A Systematic Review of the Clinical Effects of Cannabis and Cannabinoids in Posttraumatic Stress Disorder Symptoms and Symptom Clusters

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Abstract

Objective: Given the high rate of comorbid posttraumatic stress disorder (PTSD) and cannabis use, it is critical that further research be conducted to address the associated benefits and risks of cannabis use in this population. This systematic review evaluated evidence on the effects of cannabis and cannabinoids on PTSD symptoms and PTSD clusters.

Data Sources: A systematic search of PubMed, PsycINFO, and EMBASE databases was performed using terms related to cannabis, cannabinoids, and PTSD. Peer-reviewed studies available online in English and published from January 1990 through February 2023 were considered.

Study Selection: Included studies were experimental or observational in design, were conducted in cannabis-using patients with PTSD, used validated measures of PTSD, and were published in English.

Data Extraction: Extracted information included study aims, study design, sample size and sex, comparator group, cannabis-related characteristics, psychometric instruments, and relevant clinical findings regarding overall PTSD symptoms and cluster symptoms.

Results: Fourteen studies were included, 3 in a comorbid PTSD and cannabis use disorder (CUD) sample and 11 in a non-CUD sample. Of the 10 studies examining overall PTSD symptoms in a non-CUD sample, 5 suggested benefits associated with cannabis use and 5 suggested no effect or worsening of symptoms. Four studies reported benefits of cannabis for cluster B- and E-related symptoms in a non-CUD sample. All 3 studies in cannabis-using patients with a comorbid PTSD and CUD diagnosis reported risks for worsening of overall symptoms.

Conclusions: This review did not find major benefits of cannabinoids in improving overall PTSD symptoms. Some benefits with regard to cluster B and E symptoms were observed. Some risks with regard to worsening suicidal ideation and violent behavior were also reported. Individuals with a comorbid CUD diagnosis may be at greater risk for negative cannabis-related PTSD outcomes. More experimental studies are needed to determine the causal effects of cannabis and cannabinoids in PTSD.

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Posttraumatic stress disorder (PTSD) is a chronic and often debilitating psychiatric disorder that can develop after witnessing or experiencing an adverse life event. Epidemiologic studies estimate the lifetime prevalence of PTSD to be from 6.1% to 9.2%,[1,2] with 1-year prevalence rates of 3.5 to 4.7%.[1–3] Given its high prevalence relative to other serious psychiatric disorders like schizophrenia[4] and bipolar disorder,[5] PTSD has a strong impact on both society and the individual, with studies reporting significant associations with suicidal behavior,[6] impaired quality of life,[7] medical comorbidities,[8] and substance use disorders.[9]

According to the latest version of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, Text Revision (*DSM-5*-TR),[10] PTSD is characterized by at least 1 traumatic event that serves as the basis for the following 4 symptom clusters: intrusion or reexperiencing of trauma (cluster B), avoidance of trauma cues (cluster C), negative alterations in affect and cognition (cluster D), and hyperarousal and reactivity (cluster E).

Treatment for PTSD typically involves a combination of pharmacologic and psychological interventions. Among the pharmacologic options, evidence is strongest for selective serotonin reuptake inhibitors (SSRIs) like sertraline and paroxetine.[11] Psychological treatment typically involves trauma-focused interventions, where patients confront distressing memories and thoughts associated with the traumatic event. Some common

Clinical Points

- Cannabis use in patients with PTSD is common, but there is lack of consensus about the efficacy of cannabis for overall PTSD symptoms and symptom clusters.
- In patients without cannabis use disorder, only 50% of studies suggested that cannabinoids may benefit overall PTSD symptoms. In patients with cannabis use disorder, 100% of studies suggested that cannabis may contribute to worsening of overall PTSD symptoms.
- Cannabinoids may provide targeted advantages for cluster B symptoms, such as nightmares, as well as cluster E symptoms, such as sleep disturbances.

trauma-focused interventions include cognitive processing therapy and prolonged exposure.[12] Unfortunately, the effectiveness of these interventions is limited, with around 40% of individuals not responding well to SSRIs[11] and high dropout rates due to low tolerability and potential worsening of existing symptoms after addressing the traumatic event in therapy.[12]

Cannabis, Cannabinoids, and PTSD

In recent years there has been increasing interest in targeting the endogenous cannabinoid system (eCS) with exogenous cannabinoids such as Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) for mental health disorders like PTSD. The rationale behind targeting the eCS comes from several lines of research that suggests it plays a role in the pathophysiology of PTSD due to its involvement in the stress response, emotional memories, and fear extinction.[13–15] Previous studies in mice have shown basal cannabinoid 1 (CB1) receptor activation plays a role in regulating fear-related behavior, the stress response, impairing the retrieval of aversive memories, and enhancing their extinction.[16–21] Using cannabinoids that agonize CB1 receptors, like dronabinol and THC, may provide some benefits in PTSD where patients present with dysregulated fear and stress responses and elevated CB1 receptor availability.[22]

There are greater rates of cannabis use and cannabis use disorder (CUD) among those with PTSD. Approximately 28.2% of people with lifetime PTSD report past-year cannabis use,[23] and 9.2% have a comorbid CUD diagnosis,[24] nearly 3 and 4 times the rates of those without PTSD, respectively. In view of the high prevalence of cannabis use in individuals with PTSD, the need to compile evidence identifying the benefits and risks associated with cannabinoid use in this population is warranted. This systematic review examines and evaluates published evidence from experimental and observational studies that report on cannabis and cannabinoid use and PTSD. We sought to address the following aims: (1) to determine the effects of cannabinoid use (both short- and long-term) on overall PTSD symptoms and (2) to determine the effects of cannabinoid use (both short- and long-term) on PTSD cluster-related symptoms. In this paper, cluster-related symptoms consisted of cluster scores and conceptually related symptoms. For instance, cluster B is concerned with symptoms related to intrusion or reexperiencing of trauma, like nightmares. We were interested in examining the effects of cannabis and cannabinoids on overall symptoms (eg, through cluster scores) and individual cluster symptoms (eg, nightmares).

MATERIALS AND METHODS

Search Strategy and Selection Criteria

This systematic review was conducted in accordance with the guidelines for reporting of systematic reviews and meta-analyses (PRISMA).[25] Searches were performed in February 2023 using, PsycINFO, and EMBASE databases. All original, peer-reviewed studies available online in the English language between January 1990 through the end of February 2023 were considered. The following keywords were searched and adapted to each database to find appropriate articles: "posttraumatic stress disorder" AND "cannabis" OR "tetrahydrocannabinol" OR "cannabidiol" OR "marijuana" OR "cannabinoid" OR "nabilone" OR "dronabinol" OR "nabiximol" OR "medical marijuana" OR "synthetic cannabinoid." Filters were applied to automatically remove reviews from our results. Citation lists of relevant studies and reviews were also searched. Eligible papers were extracted using the following inclusion criteria: (1) original studies with experimental, cross-sectional, case-series, or cohort designs; (2) studies in adults 18 years and older with a diagnosis of PTSD as defined by the *DSM* and/or *International Classification of Diseases* (*ICD*); (3) studies in adults that report using cannabis (eg, medically, recreationally, etc); and (4) studies using validated measures to assess PTSD symptom changes. The exclusion criteria were as follows: (1) articles not published in English; (2) review papers, letters or editorials, meta-analyses, gray literature, opinion pieces or commentaries, and conference abstracts or posters; and (3) studies conducted in animals. In the absence of randomized controlled trials (RCTs), the next best available levels of evidence (eg, case series and observational studies) were included.

Data Extraction

All studies generated from the search were uploaded to Covidence, and duplicate studies were automatically removed. Title and abstract screening as well as full text review were conducted by 2 independent reviewers (J.D.R. and C.P.). All discrepancies were settled by discussion and resolved by mutual consent and/or discussion with the senior author (A.N.H.). Data were extracted independently by 2 reviewers (J.D.R. and C.P.) and reviewed with the study team. The extracted variables included (1) study

aims, (2) study design, (3) sample characteristics, (4) comparator group, (5) type of cannabinoid used, (6) dosage and route of administration, (7) assessment measures, and (8) clinical findings. We were also interested in determining if the therapeutic potential of cannabis was associated with certain symptoms from clusters B, C, D, or E. Since most studies did not share subtotal cluster scores, symptoms that were related to the corresponding cluster and assessed with validated measures were included where appropriate. The inclusion of a meta-analysis was considered; however, there was great variability in study design, making it challenging to synthesize our results using a meta-analysis.

