STLM

Systematically Testing the Evidence on Marijuana

Cannabis for the Management of Symptoms of PTSD

A Living Systematic Review

March 2021

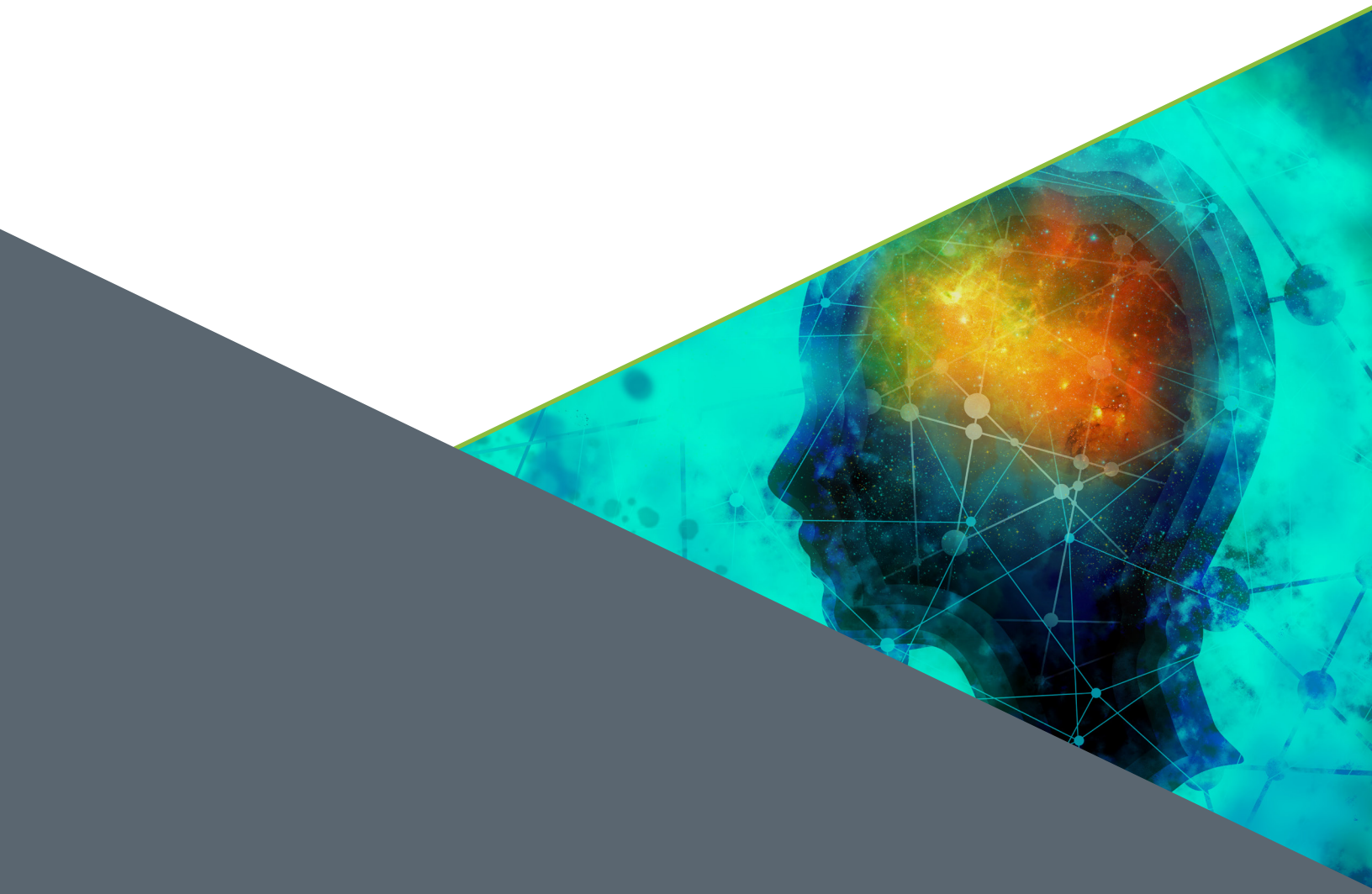

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Table of Contents

Executive Summary 2
Background 4
PICOS 4
Key Questions 5
Methods 5
Findings 6
Discussion 13
References 14
Appendix A. Methods 17
Appendix B. Full Evidence Table 21
Appendix C. Bibliography of Included Studies 27

