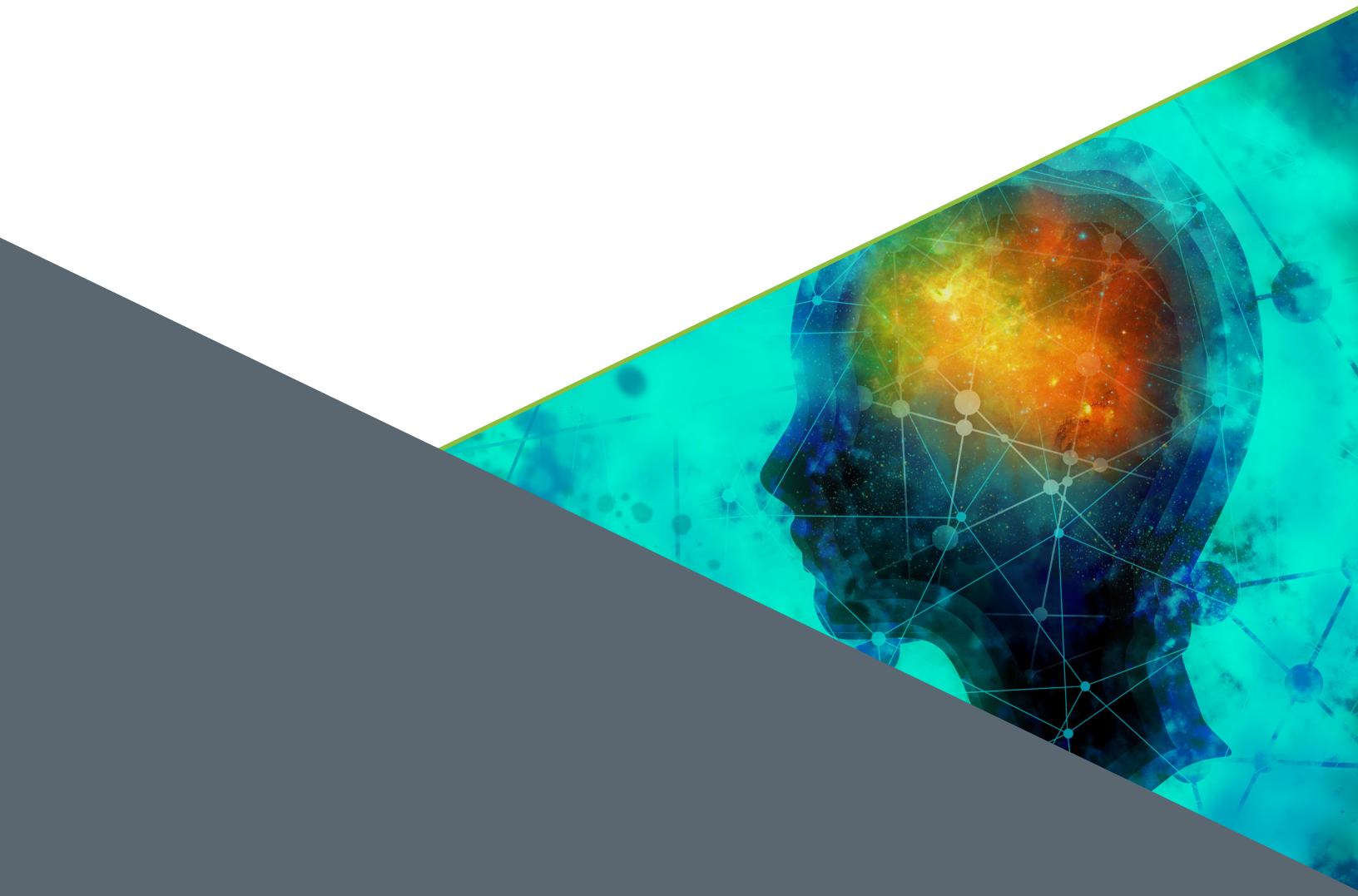
STLM

Systematically Testing the Evidence on Marijuana

Cannabis for the Management of Symptoms of PTSD - Update 1

A Living Systematic Review

December 2021



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Executive Summary

Background

With the expansion of legal access to cannabis for medical and recreational purposes in the US over the past 2 decades, cannabis use has also increased. Cannabis has been touted for its purported benefits for a wide range of medical purposes, including posttraumatic stress disorder (PTSD). This review seeks to identify and incorporate new evidence through October 2021 to address the benefits and harms of cannabis (both plant-based and synthesized) use for PTSD.

PICOS and Key Questions

KQ1. What are the effects of cannabis on health outcomes and health care utilization for adults who have PTSD?

KQ2. Do the effects differ by subgroup, such as medical and mental health comorbidities?

We included studies (controlled clinical trials and observational studies with comparison groups) that assessed the effects of plant-based cannabis preparations; whole-plant extracts (e.g., nabiximols); or US Food and Drug Administration (FDA)-approved synthesized, pharmaceutically prepared cannabinoids (e.g., dronabinol, nabilone) in nonpregnant adults with PTSD.

Methods

We searched multiple databases and grey literature sources to identify studies of cannabis use in participants with PTSD. Two reviewers independently screened all citations for inclusion, and disagreements were resolved by consensus or a third reviewer. Data from included studies were abstracted by 1 reviewer and confirmed by a second. Two reviewers independently assessed the risk of bias (RoB) of each study and the overall certainty of evidence (CoE) for each outcome using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. Disagreements were resolved through discussion. We summarized the primary literature through qualitative synthesis.

Key Findings

We identified 7 eligible studies, 2 of which were new since our original review. Two were crossover randomized controlled trials (RCTs)[2,3] and 5 were retrospective cohort studies.[4-8] We rated the RCTs as having low and high RoB. We rated 2 of the included cohort studies as having moderate RoB and 3 as having high RoB. One RCT was conducted in Canada, while the other RCT and the cohort studies were conducted in the US in largely Veteran Affairs (VA) populations. We also identified 9 ongoing studies (8 trials and 1 cohort study).

Effectiveness and Harms

- PTSD symptom severity: One low-RoB crossover RCT (N = 80) and 5 cohort studies (N range = 136 to 2,276) found no difference in PTSD symptom reduction with cannabis (low CoE).
- PTSD-related nightmares: One very small (N = 10), high-RoB crossover RCT found significant improvement in PTSD-related nightmares with nabilone (a synthetic cannabinoid) compared to placebo (mean Clinician Administered PTSD Scale [CAPS] recurring and distressing dreams item score change -3.6 [SD = 2.4] versus -1.0 [SD = 2.1], P = .03; very low CoE).
- Sleep quality: Two RCTs (N = 10 and 80) and 1 high-ROB cohort study (N = 150) found no difference in any other sleep quality measures with cannabis (very low CoE).
- Functional status: The same 3 studies found no difference in global or psychosocial functioning (very low CoE).
- Mental health: One low-RoB RCT (N = 80) found smoked cannabis no different than placebo for reduction in general depression or social anxiety (Inventory of Depression and Anxiety Symptoms [IDAS], P = .18 and P = .58 respectively; low CoE).

- No studies were identified that analyzed quality of life or utilization of health services.

Differences by Subgroups

- None of the included studies evaluated subgroups.

Applicability to Veteran populations

Most of the research in this field has been conducted in Veterans or active-duty military personnel, making it very applicable to this population.

Conclusions

Although we identified additional studies in this update, it remains uncertain whether cannabis improves symptoms of PTSD. There was low CoE that cannabis use is not associated with differences in PTSD or mental health symptoms, and very low CoE that it may improve PTSD-related nightmares but does not affect other measures of sleep quality or functional status.