Risk of Bias Assessment

Risk of bias (RoB) assessments were performed independently by J.D.R. Four tools, dependent on the study design, were used: Cochrane's RoB tool for non-randomized studies of interventions (RoBINS-I),[26] Cochrane's RoB tool for crossover trials (RoB-2),[27] the Newcastle-Ottawa Scale (NOS) for cohort studies,[28] and the Joanna Briggs Institute (JBI) critical appraisal checklist for case series.[29] The ROBINS-I tool assesses RoB across 7 domains, including baseline and time-varying confounding, participant selection, intervention classification, cointervention, missing data, outcome measurement, and selective reporting bias. Each domain and the overall RoB is rated as having low, moderate serious, critical, or unclear RoB.[26] Cochrane's RoB-2 for crossover trials assesses RoB similarly, except across 6 domains, including the randomization process, period and carryover effects, deviations from intended intervention, missing data, outcome measurement, and selective reporting bias.[27] Each domain and overall RoB is rated as having low risk, some concerns, or high RoB. The NOS allows a maximum score of 9 and assesses RoB across 3 domains: (1) selection of study groups, (2) comparability of groups, and (3) ascertainment of outcomes. Scores from 7 to 9 are considered high quality, 4 to 6 are considered high RoB, and 0 to 3 are considered very high RoB.[28] The JBI checklist assesses the quality and reporting of case series based on 10 criteria such as the complete inclusion of participants, appropriateness of the statistical analysis used, and if outcomes were measured in a valid and reliable way.[29] Here, study quality is rated from 0 to 10, and higher scores indicate higher quality.

RESULTS

Study Characteristics

The PRISMA flowchart for the article selection process is shown in Figure 1. The search yielded a total of 3,083 studies. Of these studies, 443 duplicates were removed, and 2,640 titles and abstracts were screened and 2,549 were excluded. The screen left 91 articles for full-text review. After reviewing full texts, 77 additional articles were excluded with specified reasons. The main reasons for exclusion were ineligible outcomes (n = 45) and ineligible study designs (n = 31). Examples of studies that were excluded due to ineligible outcomes or ineligible study designs were those that did not examine validated measures of PTSD over time and narrative reviews, respectively. A total of 14 studies met eligibility criteria.

The included studies had a total of 5,126 participants. Most studies (n = 8) adopted a longitudinal design, 5 with a control group and 3 without a control group, while the remaining studies were retrospective (n = 4) or RCTs (n = 2) (see Table 1 for details). In over half of the studies (n = 9), cannabis was patient-administered, and the exact type of cannabinoid was unknown, while other studies specifically examined oral nabilone (n = 2), oral THC (n = 1), oral CBD (n = 1), and various concentrations of smoked cannabis (n = 1). The cannabinoid dosage, regimen, and route of administration varied and were mostly unreported (n = 9). A small number of studies (n = 3) examined the effects of cannabis and cannabinoids in patients with comorbid PTSD and CUD. Six, 5, 4, and 7 studies reported on cluster B-, C-, D-, and E-related findings in a non-CUD sample, while 1, 1, 2, and 2 studies reported on cluster B-, C-, D-, and E-related findings in a CUD sample (see Table 2 for details).

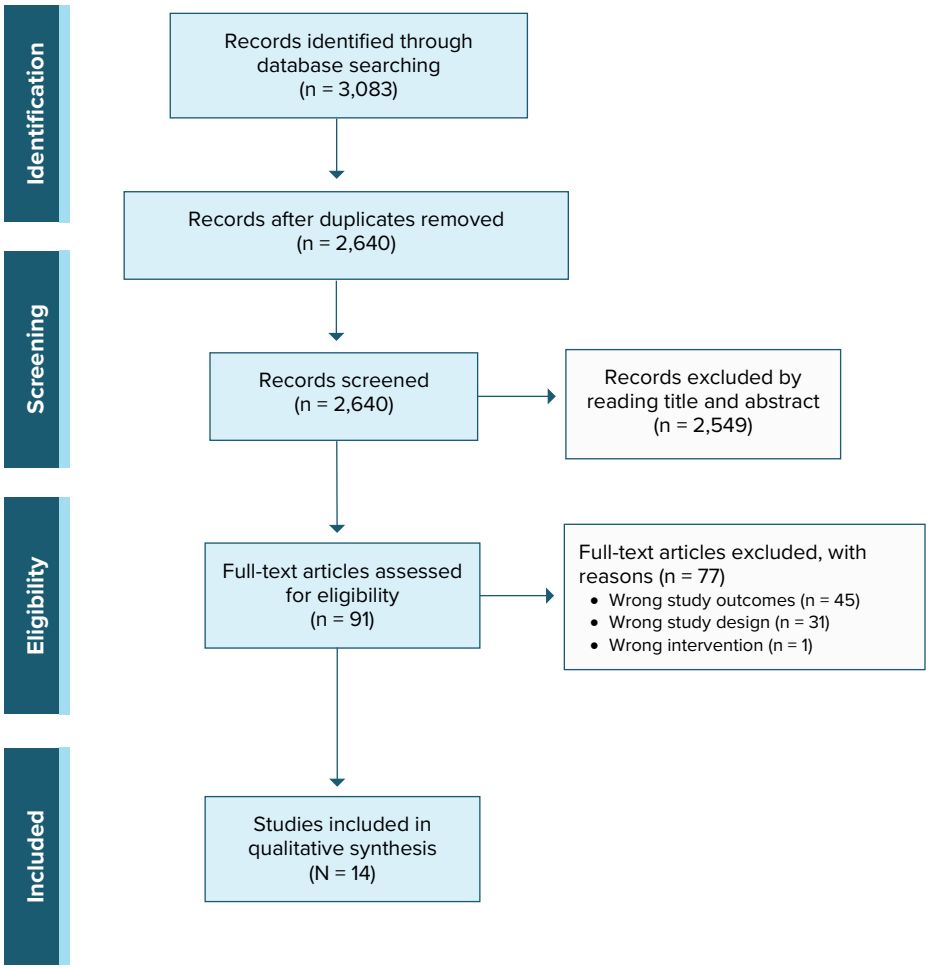
Risk of Bias

A summary of RoB is outlined in Table 1. Of the 2 crossover RCTs, 1 displayed a low RoB while the other raised some concerns regarding the randomization process and selection of the reported results. Three observational studies assessed using the RoBINS-I had serious RoB, especially with respect to confounding, selection of participants in the study, and measurement of PTSD outcomes. Of the 7 cohort studies, 6 demonstrated a high RoB, with scores ranging from 4 to 6 on the NOS, and 1 was considered high quality, with a score of 7 on the NOS. Both case series scored 70% on the JBI, suggesting medium quality.

Effects of Cannabinoids on Overall PTSD Severity

Non-CUD sample. Five studies, retrospective (n = 3) and longitudinal (n = 2) in design, suggested improvements in overall PTSD symptoms with cannabinoids.[30–34] A yearlong study examining PTSD symptoms every 3 months in cannabis-using and non–cannabis-using patients with PTSD reported significantly greater rates of PTSD symptom severity decline over time in cannabis users compared to non-users. Cannabis-using patients with PTSD were also 2.57 times more likely to not meet criteria for PTSD by the end of the study period, compared to non–cannabis-using PTSD patients.[30] In a retrospective chart review, Cameron et al[31] examined the efficacy of oral nabilone in patients at a correctional facility that treated male inmates with serious mental illness. While patients with varying comorbid diagnoses were included, approximately 90% of the study population were diagnosed with PTSD.