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). A 2017 systematic review assessed the benefits and harms of plant-based cannabis use in individuals with PTSD and identified a dearth of evidence. This review seeks to identify and incorporate new evidence 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 one reviewer and confirmed by a second. Two reviewers independently assessed the risk of bias (ROB) of each study and the overall quality of evidence (QoE) 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 5 eligible studies, 2 of which were included in the 2017 review. One was a crossover randomized controlled trial (RCT)[1] and 4 were retrospective cohort studies.[2-5] We rated the RCT as having high ROB. We rated 2 of the included cohort studies as having moderate ROB and 2 as having high ROB. The RCT was conducted in Canada and cohort studies were conducted in the US in largely Veteran Affairs (VA) populations. We also identified 8 ongoing studies (7 trials and 1 cohort study).

Effectiveness and Harms

- One very small (N = 10), high-ROB crossover RCT found significant improvement in PTSD-related nightmares and marginally significant benefits in functional status 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 QoE).
- Four moderate or high ROB cohort studies (N range = 136 to 2,276) found no difference in PTSD symptoms by cannabis use groups (very low QoE).
- No studies were identified that analyzed other mental health symptoms, quality of life, or utilization of health services.

Differences by Subgroups

- None of the included studies evaluated subgroups.

Conclusions

Although we identified additional studies in this update, it remains uncertain whether cannabis improves symptoms associated with PTSD. One high-ROB cross-over trial found nabilone was associated with benefits in patients with PTSD, but the trial included only 10 participants, and cohort studies have largely found cannabis is not associated with benefits in patients with PTSD. 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 7 ongoing trials assessing effects of cannabis on various aspects of PTSD that should be completed over the next several years.

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.[6] From 2002 to 2017, the percentage of Americans aged 12 years and older who reported past-month cannabis use rose significantly from 6.2% to 9.6%.[6] As of March 2021, 36 states and the District of Columbia (DC) have legalized the medical use of cannabis for adults, and 13 states and DC have legalized recreational use.[7]

Cannabis has been 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.[7] 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 cannabis for medical use.[8-10] 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.[11]

This review seeks to incorporate new evidence to address the benefits and harms of cannabis use for PTSD.

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)

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 non-randomized) 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 was conceived as an update of a 2017 review. As such, the research questions for this systematic review are the same as the original review. The questions were originally 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 13, 2020, to identify studies of cannabis use in participants with PTSD that have been published since the previous review's search dates. In order to update findings as new evidence emerges, we are maintaining 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 our ongoing studies database and contact with our expert panel conducted on February 4, 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 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 one 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 quality of evidence (QoE) using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, with disagreements resolved by a third rater. We applied GRADE ratings by study design (randomized and non-randomized studies) and assessed 6 outcomes:

