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Review Article

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Clinical Efficacy of Cannabinoids in PTSD Management: A Systematic Review Overcoming Limitations of Prior Evidence

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a debilitating mental health condition that affects the entire population, with a higher prevalence among military veterans. It is characterized by the re-experiencing of traumatic events, the avoidance of trauma-related stimuli, and persistent hyperarousal. PTSD is widely regarded as a disorder marked by impaired memory processing. Current therapy mostly comprises trauma-focused psychotherapies and pharmacological agents, including selective serotonin reuptake inhibitors (SSRIs) and monoamine receptor antagonists. However, currently access to specialized therapies is constrained, and pharmaceutical results remain inadequate, highlighting the necessity for innovative therapeutic approaches. Cannabinoids have surfaced as prospective therapy alternatives; however, previous reviews have been limited by restrictive inclusion criteria, a narrow range of cannabinoids, inconsistent outcome assessments, and inadequate examination of new evidence. The potential health risk associated with cannabinoid use stresses the importance of a cautious, evidence-based approach. The rapidly changing legal and regulatory landscape of cannabinoids requires a revised synthesis of contemporary studies. This systematic review assesses clinical trials examining cannabis utilization in PTSD. A thorough search strategy was implemented across primary databases, followed by study selection according to established inclusion and exclusion criteria. The risk of bias and methodological quality were evaluated utilizing validated instruments. Data were meticulously gathered and synthesized across many parameters: trial design, demographic characteristics, PTSD diagnosis techniques, cannabis type and treatment duration, outcome measures, adverse events, and study constraints. This review rectifies previous deficiencies by integrating a comprehensive evidence base, encompassing both synthetic and plant-derived cannabinoids, and standardizing data assessment. It offers a contemporary, evidence-based summary to enhance clinical practice and to direct future research in the management of PTSD with cannabinoids.

KEYWORDS post-traumatic stress disorder, cannabinoids, medical cannabis, systematic review, psychiatric treatment

INTRODUCTION

Post-traumatic stress disorder (PTSD) is recognized as a potentially incapacitating mental health condition, common in the general populace and disproportionately impacting military personnel. The clinical presentation of PTSD often includes three principal symptom clusters: re-experiencing events (intrusive memories, flashbacks, and nightmares), active avoidance of trauma-related stimuli, and sustained hyperarousal. PTSD is fundamentally characterized as an illness largely associated with impairments in memory processing systems. Current therapy options rely on trauma-focused psychotherapies which enable the reprocessing and cognitive restructuring of trauma-related memories and their psychological effects. Pharmacological therapies, including serotonin reuptake inhibitors and monoamine receptor antagonists, are recommended to alleviate symptom severity (1). Nevertheless, access to specialized trauma-focused therapies is restricted for numerous individuals, and pharmaceutical interventions frequently produce inadequate results. These constraints underline the necessity for the ongoing advancement of creative and efficacious intervention options for PTSD management. In recent years, there has been a significant rise in the utilization of cannabis for the treatment of psychiatric diseases, especially PTSD, driven by changing legal and political landscapes globally. A multitude of persons with PTSD utilize cannabinoids as a coping mechanism or for self-medication, regardless of the limited availability of substantial clinical data endorsing their effectiveness (2). The involvement of cannabis in mental health treatment is contentious, mainly due to an insufficient and inconsistent data base and exacerbated by a lack of randomized controlled trials (RCTs). Under these circumstances, a thorough and critical assessment of the therapeutic potential of cannabis for PTSD treatment is necessary. This review offers a summary of cannabis pharmacology and the justification for its application in PTSD, followed by a thorough evaluation of the current clinical evidence concerning their efficacy.

The influence of cannabinoids occurs via the endogenous cannabinoid system, a neuromodulatory network that regulates many activities and helps maintain homeostasis (3). A primary function of this system is the modulation of other neurotransmitter systems. The endocannabinoid system consists of endogenous ligands, primarily anandamide and 2-arachidonoylglycerol (2-AG), two main types of cannabinoid receptors—type 1 (CB1R) and type 2 (CB2R), and specific enzymes, such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase, that mediate the degradation of these ligands (4). The activation of CB1R, the primary class of G-protein-coupled receptors in the central nervous system, leads to the suppression of neurotransmitter release. CB1 receptors are predominantly located on GABAergic and glutamatergic nerve terminals, and are also present on terminals associated with serotonin, noradrenaline, and dopamine neurotransmission. The endogenous cannabinoids, anandamide and 2-AG, are synthesized and released from postsynaptic terminals in a way that depends on the level of activity, exerting modulatory effects by retrograde transmission to presynaptic terminals. Recent data indicates that the cannabis plant contains approximately 104 phytocannabinoids, with Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most well researched (5). THC is recognized as the principal psychoactive constituent, while CBD is nonintoxicating and has exhibited anxiolytic and antipsychotic effects. In comparison to the CB1 receptor, agonists such as THC, nabilone, and dronabinol, CBD demonstrate enhanced tolerance and a more advantageous side-effect profile. The cannabinoid composition variations among cannabis strains are believed to affect their therapeutic effects, with high-THC strains yielding different outcomes than those with balanced THC and CBD ratios.