Diagnoses of PTSD, particularly in the Veteran population, are increasing—emphasizing the need for future research to evaluate the benefits and harms of cannabis. Fortunately, there are several ongoing studies assessing effects of cannabis on various aspects of PTSD that should be completed over the next several years.

Background

The expansion of legal access to cannabis for medical and recreational purposes in the US over the past 2 decades has led to increased cannabis use.[9] The percentage of Americans aged 12 years and older who reported past-month cannabis use over that time rose significantly, from 6.2%[9] in 2002 to 11.2% in 2019.[9,10]

As of June 2021, 36 states and the District of Columbia (DC) have legalized the medical use of cannabis for adults, and 18 states and DC have legalized recreational use.[11] Cannabis is touted for its purported benefits for a wide range of medical purposes, including posttraumatic stress disorder (PTSD). A majority of states with medical cannabis laws list PTSD as an indication for cannabis use.[11] In states where medical cannabis use is legal, PTSD was listed as the primary reason for requesting cannabis by more than one-third of individuals seeking it for medical use.[12-14] Yet the evidence regarding effectiveness and harms of cannabis use to treat PTSD is minimal to date.

A 2017 systematic review assessed the benefits and harms of cannabis use in patients with PTSD, with insufficient results.[1] This review was formulated as a living systematic review to incorporate new evidence to address the benefits and harms of cannabis use for PTSD, with an initial report completed in March 2021. As part of our living systematic review protocol, we monitor the literature for new meaningful studies on cannabis for PTSD (Table 1). As a result of identifying new, meaningful studies, we have conducted a full update of our existing systematic review.

PICOS

Population

- Nonpregnant adults with PTSD
  - Mixed age (adult and < 18) or pregnancy population were also included if the majority were adults or nonpregnant

Interventions

- Any cannabis preparations alone or in combination with any other intervention, by any method of administration (e.g., smoking, vaping, edibles). Cannabis preparations could include:
  - Marijuana
  - Hashish
  - Tincture
  - Hashish oil
  - Infusion
  - Plant extracts, including:
    - Epidiolex – an FDA-approved medication containing cannabidiol
    - Nabiximols – a nonsynthetic pharmaceutical product with a standard composition and dosage
  - FDA-approved synthesized, pharmaceutically prepared cannabinoids (dronabinol and nabilone)

Comparators

- Another listed intervention (head-to-head)
- Different dose or formulation
- Standard of care
- Placebo
- No cannabis use (observational studies only)

Table 1. Topic History and Search Dates

Document Type	Date Presented	Search Dates	Number of new studies (total overall studies)
Systematic Review Update #1	November 2021	October 2020 to 10/22/21	2 (7)
Original Systematic Review	March 2021	Inception to October 2020	5

Outcomes

Any of the following:

- Validated PTSD clinical interviews and symptom inventories, such as:
  - Clinician Administered PTSD Scale (CAPS)
  - PSTD Checklist (PCL)
  - PTSD Symptom Scale (PSS)
  - Posttraumatic Diagnostic Scale (PDS)
- Validated measures of mental health symptoms commonly associated with PTSD (e.g., mood, depression, anxiety)
- Validated measures of sleep quality (including nightmares, insomnia)
- Validated measures of quality of life
- Social functioning/disability/employment
- Utilization of health services
- Reduction in benzodiazepine use or dosage
- Several of the above outcomes may be either benefits or harms depending on whether the outcome increases or decreases (e.g., an increase in depression would be considered a harm, while a decrease would be a benefit). Other adverse events (AEs) of interest include:
  - Other substance use/substance use disorders
  - Psychosis
  - Study dropout to due to AEs
  - For harms not listed here, if there was a ≥ 10% difference between groups, we reported them

Study Designs

- Controlled clinical trials (randomized and nonrandomized) of ≥ 4 weeks follow-up
- Observational studies (prospective and retrospective cohort studies and case-control studies) adjusted for important confounders

Key Questions

This systematic review is an update of a 2017 review,[1] and as such, the research questions for this systematic review are the same as the original review. The questions were developed after a topic refinement process that included a preliminary review of published peer-reviewed literature, and consultation with internal partners, investigators, and stakeholders.

The research questions are as follows:

KQ1. What are the effects of cannabis on health outcomes and health care utilization for adults who have PTSD?

KQ2. Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?

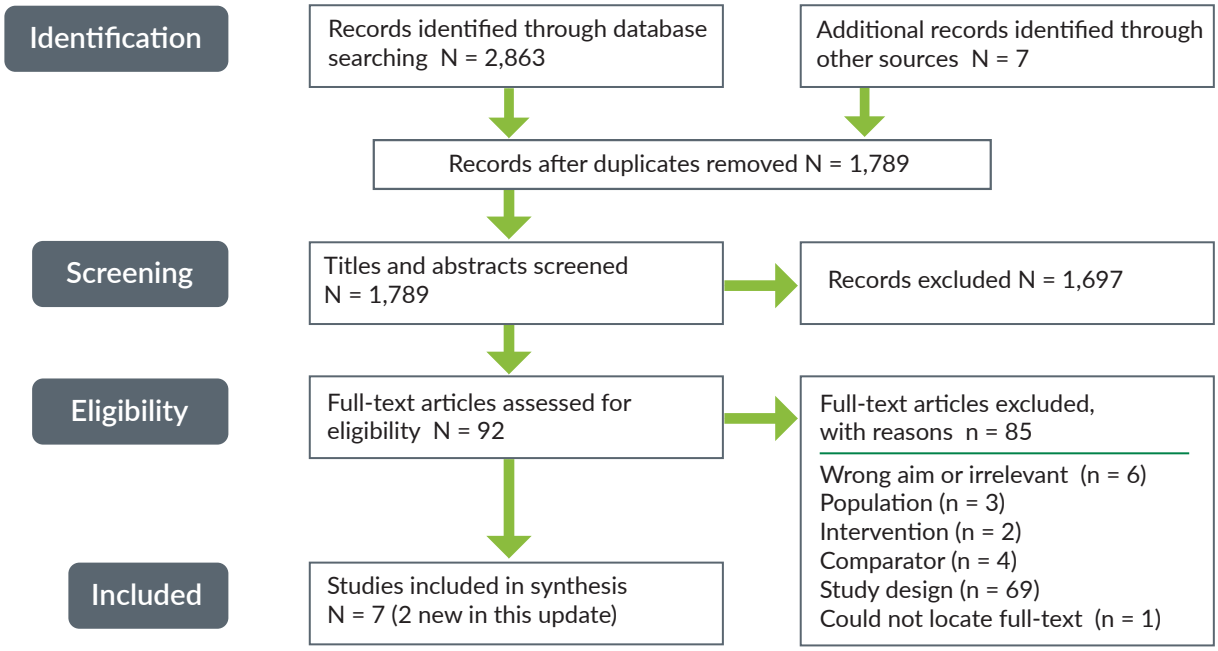
Methods

We searched multiple databases and grey literature sources from 2015 to October 22, 2021, to identify studies of cannabis use in participants with PTSD and published since the previous review's search dates. To update findings as new evidence emerges, we maintain this as a living systematic review using several approaches: 1) systematically identifying ongoing studies, and searching for the relevant publications, 2) periodically contacting experts to ask about new evidence, and 3) conducting surveillance searches of the literature.