Figure 1.
PRISMA Flow Diagram for Systematic Reviews



Patients were prescribed oral nabilone at varying doses, and analyses revealed significant decreases in PTSD symptom severity, through the PTSD Checklist—Civilian Version (PCL-C), from pre-treatment to posttreatment. In a retrospective case series, researchers analyzed the effects of 8 weeks of oral CBD given once or twice a day on a flexible dosing regimen. Ninety-one percent of patients reported decreases in PTSD symptoms after 4 weeks, and 73% of patients reported further decreases in PTSD symptoms 4 weeks after follow-up (week 8). Decreases in mean PTSD symptoms, through the PCL-5, from baseline to week 8, but not week 4, were statistically significant.[32] Additionally, results from a retrospective chart review of patients who previously applied to the New Mexico Medical Cannabis Program suggested significant reductions in total Clinician-Administered PTSD Scale for *DSM-IV* (CAPS-IV) scores when patients were using cannabis compared to when they were not.[33] Lastly, a case series of patients from the UK Medical Cannabis Registry followed current/previous cannabis users diagnosed with PTSD from baseline to 1-, 3-, and 6-month follow up. PTSD symptoms were measured using the Impact of Events Scale-Revised (IES-R), and analyses revealed statistically significant improvements in total IES-R scores from baseline to all 3 follow-up periods.[34]

Two studies, longitudinal and retrospective in design, demonstrated negative PTSD outcomes with cannabinoid use.[35,36] A 12-month study using a latent growth curve model to analyze PTSD symptoms in past and current military personnel over time found that in those with elevated symptoms of PTSD at baseline, more days using cannabis predicted increased PTSD symptoms over time.[35] A retrospective study examining the effects of cannabis use in veterans at treatment intake and 4 months post-discharge revealed similar results. Participants were divided into 4 groups based on their patterns of cannabis use: those who did not use at admission or discharge ("never used"); those who used at admission but not post-discharge ("stoppers"); those who used at admission and post-discharge ("continuing users"); and those who started

Table 1.

Characteristics of Included Studies for Review

Reference	Aims	Study design	Sample (%M)	Comparator	Cannabinoid assessed	Dosage, regimen, and route of administration	Psychometric instruments used		Findings	RoB score
							PTSD	Cannabis use		
Allan et al, 2019[35]	To assess the interactive effects of PTSD symptoms and past 30-day cannabis use on PTSD symptoms in military personnel	Longitudinal without a control group	N = 545 (88.2%)	NA	Cannabis[a]	NA	PCL-M	—	Interaction between PTSD symptoms and cannabis use significantly predicted increased PTSD symptoms	5
Bonn-Miller et al, 2013[40]	To understand the association between a current CUD diagnosis and changes in PTSD symptoms after cessation in combat-exposed military veteran patients	Longitudinal with a control group	N = 260 (100%)	Combat-exposed military veteran patients with PTSD without a CUD diagnosis	Cannabis[a]	NA	PCL-M	SCID-IV	A CUD diagnosis is associated with significantly lower levels of change in PTSD symptom severity compared to those without a CUD diagnosis between treatment intake and discharge ($\beta = -0.15$, $P < .05$)	5
Bonn-Miller et al, 2021[39]	To determine the effects of various concentrations of smoked cannabis in military veterans with PTSD	Double-blind randomized, crossover control trial	N = 80 (90%); n = 76 in stage 1; n = 74 re-randomized in stage 2	Various treatment groups	Cannabis[a]	Smoked (high THC [12% THC and < 0.05% CBD]; high CBD [11% CBD and 0.50% THC]; THC+CBD [≈7.9% THC and 8.1% CBD]); placebo (< 0.03% THC and < 0.01% CBD) (ad libitum use up to 1.8 g/d)	CAPS-5	—	All groups (including placebo) saw a significant within-subject reduction in total CAPS-5 severity scores from baseline to stage 1 endpoint; however, no significant group differences were found ($F_{3,73} = 1.85$, $P = .15$). Significant between-group differences in total severity scores were found in stage 2 ($F_{2,64} = 6.92$, $P < .01$) between participants in the high THC and THC+CBD group and between those in the high CBD and THC+CBD groups	Low
Bonn-Miller et al, 2022[30]	To assess PTSD symptoms and functioning in cannabis users vs non–cannabis users with PTSD over 1 year	Longitudinal with a control group	N = 150 (73%)	Individuals with PTSD who do not use cannabis	Cannabis[a]	NA	CAPS-5	—	Decrease in symptom severity overtime in cannabis users compared to controls ($P = .02$); cannabis users were 2.57 times more likely to no longer meet criteria for PTSD at the end of the study observation period, compared to controls ($P = .03$)	8
Cameron et al, 2014[31]	To assess the efficacy of nabilone for PTSD-related insomnia and nightmares in adult male offenders	Retrospective chart review	N = 104 (100%)	NA	Nabilone	Oral (varying, mean initial dose of 1.4 mg daily and mean final dose of 4.0 mg)	PCL-C	SCID; ASI	PCL-C scores decreased significantly from pre- to post-treatment (pre-treatment: mean, 54.7 [SD, 13.0]; post-treatment: mean, 38.8 [SD, 7.1]; $t_{57} = 10.2$, $P = .001$)	Serious

(continued)

Table 1 (continued).

Reference	Aims	Study design	Sample (%M)	Comparator	Cannabinoid assessed	Dosage, regimen, and route of administration	Psychometric instruments used: PTSD	Psychometric instruments used: Cannabis use	Findings	RoB score
Elms et al, 2019[32]	To assess the effects of CBD on PTSD symptom severity	Retrospective case series	N = 11 (27%)	NA	CBD	Oral (open-label, flexible dosing regimen, taken once or twice a day depending on symptom severity, mean initial dose of 33.18 mg, mean week 8 dose of 48.64 mg)	PCL-5	—	After 4 weeks, 91% of patients reported a decrease in PTSD symptoms; after 8 weeks, 73% of patients reported a further decrease in PTSD symptoms and 27% of patients reported worsening PTSD symptoms	70%
Greer et al, 2014[33]	To understand the association between cannabis use and PTSD symptoms overtime in patients who applied to the New Mexico Medical Cannabis Program	Retrospective chart review	N = 80 (NA)	Individuals with PTSD who do not use cannabis	Cannabis[a]	NA	CAPS for *DSM-IV*	—	Significant reduction of total CAPS-IV scores ($F_{1,79}$ = 1,119.55, P < .0001) during the cannabis condition (22.5 ± 16.9) compared to the no-cannabis condition (98.8 ± 17.6)	Serious
Jetly et al, 2015[43]	To determine the efficacy of nabilone in reducing frequency, intensity of nightmares in military personnel with PTSD	Double-blind randomized, crossover, control trial	N = 10 (100%)	Matching placebo, waitlist control	Nabilone	Oral (initial dose 0.5 mg; titrated up to 3 mg, taken once per day)	CAPS for *DSM-IV*	—	Nabilone associated with significant mean reduction in nightmares; nabilone: −3.6 ± 2.4; placebo: −1.0 ± 2.1 (P = .03)	Some concerns
Johnson et al, 2016[37]	To understand the association between cannabis use and PTSD symptoms in veterans	Longitudinal with a matched control group	N = 700 (91%)	Individuals with presumptive PTSD who do not use cannabis	Cannabis[a]	NA	PCL-C	ASSIST	No significant differences in mean PCL-C scores between cases and controls	5
Livingston et al, 2022[41]	To explore the long-term PTSD outcomes in veterans following a CUD diagnosis	Longitudinal with a control group	N = 115 (60.9%)	Veterans with PTSD without a prior CUD diagnosis	Cannabis[a]	NA	PCL-C, PCL-5	*ICD-9*	Individuals with CUD exhibited higher symptom severity at baseline and overtime, as well as a lower rate of symptom improvement over time	7
Manhapra et al, 2015[42]	Treatment outcomes for veterans with CUD and PTSD	Longitudinal with a control group	N = 623 (95.8%)	Abstinent vs non-abstinent veterans with marijuana use	Cannabis[a]	NA	MISS-SF	—	The cannabis abstinent group showed significantly greater improvements in changes of PTSD score	4
Pillai et al, 2022[34]	To assess the relationship between cannabis-based medicinal products and improvements in PTSD	Longitudinal case series without a control group	N = 162 (59.8%)	NA	Cannabis[a]	NA	IES-R	Previous cannabis status; gram years	Significant improvements in PTSD symptoms from baseline to 1-, 3-, and 6-month follow-up	70%
Roitman et al, 2014[38]	To determine the tolerance and safety of oral THC administration in individuals with PTSD	Longitudinal without a control group	N = 10 (70%)	NA	THC extract	10 mg (5 mg twice a day)	CAPS for *DSM-IV*	—	Decrease in average CAPS scores from start to end of treatment; however, results were not statistically significant	Serious
Wilkinson et al, 2015[36]	To understand the association between marijuana use and PTSD symptom severity	Retrospective cohort	N = 2,276 (96.7%)	Individuals that have stopped using, continued using, started using, and are not using cannabis	Cannabis[a]	NA	MISS-SF	—	Cannabis use was positively associated with worse outcomes in PTSD symptom severity (P < .01) compared to cannabis-stoppers and non-users	4

[a]Exact cannabinoid is unknown and could, for example, be a mix of THC and CBD; however, this was not clearly stated by the authors.