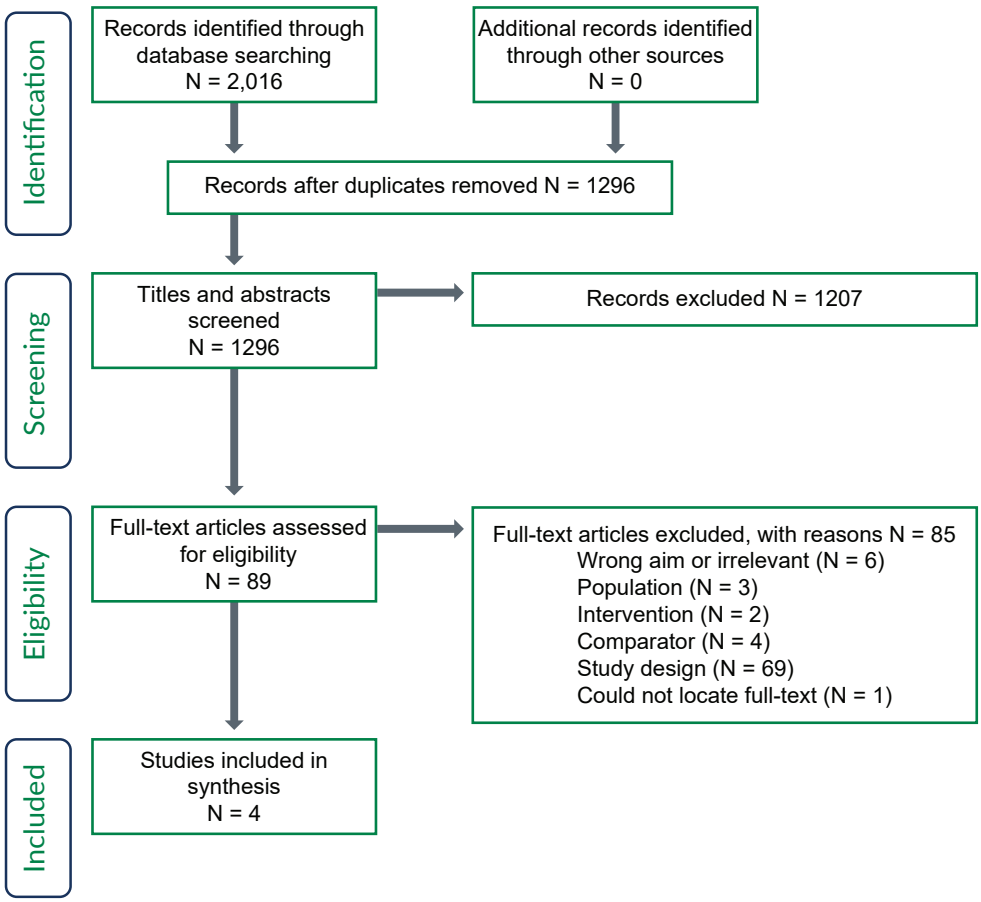
- Validated PTSD clinical interviews and symptom inventories (e.g., CAPS, PCL, PSS)
- Validated measures of mental health symptoms commonly associated with PTSD (e.g., mood, depression, anxiety)
- Validated measures of sleep quality
- Validated measures of quality of life
- Utilization of health services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

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

Findings

We reviewed a total of 1,296 citations published since 2015, of which 89 qualified for full-text review. We included 4 studies evaluating the effects of cannabis use on symptoms of PTSD: 1 crossover randomized controlled trial (RCT)[1] and 4 cohort studies.[2-5] Study size ranged from 10 to 2,276 participants. See Figure 1 for literature flow and Table 1 for study characteristics. The results are organized by outcome of interest. Detailed results can be found in Appendix B.

Figure 1. PRISMA Flow Diagram



Priority Outcomes

PTSD-related Nightmares

We found very low QoE of improvement in PTSD-related nightmares with nabilone (a synthetic cannabinoid) from 1 RCT (Table 2). This trial by Jetly et al.[1] 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.

Table 1. Characteristics of Included Studies

Author, Year N Year(s) of Study Follow-up	Setting Design Funding	Sample Description	Demographic Characteristics Age (SD) Total Pop. or EG vs. CG	Risk of Bias
Randomized Studies				
Jetly et al., 2015[1] N = 10 Year NR 4 months	Canada: Crossover RCT NR	Active-duty military with PTSD	100% male Age: 43.6 (8.2) 100% White	High
Nonrandomized Studies				
Bonn-Miller, 2020[5] N = 150	US: prospective cohort CDPHE	Colorado residents with PTSD	69% vs. 77% male Age: 44.36 (12.64) vs. 57.49 (15.32) 69% White; 15% AA/Black; 5% AI/AN; 2% multiracial; 9% other	High

Author, Year N Year(s) of Study Follow-up	Setting Design Funding	Sample Description	Demographic Characteristics Age (SD) Total Pop. or EG vs. CG	Risk of Bias
De Aquino et al., 2020[2] N = 1,413 1992-2011 4 months	US: VA retrospective cohort VHA	Veterans receiving intensive PTSD treatment, and with non-medical opioid use.	74.7% vs. 67.0% male Age: 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
Ruglass et al., 2017[4] N = 136 2006-2014 12 months[12]; 3 months[13]	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: 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[3] N = 2,276 1992-2011 4 months	US: VA retrospective cohort NIMH and VHA	Veterans receiving intensive PTSD treatment, excluding those with previous drug or alcohol use.	96.7% male Age: 51.7 (8.6) 72.7% White; 21.2% AA/Black; 6.1% other Education: 12.9 (1.9) years	Moderate

Abbreviations. CBT: cognitive behavioral therapy; CDPHE: Colorado Department of Public Health and Environment; CG: control group; EG: exposure group; 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; SD: standard deviation; SUD: substance use disorder; VA: Veterans Affairs; VHA: Veterans Health Administration.

