorder*"[tiab] OR depression[tiab] OR anxiety[tiab] OR PTSD[tiab] OR schizophrenia[tiab] OR bipolar[tiab] OR OCD[tiab] OR ADHD[tiab]) AND ("Therapeutics"[Mesh] OR "Drug Therapy"[Mesh] OR "Treatment Outcome"[Mesh] OR treatment[tiab] OR therapy[tiab])

The researchers manually searched the reference lists of eligible studies and prior reviews to identify additional relevant papers.

Study Selection. The researchers filtered all identified records based on the eligibility criteria and imported the yields into EndNote for reference management and deduplication. Two reviewers then independently screened the remaining citations in two phases. During phase I, they screened titles and abstracts. In Phase II, they conducted a

full-text screening of studies that met the inclusion criteria or had unclear decisions. The reviewers resolved discrepancies through discussion and documented the screening process in a PRISMA 2020 flow diagram.

Data Extraction. Data was extracted using a standardised extraction form designed in Microsoft Excel.

Quality Assessment. The methodological quality and risk of bias of the included studies were assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool for randomised controlled trials authors [13] and the Newcastle-Ottawa Scale (NOS) for evaluating the quality of nonrandomised studies [14].

Data Synthesis. The researchers carried out a narrative synthesis to organise the included studies by mental disorder (e.g., anxiety, PTSD, schizophrenia, depression). They summarised the intervention effects and identified thematic patterns in the outcome measures.

RESULTS AND DISCUSSION

Literature selection. The researchers conducted a systematic search in PubMed, Scopus, and EBSCOhost's PsycINFO, retrieving 485,895 records. They then applied appropriate database-specific filters to exclude articles that did not meet the eligibility criteria and used EndNote to remove duplicates, ultimately removing 484,759 articles through filtering and deduplication. Title and abstract screening of the remaining 1,136 articles resulted in the removal of 28 articles, leaving 1,108 articles for further review. Then 28 full-text articles were assessed for eligibility, and 18 articles were excluded – 7 for lacking a mental disorder diagnosis and 11 for focusing solely on substance use or recreational cannabis use. Ultimately, 10 studies met the inclusion criteria and were retained for this review [9, 15–23]. The screening process is summarised in the PRISMA 2020 flow diagram as shown in Figure 1.

Study Characteristics and Quality Assessment. This systematic review included ten studies: nine randomised controlled trials (RCTs), authors [9, 15–22] and one retrospective observational study [23]. The RCTs were carried out in several countries, including Brazil, the United States, the Netherlands, Japan, and the United Kingdom, and focused on mental health disorders such as PTSD, psychotic disorders, ADHD, and social anxiety.

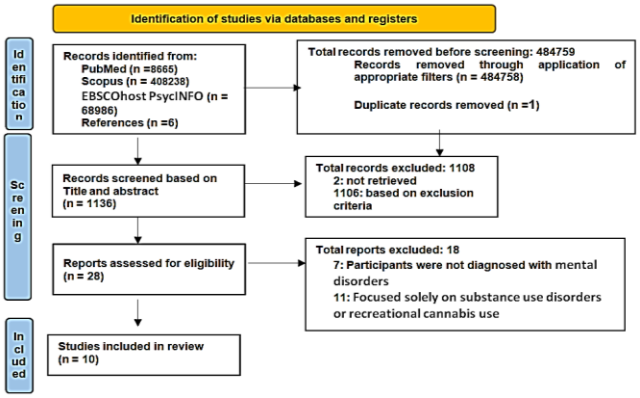

Figure 1 – Prisma Flow Diagram

The sample sizes ranged from 30 to 80 participants.

Researchers provided cannabidiol (CBD), tetrahydrocannabinol (THC), or combination formulations through oral capsules, oromucosal sprays, or smoked cannabis. All randomised controlled trials (RCTs) included recognised psychiatric outcome measures, such as the CAPS-5, PANSS, CAARS, LSAS, or neuroimaging biomarkers [9, 19]. Quality assessment using the Revised Cochrane Risk-of-Bias tool (RoB 2) revealed that six RCTs were rated as low risk of bias [9, 15, 17–20].