Abbreviations: ASI = Addiction Severity Index, ASSIST = Alcohol, Smoking, and Substance Involvement Screening Test, CAPS for *DSM-IV* = Clinician-Administered PTSD Scale for *DSM-IV,* CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, CBD = cannabidiol, CUD = cannabis use disorder, *ICD-9* = *International Classification of Diseases,* Ninth Revision, IES-R = Impact of Events Scale-Revised, M = male, MISS-SF = Mississippi Scale for Combat-Related PTSD-Short Form, NA = not available, PCL-5 = PTSD Checklist for *DSM-5*, PCL-C = PTSD Checklist—Civilian Version, PCL-M = PTSD Checklist—Military Version, PTSD = posttraumatic stress disorder, RoB = risk of bias, SCID = Structured Clinical Interview for *DSM* Disorders, THC = Δ^9-tetrahydrocannabinol.

Table 2.

Cluster B, C, D, and E Findings

Reference	Findings	Psychometric instruments used
Cluster B		
Bonn-Miller et al, 2013[40]	No significant relationship between a CUD diagnosis and changes in reexperiencing symptoms between treatment intake and discharge compared to those without a CUD diagnosis; a CUD diagnosis was not significantly predictive of PTSD reexperiencing symptoms	PCL-M
Bonn-Miller et al, 2021[39]	No significant difference between groups in mean change of intrusion symptoms in stages 1 ($F_{3,73}$ = 1.58, P = .20) or 2 ($F_{2,64}$ = 2.80, P = .07)	CAPS-5
Bonn-Miller et al, 2022[30]	The rate of change in intrusive thoughts failed to reach significance in cannabis users compared to controls	CAPS-5
Greer et al, 2014[33]	In patients using cannabis, criterion B decreased from 29.5 ± 6.4 to 7.3 ± 5.9 ($F_{1,79}$ = 734.98, P < .0001)	CAPS for *DSM-IV*
Jetly et al, 2015[43]	Significant difference in mean reduction in frequency and intensity of recurring and distressing dreams (nabilone: −3.6 ± 2.4, placebo: −1.0 ± 2.1, P = .03)	CAPS for *DSM-IV* recurrent distressing dreams item
Pillai et al, 2022[34]	Statistically significant association between initiation of cannabis-based medicinal products and improvements in intrusion scores from baseline to 1-, 3-, and 6-month follow-up (P < .0050)	IES-R intrusions
Roitman et al, 2014[38]	No statistically significant difference in intrusion symptoms; statistically significant decreases in frequency of nightmares (P < .04) and impairment attributed to nightmares (P < .002) from start to end of the trial	CAPS for *DSM-IV*, NES, NFQ
Cluster C		
Bonn-Miller et al, 2013[40]	Individuals with a CUD diagnosis reported lower levels of change in avoidance-numbing scores between treatment intake and discharge compared to those without a CUD diagnosis; a CUD diagnosis was significantly predictive of lower levels of change in avoidance-numbing symptoms between treatment intake and discharge	PCL-M
Bonn-Miller et al, 2021[39]	No significant difference between groups in mean change of avoidance symptoms in stage 1 ($F_{3,73}$ = 1.06, P = .37); significant difference in mean change between groups that received high CBD and THC+CBD ($F_{2,64}$ = 4.95, P = .01) in stage 2	CAPS-5
Bonn-Miller et al, 2022[30]	While the rate of change in avoidance scores failed to reach significance in cannabis users compared to controls, there was a trend for group differences	CAPS-5
Greer et al, 2014[33]	In patients using cannabis, criterion C decreased from 38.2 ± 8.4 to 8.7 ± 8.0 ($F_{1,79}$ = 783.73, P < .0001)	CAPS for *DSM-IV*
Pillai et al, 2022[34]	A statistically significant association between initiation of cannabis-based medicinal products and improvements in avoidance scores from baseline to 1-, 3-, and 6-month follow-up (P < .0050)	IES-R avoidance
Roitman et al, 2014[38]	No statistical difference in arousal score from start to end of the trial (P > .5)	CAPS for *DSM-IV*
Cluster D		
Allan et al, 2019[35]	In individuals with elevated PTSD symptoms at baseline, number of days using cannabis significantly predicted an increased likelihood of suicidal behavior; number of days using cannabis significantly predicted an increased likelihood of suicidal ideation after 1 month	C-SSRS
Bonn-Miller et al, 2021[39]	No significant difference between groups in mean change of CAPS-5 D subscale score in stage 1($F_{3,73}$ = 2.26, P = .09); no significant differences between groups in IDAS general depression scores in stages 1 or 2; significant difference in mean change of CAPS-5 D subscale score ($F_{2,64}$ = 8.60, P < .001) between groups who received high THC and THC+CBD and between those who received high CBD and THC+CBD in stage 2	CAPS-5, IDAS
Bonn-Miller et al, 2022[30]	Rate of change in negative alterations in mood and cognitions failed to reach significance in cannabis users compared to controls	CAPS-5
Johnson et al, 2016[37]	Cannabis users had significantly greater levels of suicidal ideation (P < .001)	Paykel questionnaire for suicidal ideations and attempts
Livingston et al, 2022[41]	No statistically significant changes in depressive symptoms over time in participants with a CUD diagnosis	PHQ
Manhapra et al, 2015[42]	Cannabis abstinence was strongly associated with improvements in suicidality scores in participants with a CUD diagnosis	MISS-SF suicidality item
Cluster E		
Bonn-Miller et al, 2013[40]	Individuals with a CUD diagnosis reported lower levels of change in hyperarousal scores between treatment intake and discharge compared to those without a CUD diagnosis; a CUD diagnosis was significantly predictive of lower levels of change in hyperarousal symptom severity between treatment intake and discharge	PCL-M
Bonn-Miller et al, 2021[39]	No significant differences between treatment groups in mean change for hyperarousal symptoms in stages 1 ($F_{3,73}$ = .84, P = .48) or 2 ($F_{3,73}$ = .84, P = .48); no significant difference between treatment groups in mean change scores for insomnia symptoms in stages 1 ($F_{9,219}$ = 1.20, P = 0.30) or 2 ($F_{6,194}$ = .38, P = .89)	CAPS-5, ISI
Bonn-Miller et al, 2022[30]	Cannabis users showed a significantly greater rate of decline for hyperarousal symptoms compared to controls; the rate of change of sleep quality and insomnia failed to reach significance; cannabis users recorded a lower rate of reduction in NWAK compared to controls	CAPS-5, ISI, PSQI, SOL, SE, WASO, NWAK, TST
Greer et al, 2014[33]	In patients using cannabis, hyperarousal symptoms decreased from 31.0 ± 6.2 to 6.6 ± 6.0 ($F_{1,79}$ = 910.79, P < .0001)	CAPS for *DSM-IV*
Jetly et al, 2015[43]	There were no effects of nabilone on sleep quality and quantity	CAPS difficulty falling and staying asleep item, sleep diary
Manhapra et al, 2015[42]	Cannabis abstinence was strongly associated with significant improvements in violence scores in individuals with a CUD diagnosis	Four-item self-report questionnaire from the National Vietnam Veterans Readjustment Study
Pillai et al, 2022[34]	A statistically significant association between initiation of cannabis-based medicinal products and improvements in hyperarousal scores from baseline to 1-, 3-, and 6-month follow-up (P < .0050); statistically significant improvements in sleep across follow-ups (P < .050)	IES-R hyperarousal, single item SQS
Roitman et al, 2014[38]	A statistically significant decrease in symptom severity in PTSD hyperarousal symptoms (P < .02) and sleep quality (P < .05) from start to end of the trial	CAPS for *DSM-IV*, PSQI
Wilkinson et al, 2015[36]	Those who initiated cannabis use after treatment showed significantly higher measures of violent behavior at follow-up than never-users, continuing-users, and stoppers	Four-item self-report questionnaire from the National Vietnam Veterans Readjustment Study