PTSD has been recognized as a research priority in numerous countries, emphasizing the necessity of exploring the therapeutic efficacy of cannabis for treatment. Research has shown that persons diagnosed with PTSD utilize cannabis more frequently than those without the condition, although they also endure more intense withdrawal symptoms from cannabis. Observational evidence indicates that a number of individuals are self-medicating with cannabis, and multiple case studies suggest that medical cannabis may significantly mitigate PTSD-related symptoms, especially sleep problems (6). Self-reported data from patients using cannabis suggests that cannabinoids have the ability to alleviate traumatic

intrusions, hyperarousal, tension, anxiety, despair, and insomnia, symptoms typically linked to PTSD. This analysis aims to consolidate findings regarding the effectiveness of synthetic cannabinoids (such as nabilone and dronabinol), pharmaceutical whole-plant extracts containing THC and CBD, as well as whole-plant cannabis products, including herbal and resin preparations which are typically smoked. This study rigorously assesses the current data employing thoroughly validated methodologies for evaluating bias risk and quality which are specifically tailored for the types of studies covered.

METHODS

Study type and design

This systematic review primarily examines the application of cannabis in the management of PTSD and encompasses both RCTs and observational studies, including cohort, case-control, cross-sectional, and case series methodologies. RCTs were chosen for their capacity to establish links between cannabinoids and PTSD therapy. Observational studies were also evaluated to provide a more comprehensive insight into real-world use and outcomes. Research involving human subjects diagnosed with PTSD, irrespective of age, gender, or ethnicity, was deemed appropriate for inclusion.

Study objectives

The main aim of this systematic review was to rigorously assess the effectiveness of cannabis in alleviating PTSD symptoms. This review specifically aimed to evaluate the therapeutic potential of diverse cannabinoids, encompassing synthetic cannabinoids such as nabilone and dronabinol, phytocannabinoids including THC and CBD, as well as whole-plant cannabis products in both herbal and resin forms. The objective was to ascertain if cannabinoid-based therapies might effectively mitigate fundamental PTSD symptoms such as intrusive memories, flashbacks, hyperarousal, avoidance behaviors, and sleep difficulties, that are frequently severe for those affected. The secondary aims of this research encompassed assessing the safety, tolerability, and adverse impact profiles linked to cannabis usage in patients with PTSD. This included examining any negative impacts such as withdrawal symptoms, and long-term hazards linked to the utilization of synthetic cannabinoids and whole-plant cannabis products. The review sought to evaluate clinical results while also investigating the neurobiological mechanisms that may underlie the therapeutic effects of cannabis in the management of PTSD. This entailed examining the interaction of cannabis with the endocannabinoid system and other neurotransmitter pathways pertinent to PTSD symptoms, encompassing the modulation of stress responses, mood control, and memory processing. The review aimed to identify significant gaps in the existing literature, particularly in areas requiring additional research needed to furnish more substantial information regarding the efficacy of cannabis in treating PTSD. Larger, more methodologically robust investigations, especially RCTs, can potentially enhance understanding of optimal dose regimens, treatment duration, and long-term effects of cannabis. This study also sought to delineate future research avenues, emphasizing the promise of innovative cannabinoid-based therapeutics for PTSD management and their incorporation into clinical practice.

Search strategy

This systematic review employed a thorough and organized search approach in compliance with PRISMA guidelines. The investigation concentrated on discovering studies that assess the effectiveness of cannabinoids in the treatment of PTSD, including synthetic cannabinoids (such as nabilone), phytocannabinoids (THC and CBD), and whole-plant cannabis products (herbal and resin formulations). Four electronic databases—PsycINFO, Scopus, PubMed, and Embase—were systematically queried utilizing the Ovid interface. The investigation was carried out from 2014 through 2023. No constraints on publication dates were imposed to help ensure a comprehensive and extensive identification of pertinent studies. Concurrent with the automated search, reference lists of all included studies and relevant review papers were manually examined to discover any new eligible studies not detected by database searches.

Study selection

A preliminary search was conducted utilizing established search methods across the chosen databases. All detected records were imported into reference management software, and duplicates entries were meticulously verified and eliminated. After deduplication, two independent reviewers evaluated the titles and abstracts of the obtained papers according to the predetermined inclusion and exclusion criteria. Studies deemed potentially eligible underwent comprehensive text evaluation. The whole texts and their corresponding reference lists were subsequently evaluated independently for eligibility. Disagreements at any stage of the screening process were resolved by discussion and consensus, with the inclusion of a third reviewer when required.

Inclusion Criteria

- Studies that examined the application of cannabinoids in the therapy or management of PTSD symptoms, encompassing:
  - Synthetic cannabinoids (e.g., nabilone, dronabinol)
  - Phytocannabinoids (e.g., THC, CBD)
  - Whole-plant cannabis products (herbal and resinous forms)
- Studies using either randomized controlled trial (RCT) methodologies or observational designs (cohort, case-control, cross-sectional, or case series).
- Human subjects possessing a clinical diagnosis of PTSD, regardless of age, gender, or ethnicity
- Documented pertinent clinical outcomes associated with PTSD symptomatology

Exclusion criteria

- Studies that failed to report clinical outcomes directly associated with PTSD
- Studies exclusively centered on animal research or *in vitro* experiments
- Studies that constituted non-original research articles, including editorials, commentaries, and opinion pieces
- Studies not published in the English language

Risk of bias

The potential for bias in the included studies was assessed using rigorous, proven tools tailored to the study design. The Cochrane Risk of Bias tool was employed for RCTs, as recommended by the Cochrane Collaboration. Non-randomized studies were evaluated using the ROBINS-I methodology, designed specifically for observational research. Both instruments assess several types of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each study was assessed according to critical criteria, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting of results, and other potential sources of bias. The risk of bias for each study was evaluated as "low," "high," or "unclear," based on the availability and clarity of the supplied information. Two independent evaluators (SRA and RR) conducted the assessment for each study, and any discrepancies in the ratings were resolved through discussion with a third evaluator (SB). This comprehensive risk of bias assessment was essential for appraising the methodological quality of the research and informing the interpretation of the findings. The potential for bias was also rigorously assessed in the evidence synthesis, particularly on the efficacy and safety of cannabis in PTSD treatment.