At the same time, three had some concerns due to small sample size, limited reporting of analysis plans, or crossover-related limitations [16, 21, 22]. The observational study [23], assessed with the Newcastle-Ottawa Scale, scored 6 out of 9, indicating moderate quality with strengths in secure exposure measurement and follow-up, but limitations in comparability due to lack of a non-exposed control group.

Overall, the methodological quality was robust, supporting a reliable synthesis of cannabinoid-related psychiatric outcomes. The details of the study characteristics and the quality assessment of the ten studies included in this review are contained in Tables 1.

Narrative Synthesis. To fully address the subject matter issue, a narrative synthesis was carried out across the 10 included papers, categorised by diagnostic category. This synthesis examines standardised clinical outcomes and neurobiological endpoints to identify patterns in therapeutic outcomes and safety profiles. The analysis is based on four primary mental health conditions represented in the included studies: posttraumatic stress disorder (PTSD), psychotic disorders, attention-deficit/hyperactivity disorder (ADHD), and anxiety disorders.

Table 1 – The characteristics of the included studies

Study ID	Country	Study Design	Population	Mean Age / Range	Intervention	Comparator	Outcome Measures	Funding Source	Risk of Bias Score
[15]	Brazil	Randomised controlled trial	Adults aged 18–60 with DSM-5 PTSD diagnosis (sexual or nonsexual trauma)	Mean age: CBD group 33.9 (SD 11.5), Placebo group 32.5 (SD 13.0)	300 mg oral CBD (single dose) administered 90 mins before trauma recall	Placebo (corn oil in identical capsules)	Subjective anxiety (VAMS), cognitive impairment, discomfort, sedation, BP, HR, salivary cortisol	FAPESP, INCT-TM, CNPq; patent interests disclosed by some authors	Low risk of bias
[16]	United States	Randomised controlled trial	US military veterans with PTSD (DSM-5, CAPS-5 ≥25, symptoms ≥6 months)	Mean age: 44.9 (SD 13.8)	Smoked cannabis (High THC ~12%, High CBD ~11%, THC+CBD ~8% each), ad libitum use up to 1.8 g/day for 3 weeks	Placebo cannabis (<0.03% THC/CBD)	CAPS-5 (PTSD severity), PCL-5, IDAS (Depression, Anxiety), IPF (Functioning), ISI (Sleep)	Colorado Dept. of Public Health & Environment, MAPS; multiple authors reported industry ties	Some concerns
[17]	United States	Randomised controlled trial	Trauma-exposed adults aged 20–45; 21 met PTSD criteria (DSM-5 via CAPS-5), 30 were trauma-exposed controls (TEC)	Mean age: 25.15 (SD 5.65)	7.5 mg oral THC (dronabinol), single dose, administered 120 min prior to fMRI scan	Placebo capsule containing dextrose	fMRI brain activation during emotion regulation task; subjective ratings of negative affect, arousal, and valence	National Institute of Mental Health (MH101123)	Low risk of bias
[18]	Netherlands	Randomised controlled trial	Adults with recent-onset psychotic disorder (<5 years); DSM-IV schizophrenia spectrum disorders	Mean age: CBD 24.7 (SD 6.3); Placebo 27.5 (SD 6.6)	600 mg/day oral CBD for 28 days (adjunct to antipsychotic)	Matched placebo capsules	Resting-state functional connectivity (fMRI), prefrontal metabolite levels (1H-MRS), reward processing (task fMRI), PANSS, HAM-D, GAF, BACS	Netherlands Organization for Scientific Research, Trigal Pharma GmbH	Low risk of bias
[19]	United Kingdom	Randomised controlled trial	Antipsychotic-naïve individuals at clinical high risk (CHR) for psychosis	CHR group: 18–35 years (mean age ~23–24)	Single 600 mg oral dose of CBD (dronabinol); administered ~180 mins prior to fMRI	Placebo capsule	Brain activity during motivational salience task (fMRI); CAARMS positive symptom scores; reaction time (RT); false-starts	Medical Research Council (UK), NIHR, Netherlands Organisation for Scientific Research	Low risk of bias
[20]	United States	Randomised controlled trial	Adults aged 21–45; trauma-exposed with and without PTSD; PTSD confirmed by CAPS-5 and DSM-5	Mean age: approx. 26.5 years	7.5 mg oral THC (dronabinol), single dose administered 120 min prior to extinction learning	Placebo (dextrose capsule)	Neural activation during extinction learning, recall, and fear renewal (fMRI); behavioral measures: US expectancy, SUDs, SCR (limited data)	NIMH grants K01MH101123 and F31MH124279	Low risk of bias
[21]	United Kingdom	Randomised controlled trial	Adults aged 18–55 with DSM-5 diagnosed	Mean age: Sativex 36.91	Sativex Oromucosal Spray (1:1 THC/CBD),	Matched placebo Oromucosal Spray	Primary: QbTest (cognition/activity); Secondary: CAARS, WRAADS,	NIHR BRC, EU FP7, GW Pharma provided drug	Some concerns