Abbreviations: CAPS for *DSM-IV* = Clinician-Administered PTSD Scale for *DSM-IV*, CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, C-SSRS = Columbia-Suicide Severity Rating Scale, IDAS = Inventory of Depression and Anxiety Symptoms, IES-R = Impact of Events Scale-Revised, ISI = Insomnia Severity Index, MISS-SF = Mississippi Scale for Combat-Related PTSD-Short Form, NES = Nightmare Effects Survey, NFQ = Nightmare Frequency Questionnaire, NWAK = number of awakenings, PCL = PTSD Checklist, PCL-M = PTSD Checklist-Military Version, PHQ = Patient Health Questionnaire, PSQI = Pittsburgh Sleep Quality Index, PTSD = posttraumatic stress disorder, SE = sleep efficiency, SOL = sleep-onset latency, SQS = Sleep Quality Scale, TST = total sleep time, WASO = wake after sleep onset.

using post-discharge but not at admission ("starters"). The study revealed that starting cannabis was associated with greater PTSD symptoms at 4-month follow-up compared to individuals who never used cannabis. Additionally, those who never used cannabis had the lowest PTSD symptoms at follow-up, and those who stopped using cannabis during treatment saw greater improvements in symptoms.[36]

The 3 remaining studies, longitudinal (n = 2) and experimental (n = 1) in design, suggested no significant relationship between cannabinoids and PTSD symptoms.[37–39] A matched longitudinal study examining cannabis use and mental health symptom severity in veterans with probable PTSD did not find cannabis use to be associated with overall PTSD symptomatology. Upon examining patterns of cannabis use within cases, they also demonstrated that PCL-C scores were unrelated to the odds of daily versus non-daily use.[37] In an open-label study by Roitman and colleagues,[38] patients with chronic PTSD received 2.5 mg of oral THC twice daily as add-on treatment. Researchers noted decreases in average total CAPS scores between pre- and post-treatment; however, the results were not statistically significant. Lastly, in stage 1 of a crossover RCT, researchers tested the effects of 3 active (high THC [~12% THC and < 0.05% CBD], high CBD [~0.50% THC and 11% CBD], THC+CBD [~7.9% THC and 8.1% CBD]) and 1 placebo (< 0.03% THC and < 0.01% CBD) concentration of smoked cannabis in veterans with PTSD. No significant differences in total CAPS-5 symptom severity were observed. In stage 2 of the trial, participants were re-randomized into 3 active treatment groups (high THC, high CBD, THC+CBD), and all treatment groups experienced decreases in total PTSD scores; however, no significant group differences were detected.[39]

CUD sample. Three longitudinal studies suggested risks of cannabis use in individuals with comorbid PTSD and CUD.[40–42] A prospective investigation in male veterans attending residential treatment examined the association between a current CUD diagnosis and changes in PTSD symptoms over time after cannabis cessation. After accounting for several variables (eg, co-occurring substance use disorders and trauma severity), they found that the presence of a CUD diagnosis was significantly predictive of lower levels of change in PTSD symptom severity compared to patients without a CUD diagnosis.[40] A case-control study exploring the long-term effects of CUD in veterans found that when compared to veterans without a prior CUD diagnosis, those with a documented CUD reported higher symptom severity at baseline and over time, as evidenced through a slower rate of symptom improvement.[41] Similarly, a study examining treatment outcomes for veterans with comorbid PTSD and CUD found significant differences in the change of symptom scores, where the cannabis-abstinent group showed greater improvements relative to the non–cannabis-abstinent group.[42]

Effects of Cannabinoids on Cluster B–Related Symptoms

Non-CUD sample. Six studies, longitudinal (n = 3), experimental (n = 2), and retrospective (n = 1) in design, reported on the effects of cannabinoids on symptoms related to reexperiencing trauma, including nightmares and intrusive thoughts and memories.[30,33,34,38,39,43] Four of these studies reported the effects of cannabis on overall reexperiencing scores via the CAPS, PCL-M, and IES. Two found benefits of cannabis use, noting significant decreases in CAPS-IV cluster B symptoms from no-cannabis to cannabis-use conditions[33] and significant improvements in IES-R intrusion scores from baseline to 1-, 3-, and 6-month follow-up in patients prescribed cannabis-based medicinal products for PTSD.[34] The remaining 2 studies did not find any significant differences between treatment groups or between cannabis users and non-users in overall cluster B scores.[30,39]

Two studies, longitudinal and experimental, investigated the impact of cannabinoids on symptoms associated with distressing dreams and nightmares. Using validated sleep measures like the CAPS-IV Recurring and Distressing Dream Score and Nightmare Effects Survey (NES), both studies reported associations between cannabis use and either cessation or significant reductions in nightmares from pre- to post-treatment.[38,43]

CUD sample. Only 1 longitudinal study examined the relationship between a CUD diagnosis and changes in cluster B severity. The study concluded that the presence of a CUD diagnosis was not significantly predictive of reexperiencing symptoms as measured by the PCL-M.[40]

Effects of Cannabinoids on Cluster C–Related Symptoms

Non-CUD sample. Five studies, longitudinal (n = 3), experimental (n = 1), and retrospective (n = 1) in design, reported on the effects of cannabinoids on symptoms related to avoidance of trauma-related thoughts, memories, feelings, and external reminders of the traumatic event.[31,32,35,40,41] Of these studies, 2 demonstrated significant benefits of cannabis use. Greer and colleagues[33] suggested a significant reduction in CAPS-IV cluster C score when individuals were using cannabis compared to when they were not. Similarly, individuals using cannabis-based medicinal products for PTSD symptoms reported improvements in IES-R avoidance scores from baseline to 1-, 3-, and 6-month follow-up.[34] Three studies did not report any statistically significant differences between treatment groups, from pre- to post-treatment or between cannabis-using and non–cannabis-using patients with PTSD.[30,38,39]

CUD sample. One longitudinal study[40] highlighted the effects of a CUD diagnosis on cluster C symptoms and found that individuals with a CUD diagnosis reported lower levels of change in PCL-M avoidance-numbing scores during the course of treatment. They

also revealed that the presence of a CUD diagnosis was significantly predictive of lower levels of change in avoidance-numbing symptoms between treatment intake and discharge; however, after splitting the cluster into avoidance and numbing, this relationship was found to be significant only for numbing symptoms.[40]

Effects of Cannabinoids on Cluster D–Related Symptoms

Non-CUD sample. Four studies, longitudinal (n = 3) and experimental (n = 1) in design, reported on the effects of cannabinoids on symptoms related to cognition and affect, including negative emotional states, distorted cognition, and mood.[30,35,37,39] Only 2 of these studies examined total cluster D scores, which suggested no significant differences between active and placebo groups and between cannabis-using and non–cannabis-using PTSD patients.[30,39] The 2 remaining longitudinal studies investigating the relationship between cannabis use and suicidality in individuals with PTSD suggested cannabis use was positively associated with suicidal thoughts and behaviors.[35,37] A yearlong study examining the interactive effects of days using cannabis and PTSD symptoms on suicidal ideation and behavior found that in those with elevated PTSD symptoms at baseline, the number of days using cannabis significantly predicted an increased likelihood of suicidal behavior. They also found that the number of days using cannabis significantly predicted an increased likelihood of suicidal ideation after 1 month.[35] Using the Paykel questionnaire for suicidal ideations and attempts, a matched case-control study found that cannabis users had significantly greater levels of suicidal ideation relative to non–cannabis-using controls with PTSD.[37]

CUD sample. Two longitudinal studies reported on the effects of a CUD diagnosis on depression and suicidality in veterans with PTSD. Veterans with co-occurring CUD reported no significant differences in depression scores compared to those without CUD.[41] In contrast, 4 months of cannabis abstinence was strongly associated with greater improvements in suicidality scores in veterans with co-occurring CUD and PTSD relative to the non–cannabis-abstinent group with co-occurring CUD and PTSD.[42]