Data collection

Data extraction was conducted systematically and independently by two reviewers employing a consistent methodology to guarantee precision and uniformity. For each study included, the subsequent information was taken and organized in a table: study particulars, encompassing author, publication year, and digital object identifier (DOI); type of cannabinoid intervention (synthetic cannabinoids like nabilone or dronabinol, phytocannabinoids such as THC or CBD, or whole-plant cannabis products), including dosage and method of administration; study design (randomized controlled trial, cohort study, case-control study, cross-sectional study, or case series); methodology employed for PTSD diagnosis and any further inclusion or exclusion criteria delineated; duration of the intervention; sample size and demographic characteristics of participants; level of evidence as per the Oxford Centre for Evidence-Based Medicine – Levels of Evidence guideline; primary outcome measures assessing

PTSD symptomatology (e.g., Clinician-Administered PTSD Scale, PTSD Checklist); findings of the principal outcomes; secondary outcomes pertaining to associated symptoms such as anxiety, depression, sleep disturbances, and substance use; results of the secondary outcomes; and documented adverse effects or concerns regarding tolerability.

The principal outcomes of interest encompassed decreases in PTSD symptoms, including intrusive thoughts, flashbacks, avoidance behavior, hyperarousal, and insomnia. Secondary data encompassed concomitant psychiatric symptoms and functional outcomes. The data extraction approach included meticulous documenting of intervention regimens, participant follow-up durations, and reported attrition rates. Discrepancies among reviewers were reconciled through conversation, and a third reviewer was consulted where consensus was unattainable. This meticulous methodology guaranteed that all pertinent clinical and methodological information was systematically recorded and evaluated for inclusion in the synthesis.

Quality assessment

The methodological quality of the included studies was rigorously evaluated using standardized and validated instruments appropriate for their respective study designs. Alongside the CONSORT (Consolidated Standards of Reporting Trials), Statement checklist was employed as an additional framework to improve the assessment and reporting of trial quality. The CONSORT checklist is comprised of 25 essential questions that assess the design, analysis, and interpretation of trials, ensuring transparency and thoroughness in reporting. The ROBINS-I tool was utilized to evaluate bias in non-randomized and observational studies, including cohort, case-control, and cross-sectional designs, across several domains such as confounding, participant selection, intervention classification, and outcome assessment. An eight-item checklist focusing on selection, ascertainment, causation, and reporting domains was employed to enhance the evaluation of research quality in observational studies, providing a systematic approach for consistent assessment. The GRADE (grading of recommendations assessment, development and evaluation) technique was employed to assess the overall quality and strength of evidence across research. This entailed assessing issues including study constraints, outcome inconsistency, evidence indirectness, imprecision, and publication bias. The incorporation of these quality assessment tools provided a thorough evaluation of the strength and dependability of the evidence and enhanced the validity of the results reached in this systematic review.

Data synthesis

A thorough qualitative synthesis of the data was performed to consolidate and describe the principal findings from the included trials, emphasizing the effectiveness of cannabis in mitigating the primary symptoms of PTSD. Due to the variability in study designs, participant demographics, cannabis therapies, and evaluated outcomes, a meta-analysis proved impracticable. The data were classified according to the type of cannabinoid intervention (synthetic cannabinoids such as nabilone and dronabinol, phytocannabinoids like THC and CBD, and whole-plant cannabis products) and the specific PTSD symptom clusters they targeted, including intrusive memories, hyperarousal, sleep disturbances, and mood alterations. The synthesis process included a detailed examination of the findings, which emphasized both the advantages and drawbacks of cannabis use in alleviating PTSD symptoms. Critical results, including enhancements in sleep quality, diminishment of anxiety, and mitigation of hyperarousal, were analyzed in terms of types of cannabis and treatment duration. Subgroup analyses were performed to investigate differences in treatment efficacy potentially influenced by parameters like cannabis dosage, administration route, and participant characteristics (e.g., age, gender, severity of PTSD symptoms). The findings were also examined for study quality, bias risk, and methodological constraints inherent in the included studies. The potential for reporting biases, diversity in symptom classifications, and disparities in participant demographics were recognized as factors that may have affected the generalizability of the findings. Observational studies frequent reliance on self-reported data and the absence of control groups were recognized for their shortcomings in establishing causal

links. Despite these constraints, trends indicate that cannabinoids, particularly CBD, may provide therapeutic advantages, especially in mitigating sleep difficulties and anxiety frequently linked to PTSD. The findings were assessed within the wider context of the changing legal and political environment surrounding cannabis usage, which may affect public perception and clinical implementation of these treatments.

RESULTS

Study selection

The PRISMA flowchart (Figure 1) delineates the study selection procedure utilized in this systematic review. It enumerates the aggregate number of records obtained from several databases, delineates each phase of screening, articulates the rationale for exclusion, and determines the final number of studies incorporated in the analysis. This systematic and clear technique improves the reproducibility of the review and demonstrates the thoroughness employed in locating and selecting pertinent papers on the application of cannabis in PTSD.

Risk of bias

The assessment of bias risk for the included studies was conducted utilizing the Cochrane Risk of Bias (RoB 2.0) methodology, which was used to systematically examine potential bias sources across various essential methodological domains. The categories encompassed randomization processes, deviations from intended interventions, management of missing outcome data, precision and consistency in outcome measurement, and the possibility of selective result reporting. Each study was independently evaluated and classified within these domains as exhibiting low risk, some concern, or high risk of bias. The findings of this assessment are illustrated in Table 1 and Figure 2, offering a detailed summary of the methodological advantages and drawbacks of each study included. This thorough evaluation improved the transparency of the review process and aided in a more precise interpretation of the overall data, helping to ensure that conclusions were derived from studies with a well-defined risk profile.