PTSD Symptoms

The remaining eligible studies we identified were retrospective cohort studies analyzing PTSD symptoms by cannabis use exposure (rather than treatment with cannabis). There was very low QoE of no difference in PTSD symptoms between cannabis users and non-users from these studies. 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.[2,3] The third cohort study was a secondary analysis of 2 RCTs (Table 1).[4]

One of the 3 cohort studies, conducted by Wilkinson et al.,[3] was carried forward from the previous 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.
- After adjusting for multiple confounders, 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). However, as noted by O'Neil et al.,[11] 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, which analyzed a different subset of Veterans from the VA intensive PTSD treatment study, was conducted by De Aquino et al.[2] They examined the subgroup of Veterans with PTSD and non-medical 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).[2] The ROB for both of these studies was moderate primarily due to group differences in baseline characteristics (Table 1).

The third 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).[4] 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 1).

A final cohort study (N = 150) by Bonn-Miller et al.[5] followed cannabis users and non-users for a year and found that PTSD symptoms (as measured by the CAPS-5) improved to a greater extent among cannabis users than non-users 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.[14] 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.. 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; thus, it is challenging to know whether or not differences that emerged during the study period were related to a true effect of the intervention, or rather to the effect of being observed (Table 1).

Other Sleep-related Measures

There was very low QoE of no significant difference in sleep quality (or quantity) with nabilone treatment from the RCT by Jetly et al. (CAPS difficulty falling and staying asleep items and sleep diary; Table 1 and Appendix Table B1).[1]

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.[5]

Functional Status

There was very low QoE of a marginally significant difference in functional status with nabilone treatment from randomized studies. The RCT by Jetly et al. examined improvement in global functioning with nabilone compared to placebo as measured by the Clinical Global Impression of Change (CGI-C; 1.9 ± 1.1 [i.e., much improved] versus 3.2 ± 1.2 [i.e., minimally improved], P = .05; Table 1 and Appendix Table B1).[1]

The cohort study by Bonn-Miller et al. found no difference in psychosocial functioning (measured by the Inventory of Psychosocial Functioning [IPF]) between exposed and unexposed groups (Group by time interaction: 0 [95% CI, -0.02 to 0.02] ; Appendix Table B1).[5]

Other Outcomes

Other Substance Use

The 3 cohort studies all 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).[3] 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.[2] 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).[4]

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).[3]

Violent Behavior

Wilkinson et al. also examined a measure of violent behavior, a 4-item questionnaire from the

National Vietnam Veterans Readjustment Study,[15] and found starters had significantly more violent behavior than continuing users, never-users, and stoppers at follow-up ($P < .0001$).[3]

Differences by Subgroups

None of the included studies evaluated subgroups.

Table 2. Summary of Findings (GRADE)

Outcome Studies; Sample Size	Quality of the Evidence	Relationship	Rationale
Randomized Studies			
PTSD-related nightmares 1 RCT[1]; N = 10	⊕○○○ Very low	Nabilone significantly reduced frequency and intensity of recurring and distressing dreams	Downgraded 1 level each for ROB, imprecision, indirectness, and unclear consistency
Sleep quality 1 RCT[1]; N = 10	⊕○○○ Very low	No difference	Downgraded 1 level each for ROB, imprecision, indirectness, and unclear consistency
Functional status 1 RCT[1]; N = 10	⊕○○○ Very low	Nabilone showed a marginally significant (P = .05) improvement in global functioning	Downgraded 1 level each for ROB, imprecision, indirectness, and unclear consistency
Mental health symptoms	Not applicable	---	---
Quality of life	Not applicable	---	---
Utilization of health services	Not applicable	---	---
Non-Randomized Studies			
PTSD symptom severity 4 cohort studies[2-5]; N = 3,975	⊕○○○ Very low	No difference: cannabis use did not affect PTSD symptom severity	Downgraded 1 level each for ROB, inconsistency and indirectness
Sleep quality 1 cohort study[5]; N = 150	⊕○○○ Very low	No difference	Downgraded 1 level each for ROB and unclear consistency
Functional status 1 cohort study[5]; N = 150	⊕○○○ Very low	No difference	Downgraded 1 level each for ROB and unclear consistency

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

Ongoing Studies

We identified 8 ongoing studies of cannabis for PTSD, including 7 RCTs (2 crossovers), and 1 cohort study (Table 3). Sample sizes of the ongoing studies range from 6 to 176 participants. Two studies were recently completed, while the others are expected to finish within the next 3 years.