Effects of Cannabinoids on Cluster E–Related Symptoms

Non-CUD sample. Seven studies, longitudinal (n = 3), retrospective (n = 2), and experimental (n = 2) in design, reported on the effects of cannabinoids on symptoms related to hyperarousal and reactivity like aggression, problems with concentration, and sleep disturbance.[30,33,34,36,38,39,43] Five of the 7 studies investigated the relationship between cannabis and total cluster E scores, with 4 reporting potential benefits with cannabis use.[30,33,34,38] In a post hoc analysis comparing participants with PTSD using dispensary-obtained cannabis versus those with PTSD who do not use cannabis (control), researchers found that cannabis users showed a significantly greater rate of decline for CAPS-5 hyperarousal symptoms compared to controls.[30] In a study in patients evaluated for the New Mexico Medical Cannabis Program, significant decreases in hyperarousal symptoms were found when patients were using cannabis compared to when they were not.[33] Similarly, individuals using cannabis-based medicinal products for PTSD symptoms reported improvements in IES-R hyperarousal scores from baseline to 1-, 3-, and 6-month follow-up.[34] Lastly, in an open-label trial with oral THC, a statistically significant decrease from pre- to post-treatment in arousal symptoms, as measured by the CAPS-IV, was observed.[38] One RCT reported no significant differences in mean change scores between treatment groups in stages 1 or 2 of the trial.[39]

Six of the 7 studies included measures of either insomnia, sleep quality, or sleep quantity through the Pittsburgh Sleep Quality Index, Single-Item Sleep Quality Scale, Insomnia Severity Index (ISI), and CAPS sleep items. Three of these studies reported statistically significant improvements in either hours of sleep or sleep quality from pre–cannabis treatment to post–cannabis treatment.[33,34,38] The remaining studies found no significant differences in mean change ISI scores, or sleep quality and quantity as measured by the CAPS difficulty falling and staying asleep items with cannabis use.[30,39,43] One study that analyzed several sleep outcomes found a significant between-group difference over time for number of awakenings (NWAK), where cannabis-using patients with PTSD demonstrated a significantly lower rate of reduction in NWAK relative to non–cannabis using patients with PTSD.[30]

One retrospective study examined the association between cannabis use and violence in a sample of veterans with PTSD. Using a 4-item self-report questionnaire from the National Vietnam Veterans Readjustment Study, researchers demonstrated that those who started using cannabis post-discharge but not at admission (cannabis "starters") were significantly more likely to report violent behaviors relative to never-users, continuing-users, and stoppers at follow-up.[36]

CUD sample. Two longitudinal studies reported on the effects of CUD on symptoms related to hyperarousal and reactivity in participants with comorbid PTSD and CUD. In terms of violence, Manhapra and colleagues[42] found that cannabis abstinence was strongly associated with improvements in violence in individuals with comorbid CUD and PTSD. Additionally, compared to those without a CUD diagnosis, individuals with co-occurring PTSD and CUD experienced significantly lower levels of change in PCL-M hyperarousal symptoms between treatment intake and discharge.[40]

DISCUSSION

Antidepressants and trauma-focused therapy are first-line treatments for PTSD. Despite these options,

many individuals find that PTSD symptoms persist, negatively impacting daily life and contributing to high rates of psychiatric and medical comorbidity. In response, individuals with PTSD have explored both regulated and unregulated use of cannabis to alleviate their symptoms. Recognizing the need to compile evidence on the clinical effects of cannabinoids in PTSD, this article aims to investigate the therapeutic potential of cannabinoids for overall PTSD symptoms and symptom clusters.

In accordance with previous reviews,[44–46] we found mixed results for the effects of cannabinoids on overall PTSD symptomatology. With only 5 studies reporting significant improvements in overall symptoms and 5 studies concluding either no effect or negative effects of cannabinoids, this review did not find strong evidence for the use of cannabinoids in improving PTSD symptoms. These findings may be attributed in part to the differences in study methodologies, more specifically, the cannabinoid used, how it was administered, and the length of time the cannabinoid was used. The included studies examined the effects of nabilone, CBD, THC, and various concentrations of mixed THC and CBD through inhalation, tablets, and oral spray. As an analog of THC, nabilone's chemical structure is very similar, inducing comparable "cannabis-like" effects including euphoria and other psychotomimetic effects.[47] Unlike THC and its analogs, CBD is associated with anxiolytic and antiemetic effects. These differences in addition to varying routes of administration may have contributed to the mixed results. Further, the duration of response to cannabis also ranged greatly between studies. A recent study[48] looking at the short- and long-term effects of inhaled cannabis in individuals with self-reported PTSD showed that it acutely (≤ 4 hours) reduced symptoms by over 50% and had no significant effects in the long-term (31 months). While our findings did not include studies that examined the effects of cannabis after a few hours, the shortest duration of response was 3 weeks while the longest was 7 years; such variation may impact conclusions. Our results were less conflicting in individuals with a comorbid PTSD and CUD diagnosis, with 3 studies reporting significant positive associations between cannabis use and slower rates of symptom severity improvement.

Overall, studies of cannabinoids in PTSD displayed high RoB and weak research methods. Only 1 study met the criteria for low RoB, while several other studies were reported as high RoB. Bias in selection of participants was a commonly reported issue as several studies used non-probability sampling and selection of participants was related to both the intervention and the outcome. For example, to meet inclusion criteria for 1 study, participants were required to self-report "significant relief of several major PTSD symptoms when using cannabis."[33] Weak research methods also negatively affected the quality of studies. The hierarchy of evidence ranks study types based on the rigor of their research methods, with RCTs at the top of the pyramid, followed by cohort, case-control, and case studies. There was only 1 RCT that examined the effects of cannabis on overall PTSD outcomes. If one also considers the usual consensus that retrospective studies are of lower quality (in terms of the conclusions that can be drawn) relative to longitudinal and experimental studies, there are several patterns in our review that are worth noting. Specifically, in the non-CUD sample, 75% of retrospective studies suggested benefits of cannabis/cannabinoids on overall PTSD symptoms as compared to 17% of longitudinal and experimental studies; 0% vs 50% showed no change in the retrospective vs longitudinal and experimental studies, respectively; and 25% vs 33% of suggested risk for worsening of PTSD symptoms from cannabis/cannabinoids in the retrospective vs longitudinal and experimental studies, respectively. 100% of longitudinal studies in patients with comorbid PTSD and CUD also suggested risk for worsening symptoms associated with cannabis. The higher percentage of retrospective studies suggesting benefits could be due to biases or limitations inherent to retrospective research. Participants may have remembered positive outcomes more readily, leading to an overestimation of benefits. Further, the substantial portion of longitudinal and experimental studies that did not find benefits of cannabis use might reflect the more rigorous nature of these studies as they tend to have better control over variables, reducing potential biases that could inflate positive results.

Concerning cluster B symptoms, evidence from 2 studies suggests cannabinoid use may positively impact recurrent, distressing dreams. These findings coincide with preclinical research in mouse models which have demonstrated that activation of CB1 receptors impedes the retrieval of aversive memories and promotes their extinction, actions thought to be important in improving flashbacks and nightmares.[19–21] Further, in early clinical studies on the effects of cannabinoids on sleep patterns, administration of THC or marijuana extract before sleep could limit the amount of time participants spent in rapid eye movement (REM) sleep.[49–52] Since PTSD nightmares are believed to occur during the REM sleep phase, a possible explanation for the reduction in nightmares seen in cannabis-using PTSD participants may be through cannabis reducing the time spent in REM sleep.[18,53,54]

Due to mixed evidence with respect to cannabinoids and cluster C symptoms, we suggest no significant relationship between cannabinoid use and avoidance symptoms. This lack of findings may have been impacted by the fundamental differences between the CAPS-IV and CAPS-5. The previous edition of CAPS contained only 3 clusters, B, C, D, focused on reexperiencing and intrusion, avoidance and numbing of general responsiveness, and hyperarousal, respectively.[55] The updated version divides criterion C, avoidance and numbing, into 2 distinct clusters: avoidance and negative alterations in cognitions and mood.[56] As a result, criterion C went from having 7 symptoms in the CAPS-IV to just 2 in the CAPS-5.

Because criterion C in the CAPS-IV was concerned with avoidant symptoms to some extent, we included studies that used this tool; however, it is important to note that subtotal scores for this version included 5 more symptoms than the CAPS-5 that were concerned with numbing.