The Cochrane Risk of Bias evaluation indicated that most included studies exhibited either a low risk of bias or highlighted some certain concerns across the assessed domains. The prevalence of a high risk of bias was rather low, occurring in only a few research studies. The randomization process and outcome assessment were effectively implemented, with the majority of studies assessed as low-risk, indicating methodological rigor in the essential domains. Certain methodological deficiencies, however, were noted in alter-

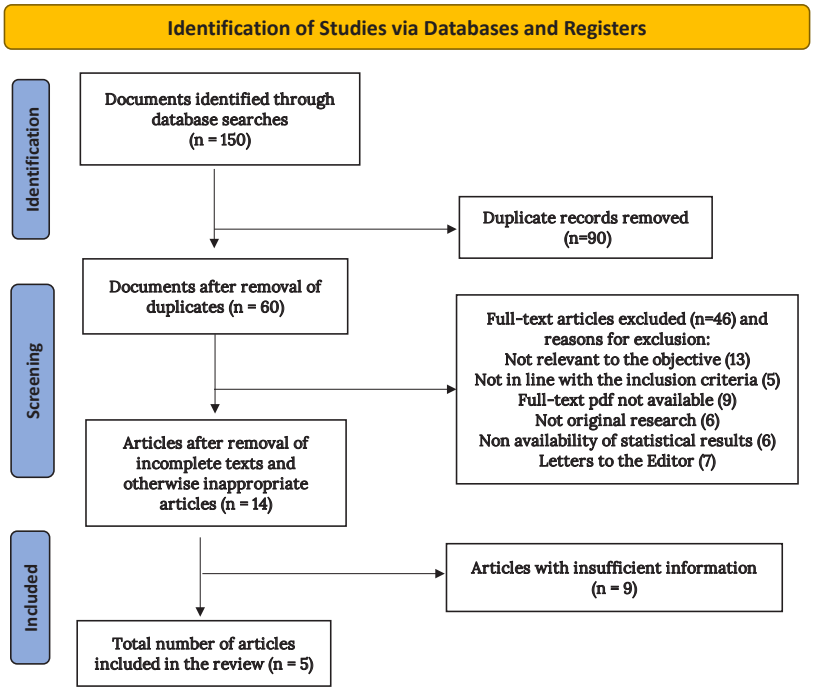

Figure 1. PRISMA flow chart

Table 1. Reviewers' judgments of each risk of bias for each criterion across all included studies

Study	Randomization process	Deviations from the intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Rabinak et al., 2020 (7)	Low	Low	Some concerns	Low	Low	Some concerns
Bonn-Miller et al., 2020 (8)	Low	Some concerns	Low	Low	Some concerns	Low
LaFrance et al., 2020 (9)	Low	High	Low	Low	Low	High
Cameron., 2014 (10)	Some concerns	Some concerns	Low	Some concerns	Low	Low
Elms et al., 2019 (11)	Some concerns	Low	Low	Some concerns	High	Some concerns

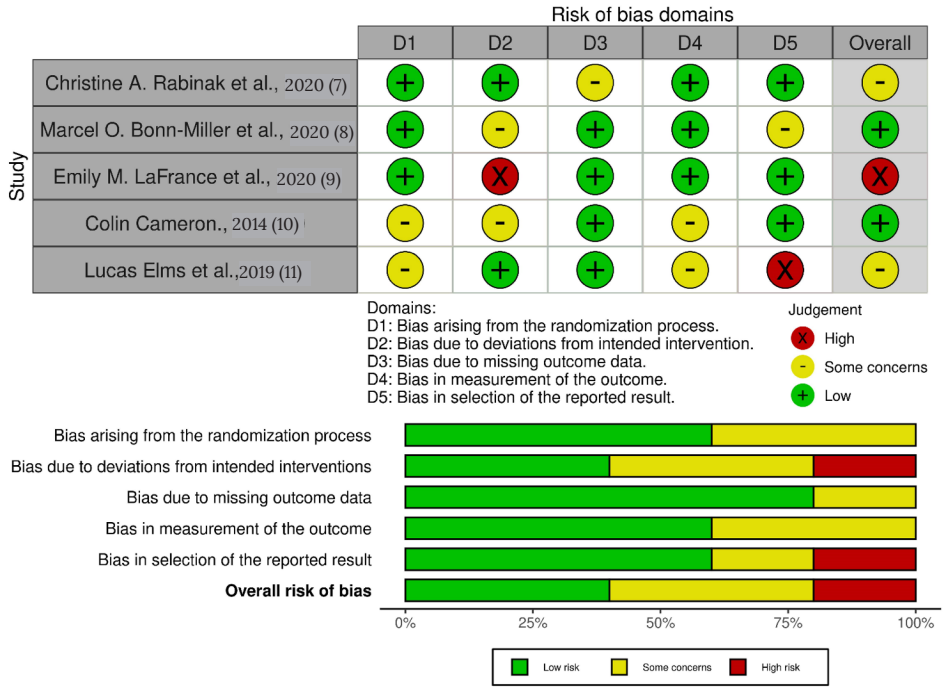

Figure 2. Risk of bias for included studies: Reviewers' judgment for each criterion expressed as a percentage

native domains. In particular, certain research revealed issues pertaining to deviation from prescribed therapies, insufficient outcome data, and/or selective reporting of findings. These flaws, although evident in some studies, were not consistently observed across all investigations, indicating diversity in study quality. Studies by LaFrance et al. (2020) and Elms et al. (2019) exhibited significant bias risk in particular areas, especially deviation from targeted interventions and the selection of reported outcomes. These findings highlight the necessity for methodological rigor in forthcoming studies to help ensure the reliability and validity of outcomes in cannabinoid-based PTSD research.