Study ID	Country	Study Design	Population	Mean Age / Range	Intervention	Comparator	Outcome Measures	Funding Source	Risk of Bias Score
			combined type ADHD	(SD 11.70); Placebo 38.90 (SD 11.54)	titrated up to max 14 sprays/day, 6-week intervention		CNS-LS, ALS, WFIRS	(no role in design/analysis)	
[23]	Canada	Retrospective observational study	Seriously mentally ill adult males in correctional facility; high rates of PTSD, substance use, chronic pain	Mean age: 32.7 years (range 19–55)	Oral nabilone (synthetic cannabinoid), mean final dose 4.0 mg; individualised dosing over mean 11.2 weeks	No control group (non-comparator observational study)	PTSD-related insomnia, nightmares (self-reported sleep, PCL-C, GAF), chronic pain, polypharmacy reduction	No external funding reported	Moderate risk of bias
[22]	Japan	Randomised controlled trial	18–19-year-old Japanese teenagers with DSM-IV diagnosed Social Anxiety Disorder (SAD) and avoidant personality disorder	Mean age: 18–19 years (12 males, 5 females CBD; 14 males, 6 females placebo)	300 mg/day oral CBD (cannabis oil) for 4 weeks	Placebo (olive oil)	Fear of Negative Evaluation Questionnaire (FNE), Liebowitz Social Anxiety Scale (LSAS)	Japanese Government (JSPS#25285201); no funder involvement in study design or analysis	Some concerns
[9]	United Kingdom	Randomised controlled trial	Antipsychotic-naïve individuals at Clinical High Risk (CHR) for psychosis, 18–35 years	CHR mean age: ~22–24 years	Single 600 mg oral dose of cannabidiol (CBD)	Placebo; Healthy controls received no treatment	Brain activation during verbal memory fMRI task (hippocampus, striatum, midbrain); CAARMS symptom scores	Funded by MRC, NIHR, King's College London Biomedical Research Centre	Low risk of bias

Table 2 – The Quality Assessment of the included studies Based on NOS for Observational study [23]

Study ID	Selection (Max 4)	Comparability (Max 2)	Outcome (Max 3)	Total Score (Max 9)
[23]	3	1	2	6

Table 3 – The Quality Assessment of the included studies Based on RoB2 for RCTs

Study ID	D1: Bias from randomisation process	D2: Bias due to deviations from intended interventions	D3: Bias due to missing outcome data	D4: Bias in measurement of the outcome	D5: Bias in selection of the reported result	Overall Risk of Bias
[15]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
[16]	Some concerns	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns
[17]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
[18]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
[19]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
[20]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
[21]	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns	Some concerns
[22]	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns	Some concerns
[9]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

Posttraumatic Stress Disorder (PTSD). Numerous investigations exploring the application of cannabinoids in the management of PTSD have provided a range of perspectives on the neurobiological and clinical impacts of these substances. A single oral CBD dosage was linked to notable decreases in subjective anxiety and cognitive impairment during trauma recall, according to the authors [15]; however, this advantage was only observed in those with non-sexual trauma histories. This finding raises the possibility that the characteristics of trauma could impact the treatment response. On the other hand, in a randomised crossover trial, authors [16] assessed three cannabis chemotypes among PTSD-affected military veterans; however, they found no discernible difference in symptom reduction between the active cannabis groups and placebo. These findings emphasised the difficulties associated with subjective outcomes in cannabinoid trials and the potent placebo effect.