Our study obtained mixed evidence concerning the relationship between cannabinoids and cluster D symptoms related to cognition, affect, and mood. We found some evidence to suggest that cannabis use in individuals with PTSD may be associated with suicidal ideation and behavior. High rates of suicidal behavior have previously been found among patients with PTSD.[6,57] Some studies have suggested that the eCB system may also play a role in the pathophysiology of suicide.[58,59] While literature in this area is limited for PTSD, a postmortem study in depressed suicide victims revealed elevated CB1 receptor and CB1-receptor–mediated G-protein signaling in the prefrontal cortex compared to healthy controls.[60]

We provide evidence to suggest a mixed but generally positive relationship between cannabinoids and symptoms related to hyperarousal. Cannabis-associated sleep improvements coincide with current knowledge of eCB signaling and sleep which proposes that activation of CB1 receptors with exogenous cannabinoids reduces wakefulness and arousal and promotes time spent sleeping in animal models.[13,61,62] Similar results were observed in a study in rats exposed to CBD in which researchers suggested that CBD might contribute to the enhancement of duration and quality of sleep.[63–65] The association between cannabinoids and cluster E becomes less clear when the cluster is broken down in terms of other hyperarousal items like aggression. Studies reporting outcomes of violent behavior found that cannabis abstinence was strongly associated with decreases in violence, while initiating cannabis use was associated with higher scores in violent behavior. Previous literature on the relationship between cannabis use and violence is conflicting, perhaps due to the multifaceted nature of violence.[66–69] One potential explanation for our findings may relate to deficits in emotion recognition and emotion regulation commonly seen in both individuals with PTSD and cannabis users.[70–72] Research suggests that deficits in emotion recognition have been associated with violence, and thus it is possible that the interaction between these clinical entities may contribute to perpetuating violent behaviors.

Study Limitations

While we performed a comprehensive review, this systematic review is not without its limitations. First, many of the studies[30,31,33] did not account for key confounding factors such as tobacco, alcohol, and other substance use. It is possible that the relationship between cannabis use and PTSD symptoms weakens after accounting for these variables. Second, as previously mentioned, there was great heterogeneity among the included studies with regard to outcome measures, study methodology, and the duration of follow-up. Many of the studies had inconsistent reporting measures of PTSD symptoms and cannabis use (eg, how it was reported, dosage, potency, frequency, and regimen and route of administration). Only 5 studies clearly stated the cannabinoid assessed and their respective dosage, while the remainder failed to include relative concentrations of THC and CBD. Third, due to the large number of studies conducted exclusively in male military personnel and veterans, the generalizability of our results for other genders and forms of trauma remains unclear. Fourth, the average RoB was high, which limits the degree to which our results accurately reflect the true effect of cannabis and cannabinoids on PTSD outcomes. Lastly, the dearth of experimental studies led us to expand our inclusion criteria to include the next best level of evidence. Since most data were observational, evidence is limited as a basis for concluding any causal relationships, and more controlled studies are warranted.

CONCLUSIONS AND FUTURE DIRECTIONS

This systematic review is the first to evaluate the effects of cannabinoids on each PTSD cluster. Our findings suggest potentially promising (although preliminary) evidence for cannabis with regard to cluster B symptoms, specifically nightmares and distressing dreams, and cluster E symptoms, such as sleep. We also found that cannabis use may be associated with negative effects including increased suicidal ideation and violence. The benefits of cannabis use for global PTSD symptoms are unclear; however, frequent use can lead to CUD, which seems to be associated with poorer symptom and treatment outcomes.

There is an urgent need for high-quality RCTs to better assess the effectiveness of cannabis and cannabinoids for PTSD symptoms and symptom clusters. To explore potential therapeutic effects, trials should consider comparing cannabis' effects with other pharmacologic treatments or psychotherapies. Future studies should also aim to incorporate more cannabis-related measures, including potency, strains, frequency, and dosage. Lastly, when possible, researchers are encouraged to use gold-standard interviews, such as the CAPS, to screen participants and monitor symptom changes during and after treatment.

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References

1. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of *DSM-IV* disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593–602.
2. Koenen KC, Ratanatharathorn A, Ng L, et al. Posttraumatic stress disorder in the World Mental Health Surveys. *Psychol Med*. 2017;47(13):2260–2274.
3. Goldstein RB, Smith SM, Chou SP, et al. The epidemiology of *DSM-5* posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *Soc Psychiatry Psychiatr Epidemiol*. 2016;51(8):1137–1148.
4. Janoutová J, Janácková P, Serý O, et al. Epidemiology and risk factors of schizophrenia. *Neuroendocrinol Lett*. 2016;37(1):1–8.
5. Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. *Ther Adv Psychopharmacol*. 2018;8(9):251–269.
6. Krysinska K, Lester D. Post-traumatic stress disorder and suicide risk: a systematic review. *Arch Suicide Res*. 2010;14(1):1–23.
7. Rapaport MH, Clary C, Fayyad R, et al. Quality-of-life impairment in depressive and anxiety disorders. *Am J Psychiatry*. 2005;162(6):1171–1178.
8. Pietrzak RH, Goldstein RB, Southwick SM, et al. Medical comorbidity of full and partial posttraumatic stress disorder in US adults: results from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosom Med*. 2011;73(8):697–707.
9. McCauley JL, Killeen T, Gros DF, et al. Posttraumatic stress disorder and co-occurring substance use disorders: advances in assessment and treatment. *Clin Psychol (New York)*. 2012;19(3):283–304.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR*. Fifth Edition, Text Revision. American Psychiatric Association Publishing; 2022.
11. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev*. 2006;2006(1):CD002795.
12. Lewis C, Roberts NP, Gibson S, et al. Dropout from psychological therapies for post-traumatic stress disorder (PTSD) in adults: systematic review and meta-analysis. *Eur J Psychotraumatol*. 2020;11(1):1709709.
13. Hill MN, Campolongo P, Yehuda R, et al. Integrating endocannabinoid signaling and cannabinoids into the biology and treatment of posttraumatic stress disorder. *Neuropsychopharmacology*. 2018;43(1):80–102.
14. Hillard CJ, Weinlander KM, Stuhr KL. Contributions of endocannabinoid signaling to psychiatric disorders in humans: genetic and biochemical evidence. *Neuroscience*. 2012;204:207–229.
15. Ney LJ, Matthews A, Bruno R, et al. Cannabinoid interventions for PTSD: where to next? *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;93:124–140.
16. Ruehle S, Rey AA, Remmers F, et al. The endocannabinoid system in anxiety, fear memory and habituation. *J Psychopharmacol*. 2012;26(1):23–39.
17. Ganon-Elazar E, Akirav I. Cannabinoid receptor activation in the basolateral amygdala blocks the effects of stress on the conditioning and extinction of inhibitory avoidance. *J Neurosci*. 2009;29(36):11078–11088.
18. Maldonado R, Cabañero D, Martín-García E. The endocannabinoid system in modulating fear, anxiety, and stress . *Dialogues Clin Neurosci*. 2020;22(3):229–239.
19. Marsicano G, Wotjak CT, Azad SC, et al. The endogenous cannabinoid system controls extinction of aversive memories. *Nature*. 2002;418(6897):530–534.
20. Niyuhire F, Varvel SA, Martin BR, et al. Exposure to marijuana smoke impairs memory retrieval in mice. *J Pharmacol Exp Ther*. 2007;322(3):1067–1075.
21. Blessing EM, Steenkamp MM, Manzanares J, et al. Cannabidiol as a potential treatment for anxiety disorders. *Neurotherapeutics*. 2015;12(4):825–836.
22. Neumeister A, Normandin MD, Pietrzak RH, et al. Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study. *Mol Psychiatry*. 2013;18(9):1034–1040.
23. Lake S, Kerr T, Buxton J, et al. Does cannabis use modify the effect of post-traumatic stress disorder on severe depression and suicidal ideation? evidence from a population-based cross-sectional study of Canadians. *J Psychopharmacol*. 2020;34(2):181–188.
24. Bilevicius E, Sommer JL, Asmundson GJG, et al. Associations of PTSD, chronic pain, and their comorbidity on cannabis use disorder: results from an American nationally representative study. *Depress Anxiety*. 2019;36(11):1036–1046.
25. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
26. Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
27. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
28. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. 2013. https://web.archive.org/web/20210716121605id_/http://www3.med.unipmn.it/dispense_ebm/2009-2010/Corso%20Perfezionamento%20EBM_Faggiano/NOS_oxford.pdf
29. Vardell E, Malloy M. Joanna Briggs Institute: an evidence-based practice database. *Med Ref Serv Q*. 2013;32(4):434–442.
30. Bonn-Miller MO, Brunstetter M, Simonian A, et al. The long-term, prospective, therapeutic impact of cannabis on post-traumatic stress disorder. *Cannabis Cannabinoid Res*. 2022;7(2):214–223.
31. Cameron C, Watson D, Robinson J. Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: a retrospective evaluation. *J Clin Psychopharmacol*. 2014;34(5):559–564.
32. Elms L, Shannon S, Hughes S, et al. Cannabidiol in the treatment of post-traumatic stress disorder: a case series. *J Altern Complement Med*. 2019;25(4):392–397.
33. Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. *J Psychoactive Drugs*. 2014;46(1):73–77.
34. Pillai M, Erridge S, Bapir L, et al. Assessment of clinical outcomes in patients with post-traumatic stress disorder: analysis from the UK Medical Cannabis Registry. *Expert Rev Neurother*. 2022;22(11-12):1009–1018.
35. Allan NP, Ashrafioun L, Kolnogorova K, et al. Interactive effects of PTSD and substance use on suicidal ideation and behavior in military personnel: Increased risk from marijuana use. *Depress Anxiety*. 2019;36(11):1072–1079.
36. Wilkinson ST, Stefanovics E, Rosenheck RA. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. *J Clin Psychiatry*. 2015;76(9):1174–1180.
37. Johnson MJ, Pierce JD, Mavandadi S, et al. Mental health symptom severity in cannabis using and non-using veterans with probable PTSD. *J Affect Disord*. 2016;190:439–442.
38. Roitman P, Mechoulam R, Cooper-Kazaz R, et al. Preliminary, open-label, pilot study of add-on oral Δ9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clin Drug Investig*. 2014;34(8):587–591.
39. Bonn-Miller MO, Sisley S, Riggs P, et al. The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: a randomized cross-over clinical trial. *PLoS One*. 2021;16(3):e0246990.
40. Bonn-Miller MO, Boden MT, Vujanovic AA, et al. Prospective investigation of the impact of cannabis use disorders on posttraumatic stress disorder symptoms among veterans in residential treatment. *Psychol Trauma*. 2013;5(2):193–200.
41. Livingston NA, Farmer SL, Mahoney CT, et al. Longitudinal course of mental health symptoms among veterans with and without cannabis use disorder. *Psychol Addict Behav*. 2022;36(2):131–143.
42. Manhapra A, Stefanovics E, Rosenheck R. Treatment outcomes for veterans with PTSD and substance use: impact of specific substances and achievement of abstinence. *Drug Alcohol Depend*. 2015;156:70–77.
43. Jetly R, Heber A, Fraser G, et al. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology*. 2015;51:585–588.
44. Botsford SL, Yang S, George TP. Cannabis and cannabinoids in mood and anxiety disorders: impact on illness onset and course, and assessment of therapeutic potential. *Am J Addict*. 2020;29(1):9–26.
45. Rehman Y, Saini A, Huang S, et al. Cannabis in the management of PTSD: a systematic review. *AIMS Neurosci*. 2021;8(3):414–434.
46. Wilkinson ST, Radhakrishnan R, D'Souza DC. A systematic review of the evidence for medical marijuana in psychiatric indications. *J Clin Psychiatry*. 2016;77(8):1050–1064.
47. Steenkamp MM, Blessing EM, Galatzer-Levy IR, et al. Marijuana and other cannabinoids as a treatment for posttraumatic stress disorder: a literature review. *Depress Anxiety*. 2017;34(3):207–216.
48. LaFrance EM, Glodosky NC, Bonn-Miller M, et al. Short and long-term effects of