Table 3. Eligible Ongoing/Unpublished Studies of Cannabis for PTSD

Clinicaltrials.gov Identifier	Study Title	Study Design	Estimated Enrollment	Estimated Primary Completion Date
NCT02759185	Study of Four Different Potencies of Smoked Marijuana in 76 Veterans with PTSD (WeCan study)	Crossover RCT	80 (actual)	January 2019 (completed, not yet published)
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	Cohort	72	March 2021
NCT03248167	Cannabidiol as a Treatment for AUD Comorbid With PTSD	RCT	48	August 2021
NCT04448808	Treating Nightmares in Posttraumatic Stress Disorder with Dronabinol	RCT	176	May 2022
NCT04550377	Cannabidiol for PTSD and TBI	RCT	120	March 2023
NCT03518801	Cannabidiol and Prolonged Exposure (CBD-PE)	RCT	136	September 2023
NCT04080427	Effects of Delta9-tetrahydrocannabinol (THC) on Retention of Memory for Fear Extinction Learning in PTSD: R33 Study	RCT	100	December 2023

Abbreviations. AUD: alcohol use disorder, CBD: cannabidiol, PTSD: posttraumatic stress disorder, RCT: randomized controlled trial

Discussion

We identified 1 small, high-ROB, crossover RCT that found significant improvements in intensity and frequency of disturbing dreams and marginal benefits in functional status with nabilone compared to placebo in Canadian military personnel with PTSD. We also included 4 retrospective cohort studies (moderate to high ROB) evaluating cannabis use on PTSD symptoms, which found mixed results. These studies did not provide sufficient data to determine if cannabis use had an effect on symptoms of PTSD compared to non-use. We did not identify any randomized or nonrandomized studies that evaluated mental health symptoms, quality of life, or utilization of health services.

Only the studies by Bonn-Miller et al. and De Aquino et al. were published since the previous systematic review, which highlights the dearth of evidence and rate of research being conducted and published on cannabis and PTSD.[2,5] The crossover RCT by Jetly et al., which we included in this update, was not included in the previous systematic review because the authors had excluded synthetic cannabinoids, instead identifying those studies through another systematic review recently published at the time.[16] Conversely, we did not include 1 study included by the previous review authors because, despite being a cohort study, the reported data were cross-sectional in nature.[17]

The existing evidence base is significantly limited by study design and quality issues. Cannabis use was self-reported 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. Although these studies will be more generalizable to a VA population, these factors limit the applicability to a larger US population that suffers from PTSD.

Other recent systematic reviews on this topic have included observational studies without comparison groups and open-label studies.[18,19] This review sought to identify only higher tier evidence by excluding these types of publications. There continues to be a dearth of literature on the effects of cannabis use on PTSD. Large controlled trials are needed to establish evidence of the efficacy and harms of cannabis for PTSD, and studies should specify the cannabinoid compounds (e.g., THC, CBD) being evaluated. Encouragingly, one such study, the WeCan study, was recently completed and results are pending,[20] and several others are ongoing and expected to be completed in the next few years.

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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.[21] 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 they were covered in another review that had been recently published at the time.[22] Given that some time has passed, this review included those interventions.

Using these pre-specified 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.

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).[23,24] 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.