The current version of this review includes studies identified through a search of ClinicalTrials.gov and contact with our expert panel conducted on November 19, 2021. We included studies (controlled clinical trials and observational studies using control groups) that assessed the effects of plant-based or FDA-approved synthesized cannabis preparations in nonpregnant adults with PTSD. Two reviewers independently screened all citations for inclusion, and disagreements were resolved by consensus or a third reviewer.

Data on study design, objectives, setting, population characteristics, subject inclusion

Figure 1. PRISMA Flow Diagram



and exclusion criteria, number of participants, duration of follow-up, the study and comparator interventions, important co-interventions, health outcomes, and harms from included studies were abstracted by 1 reviewer and confirmed by a second.

Two reviewers independently assessed the RoB of each study and disagreements were resolved through discussion. We summarized the primary literature by abstracting relevant data and qualitatively synthesizing the literature.

Two independent raters assigned select outcomes a summary judgment for the overall certainty of evidence (CoE) using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach,[15] with disagreements resolved by a third rater. We combined randomized and nonrandomized studies for our GRADE ratings and assessed 6 outcomes:

- Validated PTSD clinical interviews and symptom inventories (e.g., CAPS, PCL, PSS)
- Validated measures of mental health symptoms commonly associated with PTSD (e.g., mood, depression, anxiety)
- Validated measures of sleep quality
- Validated measures of quality of life
- Utilization of health services
- Social functioning/disability/employment

A full description of methods can be found in Appendix A.

Findings

We reviewed a total of 2,863 citations published since 2015, of which 92 qualified for full-text review. We included 7 studies evaluating the effects of cannabis use on symptoms of PTSD: 2 crossover randomized controlled trials (RCTs)[2,3] and 5 cohort studies.[4-8] Study size ranged from 10 to 2,276 participants. See Figure 1 for literature flow and Table 2 for study characteristics. The results are organized by outcome of interest. Detailed results can be found in Appendix B.

Table 2. Characteristics of Included Studies

Author, Year **N** **Year(s) of Study** **Follow-up**	**Setting Design** **Funding**	**Sample Description**	**Demographic Characteristics** *total pop.* **or** *EG vs CG*	**Risk of Bias**
Randomized Studies				
Bonn-Miller et al., 2021[3] N = 80 Year NR 10 weeks	US: Crossover RCT CDPHE and MAPS	Military Veterans with PTSD	90% male Age, mean (SD): 44.9 (13.8) 66% White Employed (full- or part-time): 29% Some college: 52.5% College graduate: 40%	Low
Jetly et al., 2015[2] N = 10 Year NR 4 months	Canada: Crossover RCT Funding NR	Active-duty military with PTSD	100% male Age, mean (SD): 43.6 (8.2) 100% White	High
Nonrandomized Studies				
Bonn-Miller, 2020[7] N = 150	US: prospective cohort CDPHE	Colorado residents with PTSD	69% vs 77% male Age, mean (SD): 44.36 (12.64) vs 57.49 (15.32) 69% White; 15% AA/Black; 5% AI/AN; 2% Multiracial; 9% Other	High
De Aquino et al., 2020[4] N = 1,413 1992-2011 4 months	US: VA retrospective cohort VHA	Veterans receiving intensive PTSD treatment, and with nonmedical opioid use	74.7% vs 67.0% male Age, mean (SD): 45.8 (10.1) vs 48.4 (9.2) 55.4% White; 27.7% AA/Black; 5.8% Latino Unemployed: 91.0% vs 88.8%	Moderate
Petersen et al., 2021[8] N = 340 2008-2016 12 sessions, min. 30 days	US: VA retrospective cohort NR	Random sample of Veterans aged 18 to 85 years with PTSD enrolled in intensive PTSD treatment	96.3% vs. 94.6% male; *P* = .77 Age, years (SD): 37.7 (15.1) vs. 39.2 (14.6); *P* = .15 White: 82.7% vs. 88.4% AA/Black: 16.0% vs. 7.3% Other: 1.2% vs. 4.2% *P* = .03 Comorbid SUD: 43.2% vs. 11.2%, P < .001	High

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Table 2. Characteristics of Included Studies (cont.)

Author, Year N Year(s) of Study Follow-up	Setting Design Funding	Sample Description	Demographic Characteristics *total pop.* **or** *EG vs CG*	Risk of Bias
Ruglass et al., 2017[6] N = 136 2006-2014 12 months[16]; 3 months[17]	US: retrospective cohort NIDA and NIAAA	Participants with co-occurring PTSD and SUDs who received CBT and Sertraline or placebo in 1 of 2 primary RCTs	47.8% male Age, mean (SD): 41.6 (9.38) vs 44 (9.18) 18.4% White; 55.1% AA/ Black; 15.4% Latino Education: 13.08 (1.88) vs 13.28 (2.52) years	High
Wilkinson et al., 2015[5] N = 2,276 1992-2011 4 months	US: VA retrospective cohort NIMH and VHA	Veterans receiving intensive PTSD treatment, excluding those with previous problematic drug or alcohol use	96.7% male Age, mean (SD): 51.7 (8.6) 72.7% White; 21.2% AA/ Black; 6.1% Other Education: 12.9 (1.9) years	Moderate

indicates new studies in this update

Abbreviations. AA: African American, AI: American Indian, AN: Alaska Native, CBT: cognitive behavioral therapy, CDPHE: Colorado Department of Public Health and Environment, CG: control group, EG: exposure group, MAPS: The Multidisciplinary Association for Psychedelic Studies, NIAAA: National Institute on Alcohol Abuse and Alcoholism, NIDA: National Institute on Drug Abuse, NIMH: National Institute of Mental Health, NR: not reported, PTSD: posttraumatic stress disorder, RCT: randomized controlled trial, SUD: substance use disorder, VA: Veterans Affairs, VHA: Veterans Health Administration.

Priority Outcomes

PTSD Symptoms

There was low CoE of no differences in PTSD symptom severity between cannabis users and nonusers from 1 RCT and 5 cohort studies (Table 3). The low-RoB crossover RCT by Bonn-Miller et al. compared 3 different smoked cannabis preparations (i.e., high THC, high CBD, and equivalent THC to CBD ratio) to placebo in Veterans. The authors found no difference in PTSD symptom reduction on either the CAPS-5 or the PCL-5 between any cannabis preparation group and placebo during a 3-week period (CAPS-5, $P = .15$; PCL-5, $P = .11$; Appendix B Table 1).[3] This trial also included a crossover phase after a 2-week washout, wherein participants were re-randomized to 1 of the 3 cannabis preparations for another 3 weeks without a placebo group. During this phase, the balanced THC to CBD ratio group experienced the greatest reduction in PTSD symptoms on both scales. We rated the RoB for this study as low (Table 1). Only the first phase with a placebo comparator was considered for the CoE.

Five retrospective cohort studies analyzing PTSD symptoms by cannabis use exposure (rather than treatment with cannabis) also contributed to the evidence. Two studies examined different subsets of participants from a large study of Veterans enrolled in intensive PTSD treatment programs in the VA between 1992 and 2011.[4,5] Another also examined Veterans in a VA single-site, intensive PTSD treatment program between 2008 and 2016.[8] A fourth was a study of Colorado

residents with PTSD,[7] and finally, there was a secondary analysis of 2 RCTs (Table 2).[6]

One of the cohort studies, conducted by Wilkinson et al.,[5] carried forward from the 2017 systematic review. The cohort consisted of 2,276 Veterans with PTSD and without problematic alcohol use or recent drug use other than cannabis. They were interviewed before entering PTSD treatment and 4 months after discharge. The cohort was analyzed by 4 groups defined as:

- "Never users" reported no cannabis use before admission or anytime during the study at follow-up
- "Continuing users" who reported cannabis use at both timepoints
- "Stoppers" who reported use at baseline, but no use at follow-up
- "Starters" who reported no baseline use but reported use 4 months after treatment

The continuing users and starters groups had significantly worse PTSD scores (using the Short-form Mississippi Scale [MISS] for PTSD) at follow-up than never-users and stoppers (P < .0001) after adjusting for multiple confounders. However, as noted by O'Neil et al.,[1] the absolute differences in scores were small (mean MISS score 36.64 for stoppers and 39.67 for starters, *P* < .01; Appendix Table B1).