PICOS framework

The PICOS framework—comprising population, intervention, comparison, outcome, and study design—functions as a fundamental instrument for formulating systematic and focused search strategies in systematic reviews (SRs). By structuring the review questions into these components, PICOS helps confirm that the study selection is directly matched with the research objectives. This systematic technique not only augments the relevance and coherence of the incorporated material but also elevates the overall methodological rigor of the review. Furthermore, by meticulously refining and explicitly delineating inclusion criteria, PICOS can help enhance search

Table 2. PICOS framework for the included studies

PICOS component	Details	Inclusion criteria	Exclusion criteria
P (Population)	Individuals diagnosed with PTSD	Human participants of any age, gender, or ethnicity with a clinical diagnosis of PTSD (based on DSM or ICD criteria), including trauma-exposed civilians and veterans	Animal or *in vitro* studies; individuals without a formal PTSD diagnosis or with unrelated psychiatric conditions
I (Intervention)	Cannabinoid-based treatments	Use of synthetic cannabinoids (e.g., nabilone, dronabinol), phytocannabinoids (e.g., THC, CBD), or whole-plant cannabis products via any administration route	Studies using interventions unrelated to cannabinoids or using cannabinoids for non-PTSD indications
C (Comparison)	Placebo or standard treatments for PTSD	Placebo, standard pharmacological or psychological therapies for PTSD (e.g., SSRIs, CBT)	Studies with no comparison group or not focused on treatment
O (Outcomes)	Clinical efficacy and safety	Primary: PTSD symptom severity (e.g., PCL-5, CAPS). Secondary: sleep quality, anxiety, depression, quality of life, adverse effects	Studies lacking PTSD-relevant clinical outcomes or insufficient outcome data
S (Study design)	Clinical human studies	RCTs, cohort studies, case-controlled and cross-sectional studies, and case series with clinical outcome reporting	Editorials, reviews, opinion pieces, non-English publications, and studies with poor methodology or high bias risk

PICOS, population, intervention, comparison, outcome, study design; PTSD, post,traumatic stress disorder; ICD, International Classification of Diseases; THC, tetrahydrocannabinol; CBT, cognitive behavioral therapy; PCL- PTSD checklist; RCTs, randomized controlled trials

accuracy, reduce the retrieval of extraneous data, and facilitate the quick discovery and screening of relevant research across several databases.

The PICOS framework delineated in Table 2 specifies the principal criteria governing the selection of studies for this systematic review of the application of cannabis in the treatment of PTSD. The cohort comprises individuals clinically diagnosed with PTSD, irrespective of age, gender, or ethnicity, including both civilian and military groups to obtain a thorough understanding of cannabis efficacy across varied demographics. The intervention emphasizes several cannabinoid-based therapies, encompassing synthetic cannabinoids (e.g., nabilone, dronabinol), phytocannabinoids (e.g., THC, CBD, and whole-plant cannabis formulations delivered by various methods. Comparators typically consist of placebo controls and recognized pharmaceutical or psychotherapy treatments for PTSD, enabling an evaluation of cannabis efficacy in comparison to standard care. The outcomes of interest include clinical efficacy, with primary assessments concentrating on PTSD symptom severity utilizing validated scales including the Clinician-Administered PTSD Scale (CAPS) and the PTSD Checklist (PCL-5). Secondary outcomes assess sleep quality, anxiety, depression, quality of life, and adverse effects to provide a thorough evaluation of therapeutic efficacy. Exclusively RCTs, cohort studies, case-control studies, cross-sectional studies, and case series performed in clinical or outpatient settings were considered to help maximize methodological rigor. Studies that did not focus on PTSD-specific outcomes, non-clinical research, and non-original papers were removed to preserve the relevance and quality of the evidence base.

Clinical studies the use of cannabis for PTSD

Table 1 provides a comparative analysis of clinical research examining the application of cannabis in the treatment of PTSD. The studies exhibit considerable variation in design, encompassing RCTs, prospective observational studies, and retrospective evaluations. Sample sizes vary from 11 to 404 people, and include various cannabinoids, e.g., THC, CBD, and synthetic analogs such as nabilone delivered via oral or inhalation methods. The majority of the studies included primarily adult participants with varied demographics and

employed a range of distinct PTSD diagnostic criteria. The duration of treatments varied from one session to one year. Preliminary data indicate therapeutic potential; discrepancies in research design and insufficient control conditions stresses the necessity for further rigorous, high-quality trials.

Study design and population characteristics

A compilation of studies exploring mental health interventions included various methodologies and diverse populations. Rabinak et al. conducted a randomized, double-blind, placebo-controlled trial involving adults aged 20-45 years with diverse demographics (7). Bonn-Miller et al. performed a longitudinal, prospective assessment with an average participant age of 50.67 years, of whom 73% were male (8). LaFrance et al. carried out an observational study using app-based symptom tracking, involving 220 women and 176 men, all self-identifying with PTSD (9). Cameron presented a retrospective evaluation focusing on male inmates with serious mental illness (10). Elms et al. conducted a retrospective case series with participants averaging 39.91 years of age, of whom 73% were female (11). The variety in study design—including randomized trials, observational studies, and retrospective analyses—along with heterogeneous populations, ranging from inmates to individuals with PTSD, highlights the broad scope and applicability of mental health research across different demographic and clinical settings (Table 3).