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 non-exposed control group	Studies with no comparison group

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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 non-randomized), 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

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).[25]

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 = 4 Studies)

Study N	Cannabis Use and Comparators Baseline PTSD symptom severity	Primary Findings	Other Findings
Randomized studies			
Jetly et al., 2015[1] 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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Study N	Cannabis Use and Comparators Baseline PTSD symptom severity	Primary Findings	Other Findings
Nonrandomized studies			
Bonn-Miller, 2020[5] 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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Study N	Cannabis Use and Comparators Baseline PTSD symptom severity	Primary Findings	Other Findings
Nonrandomized studies			
De Aquino et al., 2020[2] 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 non-medical 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;[26] 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 Non-medical Opioid Use (past 30 days) 3.13 (4.6) vs. 3.62 (5.7); *P* = .48 Number of Days of Non-medical 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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Study N	Cannabis Use and Comparators Baseline PTSD symptom severity	Primary Findings	Other Findings
Nonrandomized studies			
De Aquino et al., 2020[2] N = 1,413 *(continued)*			Number of Days of Non-medical Amphetamine Use (past 30 days) 0.09 (2.1) vs. 0.14 (1.3); *P* = .70 Number of Days of Non-medical Cannabis Use (past 30 days) 1.63 (8.3) vs. 1.49 (3.2); *P* = .88
Ruglass et al., 2017[4] 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 nd 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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Study N	Cannabis Use and Comparators Baseline PTSD symptom severity	Primary Findings	Other Findings
Nonrandomized studies			
Wilkinson et al., 2015[3] N = 2,276	Self-reported cannabis use during 4-month follow-up: Never-users: 850 Stoppers: 299[c] Continuing users: 296[d] Starters: 831[e] Concomitant treatment: all participants were receiving intensive PTSD treatment. <u>Baseline PTSD Symptom Severity (MISS SF; mean [SD]):</u> Stoppers: 39.87 (5.40) Continuing users: 39.73 (5.59) Starters: 40.20 (5.72) Never users: 39.63 (6.00) *P* = .23	<u>MISS (SF) Scores, LS Mean (SE)[f]:</u> Stoppers: 36.64 (0.39) Continuing users: 38.92 (0.38) Starters: 39.67 (0.23) Never users: 37.71 (0.23) *P* < .0001 <u>Effect of starting cannabis use (compared to never using) on PTSD symptoms[g]</u> SMD: +0.34 <u>Effect of stopping</u> SMD: −0.18 <u>Multivariate regression results</u> Change in days of marijuana used and change in[g]: PTSD symptoms (β = 0.17, t = 4.08, *P* < .0001)	<u>Violent Behavior</u> 4-item questionnaire from the National Vietnam Veterans Readjustment Study[15] (LS mean [SE]):[f] Stoppers: 0.76 (0.07) Continuing users: 0.93 (0.07) Starters: 1.25 (0.04) Never users: 0.87 (0.04) *P* < .0001 <u>Alcohol abuse</u> ASI Alcohol Index (LS mean [SE])[f]: Stoppers: 0.08 (0.01) Continuing users: 0.13 (0.01) Starters: 0.23 (0.01) Never users: 0.10 (0.01) <u>Drug abuse</u> ASI Index (LS mean [SE])[f]: Stoppers: 0.03 (0.01) Continuing users: 0.13 (0.01) Starters: 0.13 (0.003) Never users: 0.04 (0.003) *P* < .0001 <u>Employment status</u> ASI Index (LS mean [SE])[f]: Stoppers: 0.58 (0.01) Continuing users: 0.59 (0.01) Starters: 0.58 (0.01) Never users: 0.58 (0.01) *P* = .58

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Study N	Cannabis Use and Comparators Baseline PTSD symptom severity	Primary Findings	Other Findings
Nonrandomized studies			
Wilkinson et al., 2015[3] N = 2,276 *(continued)*			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).[g]

[a] *P < .01 considered significant*

[b] *1 = very much improved and 7 = very much worse*

[c] *Used cannabis before but not after admission*

[d] *Used cannabis at admission and continued using*

[e] *Did not use cannabis before admission but started afterward*

[f] *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*

[g] *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, IPF: Inventory of Psychosocial Functioning, ISI: Insomnia Severity Index, LS: least squares; MISS: Mississippi Scale for PTSD, NAB: nabilone, NEPEC: Northeast Program Evaluation Center, PBO: placebo, 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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Suggested citation: Ayers C, Harrod C, Durbin S, Shaw B, Robalino S, Paynter R, Kansagara D. *Cannabis for the management of symptoms of PTSD: systematic review update*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2021.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

VA

U.S. Department of Veterans Affairs

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