The second cohort study analyzing a different subset of Veterans from the intensive PTSD treatment study at the VA was conducted by De Aquino et al.[4] They examined the subgroup of Veterans with PTSD and nonmedical opioid use (≥ 7 days in the past month; N = 1,413). The cohort was divided into those who had versus had not used cannabis ≥ 7 days in the preceding month. There was no difference between groups in change in PTSD severity from baseline to 4-month follow-up (Appendix Table B1).[4] The RoB for both of these studies was rated as moderate primarily due to group differences in baseline characteristics (Table 2).

A single VA site, retrospective cohort study (N = 340) of Veterans in intensive PTSD treatment was conducted by Petersen et al.[8] This study compared cannabis users identified by 1 or more of several different records (i.e. diagnosis of cannabis abuse or dependence, progress notes mention cannabis use, THC-positive urinary drug screen [UDS], or medical cannabis prescription according to non-VA medication list) with those who had no record of cannabis use. They found no difference in change in PCL-5 scores (5.7 [14.7] versus 6.0 [14.0]; *P* = .79) nor odds of treatment success defined as a 5-point or more improvement on the PCL-5 (aOR, 1.4 [95% CI, 0.81 to 2.5]) between cannabis users and nonusers (Appendix Table B1). We rated this study as high RoB because of imbalance in baseline characteristics and psychological treatment, as well as the possibility of misclassification of exposure status (Table 2).

The Colorado cohort study (N = 150) by Bonn-Miller et al.[7] followed cannabis users and nonusers for a year and found PTSD symptoms (as measured by the CAPS-5) improved to a greater extent among cannabis users than nonusers over 12 months (CAPS-5 PTSD symptom severity group by time interaction: -0.32 [95% CI, -0.59 to -0.05]; Appendix Table B1). However, the absolute difference in symptom severity scores was small and below suggested thresholds for clinically meaningful change.[18] Moreover, there were several methodologic issues with the study that temper confidence in conclusions, including the presence of important baseline differences in group characteristics, a high attrition rate, and the use of complete-case analysis (i.e. those who stopped using cannabis during the study period were not included in final analyses). Further, as the authors appropriately discuss, cannabis users had been using before enrollment and yet the

baseline symptom severity was similar between groups. It is challenging to know whether differences emerging during the study period were related to a true effect of the intervention, or rather to the effect of being observed (Table 2).

The final cohort study (N = 136) by Ruglass et al. was a secondary analysis of the results of two 12-week RCTs of cognitive behavioral therapy (CBT), 1 of which also included sertraline or placebo taken concomitantly for co-occurring PTSD and substance use disorders (SUD; Table 1).[6] The study found no correlation between cannabis use days measured by the Substance Use Inventory (SUI) at baseline and PTSD symptom severity measured by the CAPS at follow-up. Additionally, higher weekly cannabis use was associated with greater weekly PTSD symptom severity (as measured by the Modified PTSD Symptom Scale Self-Report [MPSS-SR]) early in treatment, but lower weekly severity later in treatment (Appendix Table B1). The RoB for this study was high due to differences in baseline characteristics, heterogeneity in study populations and interventions, missing data, and not accounting for all important potential confounders (Table 2).

PTSD-related Nightmares

We found very low CoE of improvement in PTSD-related nightmares with nabilone (a synthetic cannabinoid) from 1 RCT (Table 3). This trial by Jetly et al.[2] was very small (N = 10) and used a crossover design to test nabilone versus placebo for PTSD-related nightmares in Canadian men on active military duty. Nabilone titrated up to 3 mg per day or matching placebo were administered for 7 weeks, followed by a 2-week washout period and crossover to another 7-week treatment period. The study found a significantly greater reduction in both frequency and intensity of recurring and distressing dreams, as measured by CAPS, with nabilone compared to placebo (mean score change -3.6 [SD = 2.4] versus -1.0 [SD = 2.1], P = .03; Appendix Table B1). The study was rated high RoB due to insufficient information on randomization and allocation concealment, lack of reporting baseline differences by group, lack of appropriate statistical methods to account for the crossover design (i.e., conditional analyses), and not reporting results for each period separately.

Other Sleep-related Measures

There was very low CoE of no significant difference in sleep quality measures between cannabis users and nonusers from 2 RCTs and 1 cohort study. The Bonn-Miller et al. trial (moderate RoB) found no difference in change in insomnia severity with the Insomnia Severity Index (ISI) for any form of smoked cannabis compared with placebo (P = .40).[3] Jetly et al. (high RoB) found no difference in sleep quality or quantity with nabilone treatment versus placebo (CAPS difficulty falling and staying asleep items and sleep diary).[2] The cohort study by Bonn-Miller et al. also found no difference on numerous sleep quality-related measures, with the exception of number of awakenings, for which cannabis users experienced greater improvement (Table 3 and Appendix Table B1).[7]

Functional Status

There was very low CoE of no difference in functional status between those using cannabis and nonusers from 2 RCTs and 1 cohort study. The RCT by Bonn-Miller et al. (N = 80) found any strain of smoked cannabis was no different than placebo for change in psychosocial functioning on the Inventory of Psychosocial Functioning (IPF; P = .27).[3] The small (N = 10) and high-RoB RCT by Jetly et al. examined improvement in global functioning with nabilone compared with placebo as measured by the Clinical Global Impression of Change and found marginally significant difference (CGI-C; 1.9 ± 1.1 [i.e., much improved] versus 3.2 ± 1.2 [i.e., minimally improved], P = .05).[2] The cohort study by Bonn-Miller et al. found no difference in psychosocial functioning (measured by the IPF) between

exposed and unexposed groups (group by time interaction: 0 [95% CI, -0.02 to 0.02]; Appendix Table B1).[7]

Mental Health Symptoms

There was low CoE from the moderate-RoB Bonn-Miller et al. RCT that any preparation of smoked cannabis was no different than placebo for reduction in general depression (P = .18) or social anxiety (P = .58) as measured by the Inventory of Depression and Anxiety Symptoms (IDAS; Table 2 and Appendix Table B1).[3]

Table 3. Summary of Findings (GRADE)

Outcome Studies; Sample Size	Certainty of Evidence (CoE)	Relationship	Rationale for CoE rating
PTSD symptom severity 1 RCT[3]; N = 80 5 cohort studies[4-8]; N = 4,315	⊕⊕◯◯ Low	No difference: Cannabis was not associated with clinically significant improvement in symptom severity in the trial or cohort studies	Downgraded 1 level each for RoB and indirectness
PTSD-related nightmares 1 RCT[2]; N = 10	⊕◯◯◯ Very low	Nabilone significantly reduced frequency and intensity of recurring and distressing dreams	Downgraded 1 level each for RoB, imprecision, and indirectness
Sleep quality 2 RCTs[2,3]; N = 90 1 cohort study[7]; N = 150	⊕◯◯◯ Very low	No difference: No difference in insomnia, or sleep quality or quantity with cannabinoids compared to placebo in RCTs and no association with any sleep quality measures in the cohort study	Downgraded 1 level each for RoB, imprecision, and indirectness
Functional status 2 RCTs[2,3]; N = 90 1 cohort study[7]; N = 150	⊕◯◯◯ Very low	No difference: No difference in global functioning or psychosocial functioning in RCTs or cohort study	Downgraded 1 level each for RoB, imprecision, and indirectness
Mental health symptoms 1 RCT[3]; N = 80	⊕⊕◯◯ Low	No difference: Smoked cannabis was no different than placebo for reduction in general depression or social anxiety	Downgraded 1 level each for imprecision and indirectness
Quality of life	Not applicable	---	---
Utilization of health services	Not applicable	---	---

Abbreviations. CoE: Certainty of Evidence, GRADE: Grading of Recommendations, Assessment, Development, and Evaluation, PTSD: posttraumatic stress disorder, RCT: randomized controlled trial, RoB: risk of bias.