Authors [20] provided additional information by assessing the impact of THC on extinction learning and fear renewal in PTSD using neuroimaging. THC enhanced activation in the amygdala and ventromedial prefrontal cortex, suggesting a possibly facilitative influence on brain pathways that support trauma processing, even though no behavioural changes were observed. Complementing these experimental studies, authors [23] reported observational findings from a correctional psychiatric setting where synthetic cannabinoids (nabilone) led to improved sleep, reduced nightmares, and reduced use of adjunct psychotropic medications in inmates with PTSD. While limited by its retrospective design, the study contributed real-world evidence of therapeutic benefit and functional improvement.

Together, these studies suggest that cannabinoids – particularly CBD and THC – actively modulate anxiety and fear responses in PTSD, although individual trauma history and trial design likely influence these effects. Adverse effects were infrequent and generally mild, with no reports of sustained harm.

Psychotic Disorders. In the context of psychotic disorders and individuals at clinical high risk (CHR) for psychosis, cannabinoids – specifically cannabidiol (CBD) – were evaluated for their potential antipsychotic properties. Authors [18] administered CBD daily over 28 days in patients with recent-onset psychosis, noting improved default mode network (DMN) connectivity and a reduction in glutamate and N-acetylaspartate levels, markers associated with psychotic pathology. Although clinical symptoms showed modest changes, the neurobiological shifts suggest a stabilising effect on brain function.

Building on this, authors [19] investigated how a single dose of CBD influenced the way individuals in the Clinical High Risk (CHR) category perceived motivational salience. According to the study, the degree of psychotic symptoms was correlated with the normalisation of insular cortex activity, suggesting that CBD has a neuromodulatory effect on areas linked to abnormal salience. In a similar vein, authors [9] discovered that CBD changed the activity of the striatum, midbrain, and medial temporal lobe in CHR individuals during verbal learning tasks, which again mirrored patterns observed in healthy controls. Together, these studies show that CBD actively alters the functioning of neural pathways affected in psychosis.

It is noteworthy that the safety profile of CBD remained encouraging in all three studies [9, 18. 19], with no notable side events being observed. Although there was a slight improvement in clinical symptoms, persistent brain modulation suggests a therapeutic mechanism that warrants further investigation in larger, longer-term trials.

Attention-Deficit/Hyperactivity Disorder (ADHD). In a pilot randomised controlled trial, authors [21] examined the potential of cannabinoids as a treatment for ADHD. In this study, people with mixed-type ADHD were given a combination THC/CBD oromucosal spray. In addition to showing apparent improvements in impulsivity and hyperactivity, participants in the active treatment also showed new patterns in emotional lability and attention management. It is noteworthy that cognitive function did not change, allaying prevalent worries about cognitive damage brought on by cannabis.

The results show that cannabinoids may be able to modulate the main symptoms of ADHD, despite the small sample size. Additionally, the study found that the side effects were minimal and the tolerance was good. These early findings imply that marijuana could be a valuable supplement for the treatment of ADHD, especially in situations where traditional medication is ineffective. However, larger studies are required to validate this.

Anxiety Disorders. In a randomised, placebo-controlled study of Japanese teenagers with social

anxiety disorder, authors [22] further demonstrated the anxiolytic properties of cannabidiol. According to the LSAS and FNE scales, social anxiety significantly decreased after receiving 300 mg of CBD daily for four weeks. An intriguing follow-up observation was that participants in the CBD group showed a higher likelihood of engaging with mental health services post-intervention, suggesting that symptom relief may facilitate help-seeking behaviour.

The study's strengths lie in its focus on a youth population and its use of standardised outcome measures. Future researchers should address limitations such as a modest sample size and the lack of comprehensive adverse effect monitoring. Nevertheless, these findings align with other evidence suggesting that CBD may influence serotonergic and limbic pathways involved in anxiety regulation.

Summary of Effectiveness and Safety. Across diagnostic groups, the effectiveness of cannabinoid-based interventions appears most consistent in modulating neurobiological substrates of mental illness, particularly in PTSD and psychosis-related disorders. Some studies reported improvements in clinical symptoms, especially in anxiety, although the results were often modest and heterogeneous. Variability in formulation, dosing, and sample characteristics may account for these differences.