PTSD diagnosis

Reviewed studies investigated PTSD using varied inclusion criteria and participant profiles. Rabinak et al. examined trauma-exposed adults, including individuals diagnosed with PTSD, trauma-exposed controls, and healthy controls (7). Bonn-Miller et al. applied DSM-5 criteria for PTSD and included participants aged 18 and older (8). In contrast, LaFrance et al. relied on self-identified PTSD cases without clinical confirmation, potentially affecting diagnostic consistency (9). Cameron focused on individuals with serious mental illness accompanied by PTSD-related insomnia and nightmares, suggesting a more symptom-specific participant pool (10). Elms et al. used both a formal DSM-5 PTSD diagnosis and a minimum PCL-5 score of 33 to ensure a standardized threshold for inclusion (11). These studies collectively highlight the diverse diagnostic approaches and inclusion criteria ranging from structured clinical assessments to self-identification, emphasizing the variability in PTSD research and the importance of consistent diagnostic methodologies for comparability and clinical relevance. The variability in diagnostic approaches and inclusion criteria in PTSD research underlines the need for standardized thresholds and methodologies to ensure consistency and accuracy in results. By establishing clear criteria for inclusion, researchers can more effectively identify and study specific populations, such as those with co-occurring mental illnesses like PTSD-related insomnia and nightmares. This can ultimately lead to more targeted interventions and improved clinical outcomes for individuals struggling with complex mental health issues (Table 3).

Type of cannabinoid and length of treatment

various studies have explored the therapeutic potential of cannabinoids across different treatment durations and cannabinoid types. Christine A. Rabinak et al. investigated the effects of a single acute dose of Δ9-THC, highlighting its immediate impact (7). In contrast, Bonn-Miller et al. conducted a longitudinal study for over a year, using THC-dominant cannabis with quarterly assessments to monitor outcomes (8). LaFrance et al. analyzed data collected over a 31-month period, focusing on both THC and CBD concentrations to understand their combined influence (9). Cameron assessed the efficacy of nabilone, a synthetic cannabinoid, over varied treatment periods, with an average duration of around 20 weeks (10) while Elms et al. examined the effects of CBD over an 8-week period (11). Collectively, these studies demonstrate the diverse methodologies and cannabinoid profiles used in research, reflecting the growing interest in cannabis-based interventions for therapeutic use (Table 3).

Primary outcome measure and result

A series of studies have explored the therapeutic potential of cannabis and its derivatives in managing PTSD symptoms. Rabinak et al. found that THC significantly reduced amygdala reactivity and enhanced mPFC activation during

Table 3. Overview of clinical studies on cannabinoids for ptsd treatment

Study Reference	Rabinak et al., 2020 (7)	Bonn-Miller et al., 2020 (8)	LaFrance et al., 2020 (9)	Cameron, 2014 (10)	Elms et al., 2019 (11)
Study design	Randomized, double-blind, placebocontrolled	Longitudinal, prospective assessment	Observational study with app-based symptom tracking	Retrospective evaluation	Retrospective case series
Sample size	71 participants	150 participants	404 medical cannabis users	104 male inmates	11 adult patients
type of cannabinoid	Δ9-tetrahydrocannabinol	THC-dominant cannabis	THC and CBD concentrations	Nabilone (synthetic cannabinoid)	Cannabidiol
drug/dose/ route of administration	THC, 7.5 mg capsule, oral	Dispensary-obtained cannabis, unspecified doses	Various cannabis strains; inhaled, self-reported dose	Mean final dose 4.0 mg, oral (capsules)	Oral CBD, flexible dosing regimen
Type of study	Experimental	Observational study comparison	Observational study	Observational	Clinical observation
PTSD diagnosis/additional inclusion criteria	Trauma-exposed adults; PTSD, trauma-exposed controls, healthy controls	DSM-5 criteria for PTSD, age 18+	Self-identified PTSD, no clinical verification	Serious mental illness, PTSD-related insomnia and nightmares	DSM-5 PTSD diagnosis, PCL-5 score ≥ 33
Length of treatment	Single acute dose/ session	1 year, with assessments every 3 months	Data collected over 31 months	Varied; mean around 20 weeks for some	8 weeks
Population characteristics	Adults (20-45 years), diverse demographics	Average age 50.67 years, 73% male	220 women, 176 men, self-identified PTSD	Male inmates with serious mental illness	Average age 39.91, 73% female
Level of evidence	Preliminary evidence supporting cannabinoids for PTSD	Observational study; lower on evidence hierarchy	Lower strength due to observational design	Moderate (retrospective, no control group)	Preliminary evidence (case series)

THC, Δ9-tetrahydrocannabinol; CBD THC- cannabidiol Δ9-tetrahydrocannabinol; PTSD THC, post-traumatic stress disorder Δ9-tetrahydrocannabinol

threat processing in PTSD patients, indicating a modulation of the fear response (7). Bonn-Miller et al. reported a marked decline in PTSD symptom severity among cannabis users over time (8). Similarly, LaFrance et al. observed substantial reductions in specific symptoms, including a 62% decrease in intrusions, 51% in flashbacks, 67% in irritability, and 57% in anxiety (9). Cameron demonstrated improved sleep duration, reduced nightmare frequency, and overall reduction of PTSD symptoms, measured using the PCL-C and GAF (10). Finally, Elms et al. recorded a 28% decrease in PCL-5 scores, further supporting cannabis' role in symptom mitigation (11). Collectively, these findings stress the potential efficacy of cannabinoids in PTSD treatment and symptom management. These studies provide strong evidence of the positive impact of cannabinoids on PTSD symptoms, with significant reductions in intrusive thoughts, flashbacks, irritability, anxiety, and overall symptom severity. The improvements in sleep duration, nightmare frequency, and overall PTSD symptoms as measured by various assessment tools further highlight the potential benefits of using cannabis in treating PTSD. The consistent decrease in PCL-5 scores across the study exemplify the reason for the growing support for the role of cannabinoids in mitigating the symptoms of PTSD (Table 4).