Other Outcomes

Other Substance Use

Three cohort studies examined some measures of other substance use by cannabis use groups. Wilkinson et al. administered the Addiction Severity Index (ASI). In general, those who started or continued to use cannabis during the study had higher alcohol and substance abuse scores than those who never used or quit. Specifically, they found cannabis starters had significantly more alcohol misuse than continuing users, never-users, and stoppers, while continuing users had significantly more alcohol misuse than stoppers. Continuing users and starters also had significantly more misuse of other substances than never-users and stoppers ($P < .01$ for paired comparisons).[5] De Aquino et al. also analyzed ASI substance use indices and other substance use measures and found no difference between veterans with PTSD who were using opioids and cannabis, and those who reported no cannabis use.[4] Finally, Ruglass et al. found baseline days of cannabis use were not a significant predictor of other substance use at the end of treatment ($P = .84$).[6]

Employment

Wilkinson et al. reported results of the ASI employment item at follow-up and found no significant differences in employment status between cannabis use groups ($P = .58$).[5]

Violent Behavior

Wilkinson et al. also examined a measure of violent behavior, a 4-item questionnaire from the National Vietnam Veterans Readjustment Study,[19] and found starters had significantly more violent behavior than continuing users, never-users, and stoppers at follow-up ($P < .0001$).[5]

Other Harms

Only the RCT by Bonn-Miller et al. reported between-group rates of other harms. One or more of the cannabis use groups had > 10% higher rates of dry mouth, back pain, dizziness, somnolence, irritability, and paranoia than the placebo group.[3] For details see Appendix Table B1.

Differences by Subgroups

None of the included studies evaluated subgroups.

Ongoing Studies

We identified 9 ongoing studies of cannabis for PTSD, including 8 RCTs (1 crossover), and 1 cohort study (Table 3). Sample sizes of the ongoing studies range from 6 to 325 participants. One study was recently completed, while most others are expected to finish within the next 1 to 4 years.

Table 4. Eligible Ongoing/Unpublished Studies of Cannabis for PTSD

Clinicaltrials.gov Identifier	Study Title	Study Design	Estimated Enrollment	Estimated Primary Completion Date
NCT02517424	Evaluating Safety and Efficacy of Cannabis in Participants with Chronic Posttraumatic Stress Disorder	Crossover RCT	6 (actual)	March 2019 (completed, not yet published)
NCT02874898	Short-term Exposure for PTSD (STEP)	Cohort	72	March 2022
NCT03248167	Cannabidiol as a Treatment for AUD Comorbid With PTSD	RCT	48	January 2022
NCT04448808	Treating Nightmares in Posttraumatic Stress Disorder With Dronabinol	RCT	176	May 2022

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Table 4. Eligible Ongoing/Unpublished Studies of Cannabis for PTSD (cont.)

NCT04550377	Cannabidiol for PTSD and TBI	RCT	120	May 2023
NCT03518801	Cannabidiol and Prolonged Exposure (CBD-PE)	RCT	136	September 2024
NCT04080427	Effects of Delta 9-tetrahydrocannabinol (THC) on Retention of Memory for Fear Extinction Learning in PTSD: R33 Study	RCT	100	December 2024
NCT04592159	Study of the Safety and Efficacy of Nabiximols Oromucosal Spray Versus Placebo in Patients With Posttraumatic Stress Disorder	RCT	325	March 2023
Not yet registered	THC in Veterans With PTSD[a20]	RCT	TBD	Not available

[a] *Identified by personal communication (Mark S. Kindy, PhD, email communication, November 20, 2021).*
Abbreviations. AUD: alcohol use disorder, CBD: cannabidiol, PTSD: posttraumatic stress disorder, RCT: randomized controlled trial.

Discussion

We identified 2 crossover RCTs (1 low and 1 high RoB) and 5 cohort studies (2 moderate and 3 high RoB) that provided evidence regarding cannabis use for PTSD. There was low CoE of no difference with cannabis for reduction in severity of PTSD symptoms, and very low CoE for improvement in intensity and frequency of disturbing dreams with nabilone. For all other sleep quality measures, there was very low CoE of no difference between cannabis users and nonusers. There was also low CoE that cannabis had no evidence of an effect on social anxiety or general depression and very low Coe of no difference in functional status with cannabis use. We did not identify any randomized or nonrandomized studies that evaluated quality of life, or utilization of health services.

Four of the included studies have been published since the 2017 review, and 2 of those, Petersen et al. and the Bonn-Miller et al. RCT, were in the past year since our previous version of the report, which highlights the overall low rate and volume of research being conducted and published on cannabis for PTSD.[4,7]

Limitations

The existing evidence base is significantly limited by study design and quality issues. We rated all but 1 of the included studies as moderate or high RoB. Cannabis use was self-reported or deduced from electronic health records in all observational studies with no measures of dose, compounds, or modes of administration. Additionally, the applicability of existing studies is limited by inclusion of dual-substance use, heavily male study populations, and inclusion of only Veterans also receiving intensive PTSD treatment and active military personnel. Only 2 studies included nonmilitary or nonveteran participants; one was restricted to residents of Colorado, while the other was in adults with both PTSD and SUDs receiving therapy. These factors limit the applicability to the larger US population that suffers from PTSD.

Conclusions

There was low certainty evidence cannabis use is not associated with differences in PTSD or mental health symptoms, and very low CoE it may improve PTSD-related nightmares but does not affect other measures of sleep quality or functional status. There continues to be a dearth of literature on the effects of cannabis use on PTSD, and the continued status of cannabis as a Schedule 1 substance likely contributes to this.

As cannabis continues to be decriminalized and legalized by states across the country, access will increase. Large, controlled trials are needed to establish evidence on the efficacy and harms of cannabis for PTSD, and studies should specify the cannabinoid compounds (e.g., THC, CBD) being evaluated. Several such studies are ongoing and expected to be completed in the next few years.

Applicability to Veteran populations

Most of the research in this field has been conducted in Veterans or active-duty military personnel. As such, the evidence base is highly applicable to these groups. However, overall, it is still unclear whether cannabis is an efficacious and safe intervention to manage PTSD symptoms in Veterans.