cannabis on symptoms of post-traumatic stress disorder. *J Affect Disord*. 2020;274:298–304.
49. Feinberg I, Jones R, Walker JM, et al. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. *Clin Pharmacol Ther*. 1975;17(4):458–466.
50. Feinberg I, Jones R, Walker J, et al. Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. *Clin Pharmacol Ther*. 1976;19(6):782–794.
51. Schierenbeck T, Riemann D, Berger M, et al. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. *Sleep Med Rev*. 2008;12(5):381–389.
52. Bolla KI, Lesage SR, Gamaldo CE, et al. Sleep disturbance in heavy marijuana users. *Sleep*. 2008;31(6):901–908.
53. Ross RJ, Ball WA, Dinges DF, et al. Rapid eye movement sleep disturbance in posttraumatic stress disorder. *Biol Psychiatry*. 1994;35(3):195–202.
54. Singareddy RK, Balon R. Sleep in posttraumatic stress disorder. *Ann Clin Psychiatry*. 2002;14(3):183–190.
55. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Includes ICD-9-CM Codes Effective October 1, 1996. Fourth Edition. 1998.
56. Weathers FW, Bovin MJ, Lee DJ, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): development and initial psychometric evaluation in military veterans. *Psychol Assess*. 2018;30(3):383–395.
57. Gradus JL, Qin P, Lincoln AK, et al. Posttraumatic stress disorder and completed suicide. *Am J Epidemiol*. 2010;171(6):721–727.
58. Sher L. Neurobiology of suicidal behavior in post-traumatic stress disorder. *Expert Rev Neurother*. 2010;10(8):1233–1235.
59. Vinod KY. Role of the endocannabinoid system in the neurobiology of suicide. In: Dwivedi Y, ed. *The Neurobiological Basis of Suicide*. CRC Press/Taylor & Francis; 2012.
60. Hungund BL, Vinod KY, Kassir SA, et al. Upregulation of CB1 receptors and agonist-stimulated [35S]GTPgammaS binding in the prefrontal cortex of depressed suicide victims. *Mol Psychiatry*. 2004;9(2):184–190.
61. Pava MJ, den Hartog CR, Blanco-Centurion C, et al. Endocannabinoid modulation of cortical up-states and NREM sleep. *PLoS One*. 2014;9(2):e88672.
62. Pava MJ, Makriyannis A, Lovinger DM. Endocannabinoid signaling regulates sleep stability. *PLoS One*. 2016;11(3):e0152473.
63. Chagas MH, Crippa JA, Zuardi AW, et al. Effects of acute systemic administration of cannabidiol on sleep-wake cycle in rats. *J Psychopharmacol*. 2013;27(3):312–316.
64. Hsiao YT, Yi PL, Li CL, et al. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. *Neuropharmacology*. 2012;62(1):373–384.
65. Bitencourt RM, Takahashi RN. Cannabidiol as a therapeutic alternative for post-traumatic stress disorder: from bench research to confirmation in human trials. *Front Neurosci*. 2018;12:502.
66. Carabellese F, Candelli C, Martinelli D, et al. Cannabis use and violent behaviour: a psychiatric patients cohort study in southern Italy. *Riv Psichiatr*. 2013;48(1):43–50.
67. Norström T, Rossow I. Cannabis use and violence: is there a link? *Scand J Public Health*. 2014;42(4):358–363.
68. Sorkhou M, Johnstone S, Kivlichan AE, et al. Does cannabis use predict aggressive or violent behavior in psychiatric populations? a systematic review. *Am J Drug Alcohol Abuse*. 2022;48(6):631–643.
69. Dellazizzo L, Potvin S, Dou BY, et al. Association between the use of cannabis and physical violence in youths: a meta-analytical investigation. *Am J Psychiatry*. 2020;177(7):619–626.
70. Bayrakçı A, Sert E, Zorlu N, et al. Facial emotion recognition deficits in abstinent cannabis dependent patients. *Compr Psychiatry*. 2015;58:160–164.
71. Castro-Vale I, Severo M, Carvalho D. Lifetime PTSD is associated with impaired emotion recognition in veterans and their offspring. *Psychiatry Res*. 2020;284:112666.
72. Zimmermann K, Walz C, Derckx RT, et al. Emotion regulation deficits in regular marijuana users. *Hum Brain Mapp*. 2017;38(8):4270–4279.