Safety outcomes were uniformly favourable. The majority of studies reported either no adverse effects or only mild symptoms such as drowsiness, dry mouth, or mild cognitive slowing. Notably, no study reported persistent or severe harm, supporting the tolerability of cannabinoid-based treatments within controlled settings.

This study provides a comprehensive examination of cannabinoids' therapeutic and safety profiles across diverse psychiatric conditions. Our narrative synthesis of ten studies reveals emerging yet preliminary evidence of efficacy, most notably for cannabidiol (CBD) across PTSD, psychosis-spectrum disorders, ADHD, and social anxiety.

Clinical Perspectives. In PTSD, studies such as those by authors [15, 29] demonstrated symptom reduction and facilitation of fear extinction through CBD and THC, respectively. These findings are consistent with broader literature reporting modest improvements in PTSD symptoms and sleep disturbances with cannabinoids [24]. Nevertheless, authors' [16] null findings underscore the substantial placebo response in trauma-related studies, a recurrent theme in cannabinoid research.

In psychosis, consistent neuromodulatory effects have been reported across three randomised controlled trials (RCTs) [9, 18, 19], including improved default mode network activity and normalised striatal activation. These align with prior studies suggesting that CBD modulates functional connectivity like antipsychotics but with fewer side effects [8]. While symptom-level improvements remain inconsistent, the physiological changes offer a mechanistic rationale for further trials.

For ADHD, authors [21] reported nominal improvements in hyperactivity and emotional lability using a THC/CBD spray formulation. This study contributes to a growing discussion about cannabinoids in neurodevelopmental disorders, where reviews have noted only limited support for clinical efficacy [21].

In social anxiety disorder, Masataka (2019) demonstrated reductions in Liebowitz Social Anxiety Scale (LSAS) and Fear of Negative Evaluation (FNE) scores following four weeks of CBD use. These findings build on earlier evidence of CBD's anxiolytic effects in public speaking paradigms [25] and suggest potential long-term benefits in youth populations.

Our findings reflect broader reviews that characterise the field as promising but methodologically underdeveloped. Systematic reviews have highlighted small sample sizes, inconsistent cannabinoid formulations, and variable outcome measures as barriers to clear clinical guidance [5]. Still, the neurobiological convergence observed in psychosis-related studies strengthens the argument for continuing mechanistic research.

Future research should prioritise:

a) Larger, pre-registered RCTs with standardised CBD/THC formulations and active comparators,
b) Longitudinal trials to evaluate sustained efficacy and safety,

c) Biomarker-based endpoints to elucidate the mechanism of action,

d) Formulation-specific studies grounded in pharmacokinetic evidence, and

e) Exploration of underserved populations, including adolescents and those with comorbidities.

CONCLUSIONS

This systematic review demonstrates that cannabinoid-based interventions, particularly cannabidiol (CBD), show emerging efficacy and favourable safety in treating selected mental disorders, including PTSD, psychosis-spectrum conditions, ADHD, and anxiety. While the clinical symptom improvements are modest and vary by diagnosis, consistent neurobiological changes, especially in psychosis and trauma-related conditions, suggest therapeutic potential worth further exploration.

Overall, cannabinoid-based treatments are generally safe and may offer effectiveness in managing psychiatric symptoms, particularly when conventional therapies are limited. However, heterogeneity in study design, sample size, and formulation underscores the need for larger, standardised trials to establish cannabinoids as evidence-based options in mental health care. Future research should aim to optimise dose, duration, and patient selection.

Data availability: The authors provide data from this study within the article and the reference section.

Competing Interests: The final manuscript was read and approved by all authors, and all authors declare no conflict of interest.

Ethical Considerations: The authors utilised publicly available data from published literature, thereby exempting them from the requirement for ethical approval.

Consent for publication: Not applicable.

Authors' Contributions: NT, VUN and OZM were responsible for conceptualising the idea, conducting the literature search and selection, as well as quality assessment of the included studies. EBO and CEE played a crucial role in synthesising the data. OOF, DOB, and KKE collaborated on writing the manuscript. All authors reviewed and approved the final manuscript.

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