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Appendix A. Methods

Literature Search Strategies

We conducted a primary review of the literature by systematically searching, reviewing, and analyzing the scientific evidence as it pertained to the key questions. Search strategies were developed in consultation with a research librarian, and peer reviewed by a second research librarian using Peer Review of Electronic Search Strategies (PRESS) guidelines.[27] To identify relevant articles, we searched Ovid MEDLINE ALL, Embase.com, Ovid PsycINFO, PTSDpubs, Ovid EBM Reviews (Cochrane Central, CDSR), and grey literature sources. This updated search strategy was expanded to include updated MeSH and keyword terms, new FDA-approved formulations, and trialed medical marijuana dispensary products not searched in the 2017 review. Full search strategies available in the Supplement. We further consulted experts and reviewed the bibliographies of relevant articles to identify additional studies. Only English-language publications were included.

Study Selection

We included studies (controlled clinical trials and observational studies using control groups) that assessed the effects of plant-based cannabis preparations, whole-plant extracts (e.g., nabiximols), or FDA-approved synthesized pharmaceutically prepared cannabinoids (e.g., dronabinol, nabilone) in nonpregnant adults with PTSD. The full criteria for patient populations, interventions, comparators, outcomes, timing, settings, and study designs (PICOTS) are specified in Table A1. A minor modification to the original review criteria in this update was the inclusion of FDA-approved synthesized cannabinoids. The original review excluded these because these were covered in another review recently published at the time.[28] Given some time has passed, this review included those interventions.

Using these prespecified inclusion/exclusion criteria (Table A1), all citations were reviewed for potential relevance using DistillerSR (Evidence Partners, Ottawa, Canada). Two reviewers independently screened the title and abstract of each citation, and inclusion by both of those reviewers progressed the citation to full-text review. An initial calibration round was held in which 100 titles/abstracts were screened by all members of the review team, and concordance was discussed. At the full-text screening stage, 2 independent reviewers agreed on a final inclusion/exclusion decision for all articles; any disagreements were resolved through consensus or consultation with a third reviewer. Articles meeting eligibility criteria were included for data abstraction.

Table A1. PICOTS for Systematic Review of Cannabis for the Management of Symptoms of Posttraumatic Stress Disorder

Key Question	KQ1. What are the effects of cannabis on health outcomes and health care utilization for adults who have posttraumatic stress disorder (PTSD)? KQ2: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?	
	INCLUDE	**EXCLUDE**
Population	Nonpregnant adults with PTSD. Studies with mixed-age (adult and < 18) population may be included.	Majority of the study participants are either of the following: Younger than age 18 Adults who are pregnant No other exclusions
Intervention/ Exposure	Cannabis preparations, including marijuana, hashish, tincture, hashish oil, infusion, and plant extract (including Epidiolex – an FDA-approved medication containing cannabidiol; and nabiximols [brand-name: Sativex] – a nonsynthetic pharmaceutical product with a standard composition and dosage) or FDA-approved synthesized, pharmaceutically prepared cannabinoids (Dronabinol [brand-names: Marinol and Syndros], Nabilone [brand-name: Cesamet]), alone or in combination with other intervention(s) All methods of administration (e.g., smoking, vaping, edibles)	Other synthesized cannabinoids (e.g., synthetic marijuana, spice, K2)
Comparator	Any other intervention or a nonexposed control group	Studies with no comparison group

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Table A1. PICOTS for Systematic Review of Cannabis for the Management of Symptoms of Posttraumatic Stress Disorder (cont.)

Key Question	KQ1. What are the effects of cannabis on health outcomes and health care utilization for adults who have posttraumatic stress disorder (PTSD)? KQ2: Do the effects differ by patient subgroup, such as patient medical and mental health comorbidities?	
Outcomes effectiveness outcomes and specific adverse effects of interest	Validated PTSD clinical interviews and symptom inventories, such as: • Clinician Administered PTSD Scale (CAPS) • PSTD Checklist (PCL) • PTSD Symptom Scale (PSS) • Posttraumatic Diagnostic Scale (PDS), etc. • Validated measures of mental health symptoms commonly associated with PTSD (mood, depression, anxiety) • Validated measures of sleep quality (including nightmares, insomnia) • Validated measures of quality of life • Social functioning/disability/employment • Utilization of health services • Reduction in benzodiazepine use or dosage Harms: Several of the above outcomes may be either benefits or harms. Other adverse effects (AEs) of interest include: • Other substance use/substance use disorders • Psychosis • Study dropout to due to AEs • For harms not listed here, if there is a 10% or greater difference between groups, then we will report	Laboratory, blood, or imaging findings All other outcomes
Timing	Short- and long-term outcomes Four-week minimum for efficacy outcomes	All outcomes of interest reported for duration of < 4 weeks
Setting	Any setting. All countries.	---
Study design	Controlled clinical trials (randomized or nonrandomized), and methodologically rigorous observational studies with a comparison group (case control/cohort studies) that adjust for important confounders	Case studies, case series, and cross-sectional studies

Abbreviations: FDA: Food and Drug Administration; PICOTS: population, interventions, comparators, outcomes, timing, setting, study design; PTSD: posttraumatic stress disorder.

Data Abstraction

Data from published reports were abstracted into a customized database by 1 reviewer and confirmed by a second reviewer. From each study, we abstracted the following where available: study design, objectives, setting, population characteristics, subject inclusion and exclusion criteria, number of participants, duration of follow-up, the study and comparator interventions (including formulation, strength, etc.), important co-interventions, health outcomes, and harms.

Assessment of Risk of Bias of Individual Studies

Two reviewers independently assessed the risk of bias of each study using a tool developed by the Scottish Intercollegiate Guidelines Network (SIGN).[29,30] Disagreements were resolved through discussion. Each trial was given an overall summary assessment of low, moderate, or high risk of bias.

Data Synthesis

We summarized the primary literature by abstracting relevant data and qualitatively synthesizing the literature for each key question. We determined it was not feasible to complete a quantitative synthesis (i.e., meta-analysis) to estimate summary effects due to the low volume of relevant literature and conceptual homogeneity of the included studies.

Assessment of the Overall Quality of Evidence

We assigned select clinically- and patient-important outcomes a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[31] Two independent experienced researchers assigned ratings, with disagreements resolved by a third rater. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High**: Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
- **Moderate**: Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low**: Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are randomized controlled trials with serious limitations or nonrandomized studies without special strengths.
- **Very low**: Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable**: Researchers did not identify any eligible articles.

Appendix B. Full Evidence Table

Table B1. Findings from Eligible Studies (N = 7 Studies)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
Randomized studies			
Bonn-Miller et al., 20213 N = 80	*Stage 1* (3 wks) – 3 groups smoked cannabis (High THC, High CBD, THC+CBD) and 1 PBO 2-week washout *Stage 2* (3 wks) – 3 groups smoked cannabis (High THC, High CBD, THC+CBD) Baseline PTSD severity (PCL-5) mean (SD): 43.7 (15.0)	<u>CAPS-5 total severity mean change (SD)</u> *Stage 1* High THC: -15.2 (11.03); P < .05 High CBD: -8.4 (10.09); P < .05 THC + CBD: -8.5 (9.88); P < .05 Placebo: -13.1 (12.10); P < .05 between groups analysis of differences: F(3, 73) = 1.85, P = .15 *Stage 2* High THC: -3.3 (8.22); P ≥ .05 High CBD: -0.48 (9.07); P ≥ .05 THC + CBD: -11.8 (12.97); P < .05 No placebo between groups analysis of differences: F(2, 64) = 6.92, P = .002 <u>PCL-5 mean change (SD)</u> *Stage 1* High THC: -23.5 (16.5); P < .05 High CBD: -12.1 (16.2); P < .05 THC + CBD: -16.4 (9.1); P < .05 Placebo: -14.6 (15.6); P < .05 between groups analysis of differences: F(3, 71) = 2.10, P = .11 *Stage 2* High THC: -9.1 (11.0); P < .05 High CBD: -5.7 (9.3); P ≥ .05 THC + CBD: -16.4 (16.0); P < .05 between groups analysis of differences: F(2, 63) = 4.06, P = .02	<u>General depression, IDAS mean (SD)</u> *Stage 1* High THC: -16.1 (12.6); P < .05 High CBD: -11.4 (11.7); P < .05 THC + CBD: 8 -13.4 (9.1); P < .05 Placebo: -8.3 (11.2); P < .05 between groups analysis of differences: F(3, 72) = 1.67, P = .18 *Stage 2* High THC: -9.0 (11.1); P < .05 High CBD: -4.4 (12.4); P ≥ .05 THC + CBD: -13.4 (10.9); P < .05 between groups analysis of differences: F(2, 63) = 3.08, P = .05 <u>Social anxiety, IDAS mean (SD)</u> *Stage 1* High THC: -3.7 (4.2); P < .05 High CBD: -2.7 (2.7); P < .05 THC + CBD: -2.2 (2.0); P ≥ .05 Placebo: -2.4 (4.3); P ≥ .05 between groups analysis of differences: F(3, 72) = .67, P = .58 *Stage 2* High THC: -1.8 (3.1) High CBD: -0.04 (2.7) THC + CBD: -2.8 (3.9) between groups analysis of differences: F(2, 63) = 3.76, P = .03