Table 4. Study outcomes and adverse events in cannabinoid treatment for PTSD

Study Reference	Rabinak et al., 2020 (7)	Bonn-Miller et al., 2020 (8)	LaFrance et al., 2020 (9)	Cameron, 2014 (10)	Elms et al., 2019 (11)
Methodology	Randomized, double-blind, placebo-controlled design with fMRI	Longitudinal study tracking cannabis users and controls for one year, assessing PTSD symptoms	Analyzed data from Strainprint® app users	Retrospective evaluation of 104 male inmates prescribed nabilone	Retrospective chart review, patient-completed PCL-5 assessments
Primary outcome measures	Amygdala reactivity and mPFC activation during threat processing	Change in total severity scores on the Clinician-Administered PTSD Scale (CAPS-5)	PTSD symptom severity (intrusions, flashbacks, irritability, anxiety) before and after cannabis	Sleep hours, nightmare frequency, PTSD symptoms (PCL-C), Global Assessment of Functioning (GAF)	PTSD symptom severity via PCL-5 scores
Primary outcome result	THC reduced amygdala reactivity and increased mPFC activation in PTSD participants	Cannabis users experienced a significantly greater decline in PTSD symptom severity over time	Substantial symptom reduction observed: 62% intrusions, 51% flashbacks, 67% irritability, 57% anxiety relief	Significant improvement in sleep hours and reduced nightmares; PTSD symptoms decreased	Mean PCL-5 score decreased by 28%
Secondary outcomes measures	Functional coupling between amygdala and mPFC during threat	Outcomes included psychosocial functioning, insomnia severity, overall sleep quality, and activity levels	Long-term changes in dose and baseline symptom severity across multiple cannabis use sessions	Chronic pain improvement, harm reduction, polypharmacy reduction	Patient-reported side effects and symptoms
Secondary outcome results	THC enhanced amygdala-mPFC connectivity compared to placebo	No significant differences in psychosocial functioning; cannabis users had lower fewer awakenings recorded	Baseline symptom severity consistent; increased cannabis doses over time indicated potential tolerance development	89.6% reported pain improvement; no cannabis use detected	Fatigue and gastrointestinal discomfort reported by few patients
Adverse events	No significant adverse events reported during the study	Adverse events were not specifically detailed; safety and tolerability considerations were addressed generally	No specific adverse events recorded	No significant adverse effects or abuse concerns reported	No discontinuations due to side effects observed

PTSD, post-traumatic stress disorder; fMRI, functional magnetic resonance imaging; PCL-5, PTSD checklist for DSM-5; CAPS-5, clinician-administered PTSD Scale for DSM-5; mPFC, medial prefrontal cortex; THC, Δ9-tetrahydrocannabinol; CBD, cannabidiol; PCL-C, PTSD checklist – civilian version

Secondary outcome measures and results

The reviewed studies explored the secondary outcomes of cannabis use across various clinical settings. Rabinak et al. reported that THC significantly enhanced functional coupling between the amygdala and medial prefrontal cortex (mPFC) during threat-related tasks, indicating potential anxiolytic effects (7). Bonn-Miller et al. observed no notable differences in psychosocial functioning among users, though cannabis users reported fewer sleep disturbances, suggesting a potential benefit for insomnia (8). LaFrance et al. identified

consistent baseline symptom severity across sessions, while increases in cannabis doses over time hinted at the development of tolerance (9). Cameron highlighted improvements in chronic pain, harm reduction, and decreased polypharmacy, with 89.6% of participants reporting pain relief and no ongoing cannabis use (10). Finally, Elms et al. documented patient-reported side effects, with fatigue and gastrointestinal discomfort being the most common (11). Collectively, these studies suggest that cannabis may offer therapeutic benefits, although individual responses and tolerance must be carefully monitored. While the studies mentioned show potential benefits of cannabis use for chronic pain, it is important to consider the long-term effects and potential risks associated with increased tolerance and side effects such as fatigue and gastrointestinal discomfort. Individual responses to cannabis can vary greatly, highlighting the need for personalized monitoring and care (Table 4).

Adverse events and limitations of each of the studies

In the studies conducted by Rabinak et al., Bonn-Miller et al., LaFrance et al., Cameron, and Elms et al., adverse events were generally minimal or not specifically detailed (7-11). Most studies reported no significant adverse effects, no discontinuations due to side effects, and broadly addressed safety and tolerability without detailed accounts. However, several limitations were consistently noted. Common issues include small sample sizes, lack of placebo or control groups, and participant exclusions based on psychiatric conditions or medication use, which may restrict the generalizability of findings. Many studies relied on self-reported data and used retrospective designs, increasing susceptibility to recall and expectancy biases. Demographic homogeneity and inconsistent dosing regimens further limit external validity. The absence of standardized symptom definitions and the influence of concurrent treatments in some studies pose further challenges to drawing definitive conclusions about efficacy and safety across diverse populations (Table 4).