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Table B1. Findings from Eligible Studies (N = 7 Studies) (cont.)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
Bonn-Miller et al., 20213 N = 80 (cont.)			<u>Insomnia, ISI mean (SD)</u> *Stage 1* High THC: -8.8 (5.20); P < .05 High CBD: -5.9 (6.50); P < .05 THC + CBD: -6.6 (5.18); P < .05 Placebo: -6.1 (5.70); P < .05 between groups analysis of differences: F(3, 71) = 1.00, P = .40 *Stage 2* High THC: -4.2 (5.45); P < .05 High CBD: -3.9 (5.68); P ≥ .05 THC + CBD: -5.5 (5.66); P < .05 between groups analysis of differences: F(2, 63) = .46, P = .63 <u>Psychosocial functioning, IPF mean (SD)</u> *Stage 1* High THC: 1.2 (11.9); P ≥ .05 High CBD: -1.2 (5.5); P ≥ .05 THC + CBD: 4.1 (8.5); P ≥ .05 Placebo: -0.2 (6.7); P ≥ .05 between groups analysis of differences: F(3, 72) = 1.34, P = .27 *Stage 2* High THC: 0.59 (7.0); P ≥ .05 High CBD: 0.28 (4.9); P ≥ .05 THC + CBD: 1.2 (8.2); P ≥ .05 between groups analysis of differences: F(2, 63) = .09, P = .91

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Table B1. Findings from Eligible Studies (N = 7 Studies) (cont.)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
Bonn-Miller et al., 20213 N = 80 (cont.)			<u>Harms with > 10% difference in rate of occurrence between groups</u> *Stage 1* High THC vs. High CBD vs. THC+CBD vs. PBO (each group N = 20) Dry mouth: 15% vs. 5% vs. 0% vs. 0% Nausea: 10% vs. 0% vs. 30% vs. 5% Upper respiratory tract infection: 10% vs. 5% vs. 5% vs. 15% Back pain: 10% vs. 0% vs. 5% vs. 0% Dizziness: 10% vs. 0% vs. 15% vs. 0% Headache: 15% vs. 5% vs. 20% vs. 25% Somnolence: 15% vs. 0% vs. 0% vs. 0% Irritability: 10% vs. 5% vs. 5% vs. 0% Paranoia: 5% vs. 0% vs. 25% vs. 0% Throat irritation: 5% vs. 20% vs. 15% vs. 30% *Stage 2* High THC (N=29) vs. High CBD (N = 27) vs. THC+CBD (N = 18) Nausea: 10.3% vs. 0% vs. 13.2% Heat exhaustion: 0% vs. 0% vs. 11.1% Irritability: 3.4% vs. 3.7% vs. 16.7% Cough: 6.9% vs. 7.4% vs. 25.9%

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Table B1. Findings from Eligible Studies (N = 7 Studies) (cont.)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
Jetly et al., 2015[2] N = 10	Group 1 — Period 1 nabilone (NAB) up to 3 mg; Period 2 placebo (PBO) Group 2 — Period 1 placebo (PBO); Period 2 nabilone (NAB) up to 3 mg 7 weeks each period with 2-week washout between Baseline PTSD severity (Global Impression of Severity of PTSD): 3.3 (0.9)	Nabilone vs. placebo Mean change (SD) PTSD-related nightmares: CAPS recurring and distressing dream items (frequency + intensity) -3.6 (2.4) vs. -1.0 (2.1); *P* = .03[a] Frequency item −1.9 (1.3) vs. −0.4 (1.4); *P* = .05[a] Intensity item −1.7 (1.3) vs. −0.6 (1.1); *P* = .06[a]	Nabilone vs. placebo Mean (SD) Functional status: Impression of change (CGI-C)[b] 1.9 (1.1) vs. 3.2 (1.2); *P* = .05[a] Sleep: Difficulty falling and staying asleep (CAPS items) No difference (scores NR) Sleep quantity, hours (sleep diary) 7.6 (1.9) vs. 7.4 (2.0); *P* = .97[a]

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Table B1. Findings from Eligible Studies (N = 7 Studies) (cont.)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
Nonrandomized studies			
Bonn-Miller, 2020[7] N = 150	Self-reported cannabis use 1+ times/week vs. no use in preceding 6 months Baseline PTSD severity (CAPS-5 total mean score [SD]): 36.88 (8.52) vs. 36.33 (8.46); P = .69	Exposure group vs. control Group by time interaction CAPS-5 PTSD symptom severity -0.32 (95% CI, -0.59 to -0.05)	Exposure group vs. control Group by time interaction Functional status: Psychosocial functioning (IPF total) 0 (95% CI, -0.02 to 0.02) Sleep: Sleep quality (PSQI total) -0.01 (95% CI, -0.12 to 0.10) Insomnia (ISI total) -0.12 (95% CI, -0.27 to 0.03) Sleep-onset latency, min 0.30 (95% CI, -0.68 to 1.28) Sleep efficiency, % 0 (95% CI, -0.26 to 0.27) Wake after sleep onset, min -0.38 (95% CI, -1.07 to 0.31) Number of awakenings 0.73 (95% CI, 0.13 to 1.33)