Main findings and recommendations

Christine et al. found that THC reduces amygdala reactivity and enhances prefrontal cortex activation during threat processing, suggesting a potential therapeutic role for THC in PTSD and related psychopathology (7). Bonn-Miller et al. reported that cannabis users exhibited significant reductions in PTSD symptom severity and higher remission rates compared to non-users, emphasizing the need for further studies on cannabis strains, dosing strategies, and long-term effects (8). LaFrance et al. observed that while cannabis significantly alleviates PTSD symptoms temporarily, it may lead to tolerance with no lasting changes in baseline severity, thus calling for more controlled research to assess long-term efficacy (9). Colin Cameron documented significant improvements in sleep, nightmares, PTSD symptoms, and pain, along with reduced polypharmacy and no abuse reports, advocating further studies on nabilone use for PTSD-related insomnia, pain, and harm reduction (10). Lucas Elms et al. noted a significant decrease in PTSD symptoms over 8 weeks, with 91% of patients showing improvement in PCL-5 scores, supporting further investigation into optimal CBD dosing and administration forms for effective PTSD management (11). (Table 5).

Limitation of systematic review

The studies conducted by Rabinak et al, Bonn-Miller et al., LaFrance et al., Cameron et al. present several limitations (7-11). Several of these studies involved small sample sizes, which may affect the generalizability of the results. Exclusion criteria in some studies, such as excluding participants with certain psychiatric conditions or medication use, further limit the applicability of findings. In some cases, self-reported biases and the lack of diversity in participant demographics may skew the results. Self-selected samples and expectancy effects may also influence the outcome of studies, making it harder to draw broad conclusions. Moreover, retrospective designs relying on self-reported data, the absence of control groups, and the use of concurrent treatments create confounding factors that weaken the reliability of findings. Inconsistent dosing regimens and the lack of placebo groups reduce the validity of some results (Table 5).

Table 5. Summary of study focus, findings, and limitations in cannabinoid-based PTSD researchD

Study Reference	Rabinak et al., 2020 (7)	Bonn-Miller et al., 2020 (8)	LaFrance et al., 2020 (9)	Cameron, 2014 (10)	Elms et al., 2019 (11)
Focus Area	THC's effects on corticolimbic activation in trauma-exposed adults with PTSD	Impact of cannabis use on PTSD symptoms and functioning in diagnosed individuals over a one-year period	Effects of cannabis on PTSD symptoms and management among medical cannabis users	Nabilone's efficacy for PTSD, insomnia, nightmares, and chronic pain in seriously mentally ill populations in correctional facilities	Investigating the clinical efficacy of CBD in alleviating symptoms of PTSD in adults
Main Findings	THC reduces amygdala reactivity and enhances prefrontal cortex activation during threat processing	Cannabis users showed significant reductions in PTSD symptom severity and higher remission rates compared to non-users	Cannabis significantly alleviates PTSD symptoms temporarily but may lead to tolerance and unchanged baseline severity over time	Significant improvements in sleep, nightmares, PTSD symptoms, and pain; reduced need for polypharmacy; no reported abuse	A significant decrease in PTSD symptoms was observed after 8 weeks, with 91% of patients showing improvement in PCL-5 scores
Recommendations	Further research on THC as a potential treatment for PTSD and related psychopathology	Further studies on cannabis strain effects, dosing strategies, and long-term impacts on PTSD symptoms are needed	Further controlled studies needed for long-term effects and comprehensive assessments of cannabis efficacy on PTSD	Further research is required to evaluate the effectiveness of nabilone in managing PTSD-related insomnia, chronic pain, and harm reduction within correctional settings.	Further investigation into optimal CBD dosing and administration forms for effective PTSD symptom management needed
Challenges and Gaps	Need for understanding of THC's effects in trauma-exposed individuals without PTSD	Legal restrictions on cannabis research, insufficient long-term data, and varied cannabis products hinder comprehensive assessments and comparisons	Lack of clinical verification for PTSD diagnoses; limited symptom assessment; absence of placebo control group	Need for education about cannabinoids; societal stigma regarding cannabis use; limited access to illicit substances	Difficulties including standardizing CBD dosage, understanding differential effects between administration forms, and addressing placebo effects in patients' responses
Limitation	Small sample size and exclusion of participants with certain psychiatric conditions and medication use	Small sample size, potential self-reporting biases, and lack of diversity in participant demographics may affect generalizability of results	Self-selected sample, potential expectancy effects, and variability in symptom definitions among users impact results' generalizability	Retrospective design; reliance on self-reported data; concurrent treatments may confound results; lack of control group	Study limitations include small participant size, lack of a placebo/control group, and inconsistent dosing regimens affecting result validity

THC, Δ-tetrahydrocannabinol; PTSD, post-traumatic stress disorder, PCL-5, PTSD Checklist for DSM -5

CONCLUSION

This systematic review, guided by rigorous methodology, synthesized evidence from diverse study designs focusing on cannabinoid use in PTSD. A comprehensive search strategy and clearly defined criteria ensured the inclusion of relevant studies, with quality and bias systematically assessed. Data revealed variable treatment durations, heterogeneous populations, and inconsistent PTSD diagnostic criteria. While primary and secondary outcomes suggested potential benefits, adverse events and methodological limit-+ations were prevalent. Despite limitations in this review, the findings highlight cannabinoids' therapeutic promise. This review underscores the importance of well-designed future trials and provides a foundational reference for clinicians and researchers exploring novel PTSD interventions.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions

S.R.A.: Conceptualization; R.R.: data curation; S.S.: data curation; A.K.: writing—draft preparation; A.K.A.: writing—draft preparation; S.B.: original draft preparation, review and editing; V.S.S.S.G.A: supervision; R.K.V.: supervision.

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