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Table B1. Findings from Eligible Studies (N = 7 Studies) (cont.)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
De Aquino et al., 2020[4] N = 1,413	Self-reported history of ≥ 7 days of concurrent non-medical opioid and cannabis use over the 30 preceding days (n = 428) vs. ≥ 7 days of nonmedical opioid use, but no cannabis use over the 30 preceding days (n = 985). Concomitant treatment: all participants were receiving intensive PTSD treatment. Baseline PTSD Symptom Severity (Combined MISS SF and VA's NEPEC PTSD assessment tool;32 mean [SD]): Exposure group 3.7 (0.4) vs. control group 3.6 (0.4)	Exposure group vs. control Mean (SD) Change in PTSD symptom scores at 4 months: Total PTSD symptom score −0.36 (0.56) vs. −0.26 (0.52); P = .03 Numbness −0.23 (0.58) vs. −0.14 (0.59); P = .03 Arousal −0.40 (0.6) vs. -0.34 (0.6); P = .15 Reexperiencing −0.34 (0.78) vs. −0.26 (0.77); P = .07 Avoidance −0.26 (1.1) vs. −0.25 (1.1); P = .83 Suicidal thoughts −0.48 (1.1) vs. −0.38 (1.0); P = .04 Irritability −0.36 (1.1) vs. −0.37 (1.1); P = .90 Violent behavior −0.99 (1.6) vs. −1.02 (1.5); P = .75	Exposure group vs. control Mean (SD) Status 4 months after the program: Change in ASI score (alcohol) −0.20 (0.38) v. −0.20 (0.30); P = .99 Change in ASI score (drug) −0.23 (0.23) vs −0.24 (0.17); P = .91 Index of substance use days (0–150) 11.3 (22.1) vs. 7.9 (17.5); P = .07 Number of different substances used 0.79 (1.3) vs. 0.58 (0.9); P = .08 Number of days of ≥ 3 drinks (past 30 days) 2.18 (6.97) vs. 2.0 (5.2); P = .69 Number of days of nonmedical opioid use (past 30 days) 3.13 (4.6) vs. 3.62 (5.7); P = .48 Number of days of nonmedical sedative use (past 30 days) 0.76 (10.2) vs. 1.42 (9.21); P = .11 Number of days of cocaine use (past 30 days) 0.71 (4.62) vs. 4.88 (0.62); P = .73

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Table B1. Findings from Eligible Studies (N = 7 Studies) (cont.)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
De Aquino et al., 2020[4] N = 1,413 (cont.)			Number of days of nonmedical amphetamine use (past 30 days) 0.09 (2.1) vs. 0.14 (1.3); P = .70 Number of days of nonmedical cannabis use (past 30 days) 1.63 (8.3) vs. 1.49 (3.2); *P* = .88
Petersen et al., 2021[8] N = 340	Any use: diagnosis of cannabis abuse or dependence, THC-positive UDS, documentation of cannabis use in progress notes, or non-VA medication list reporting medical cannabis prescription while admitted to the program vs. no cannabis use (none of the above documentation of use) Concomitant treatment: Intensive outpatient PTSD treatment including evidence-based therapy (CBT, CBT & MET, PE, supportive psychotherapy, or unspecified EBT) Baseline PTSD severity (PCL-5), mean (SD): 64.0 (9.8) vs. 61.6 (11.2), *P* = .07	Change in PCL, mean (SD): 5.7 (14.7) vs. 6.0 (14.0); *P* = .79 Treatment success[c]: 51.9% vs. 51.4%; *P* = .94 Cannabis use effect on odds of treatment success: aOR, 1.4 (95% CI, 0.81 to 2.5) Controlled for: antidepressant use and other SUDs	NR

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Table B1. Findings from Eligible Studies (N = 7 Studies) (cont.)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
Ruglass et al., 2017[6] N = 136	Self-reported cannabis use within 7 days of baseline assessment for the clinical trial (n = 32) vs. no cannabis use within 7 days of baseline (n = 104) Concomitant treatment: CBT, or CBT + Sertraline, or CBT + Placebo - aimed at treating both PTSD and SUD Baseline PTSD severity: NR	Baseline days of cannabis use were not a significant predictor of PTSD symptom severity at the end of treatment (*P* = .30). Higher weekly cannabis use was associated with greater weekly PTSD symptom severity early in treatment but lower weekly PTSD symptom severity later in treatment.	Baseline days of cannabis use were not a significant predictor of substance use at the end of treatment (*P* = .84).

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Table B1. Findings from Eligible Studies (N = 7 Studies) (cont.)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
Wilkinson et al. 2015[5] N = 2,276	Self-reported cannabis use during 4-month follow-up: Never-users: 850 Stoppers: 299[d] Continuing users: 296[e] Starters: 831[f] Concomitant treatment: all participants were receiving intensive PTSD treatment. Baseline PTSD Symptom Severity (MISS SF; mean [SD]): Stoppers: 39.87 (5.40) Continuing users: 39.73 (5.59) Starters: 40.20 (5.72) Never users: 39.63 (6.00) *P* = .23	MISS (SF) Scores, LS Mean (SE)g: Stoppers: 36.64 (0.39) Continuing users: 38.92 (0.38) Starters: 39.67 (0.23) Never users: 37.71 (0.23) *P* < .0001 Effect of starting cannabis use (compared to never using) on PTSD symptomsh SMD: +0.34 Effect of stopping SMD: −0.18 Multivariate regression results Change in days of marijuana used and change in[h]: PTSD symptoms (β = 0.17, t = 4.08, *P* < .0001)	Violent behavior 4-item questionnaire from the National Vietnam Veterans Readjustment Study[19] (LS mean [SE]):[g] Stoppers: 0.76 (0.07) Continuing users: 0.93 (0.07) Starters: 1.25 (0.04) Never users: 0.87 (0.04) *P* < .0001 Alcohol abuse ASI Alcohol Index (LS mean [SE])[g]: Stoppers: 0.08 (0.01) Continuing users: 0.13 (0.01) Starters: 0.23 (0.01) Never users: 0.10 (0.01) Drug abuse ASI Index (LS mean [SE])[g]: Stoppers: 0.03 (0.01) Continuing users: 0.13 (0.01) Starters: 0.13 (0.003) Never users: 0.04 (0.003) *P* < .0001

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Table B1. Findings from Eligible Studies (N = 7 Studies) (cont.)

Study N	Cannabis Use and Comparators Baseline PTSD Symptom Severity	Primary Findings	Other Findings
			Employment status ASI Index (LS mean [SE])[g]: Stoppers: 0.58 (0.01) Continuing users: 0.59 (0.01) Starters: 0.58 (0.01) Never users: 0.58 (0.01) *P* = .58 Multivariate regression results Change in days of marijuana used and change in: severity of violent behavior (β = 0.10, t = 2.79, *P* = .005); ASI alcohol index (β = 0.24, t = 5.60, *P* < 0.0001); ASI drug abuse index (β = 0.65, t = 21.62, *P* < .0001).[h]

[a] P < .01 considered significant; [b] 1 = very much improved and 7 = very much worse; [c] Success means ≥ 5-point decrease in PCL; [d] Used cannabis before but not after admission; [e] Used cannabis at admission and continued using; [f] Did not use cannabis before admission but started afterward; [g] Co-varying for marital status; age; race; history of incarceration; waiting list status; psychosis; chronic medical problems; war zone service; length of stay; expulsion from treatment; and baseline measures of violence, PTSD, drug and alcohol abuse, and employment; [h] Adjusted for: age, race, marital status, War Zone Service, drug and alcohol abuse, chronic medical problems; employment status at admission, violence at admission, incarceration history, willing to attend reunion, program length of stay, program expulsion, and waiting list status. Abbreviations. ASI: Addiction Severity Index, CBT: cognitive behavioral therapy, CGI-C: Clinical Global Impression of Change, EBP: evidence-based psychotherapy, IDAS: Inventory of Depression and Anxiety Symptoms, IPF: Inventory of Psychosocial Functioning, ISI: Insomnia Severity Index, LS: least squares, MET: motivational enhancement therapy, MISS: Mississippi Scale for PTSD, NAB: nabilone, NEPEC: Northeast Program Evaluation Center, PBO: placebo, PCL: PTSD checklist, PE: prolonged exposure therapy, PTSD: posttraumatic stress disorder, PSQI: Pittsburgh Sleep Quality Index, SD: standard deviation, SE: standard error, SF: short form, SMD: standard mean difference, SUD: substance use disorder, VA: Veterans Affairs.

Appendix C. Bibliography of Included Studies

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