REVIEW

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Benefits and Harms of Plant-Based Cannabis for Posttraumatic Stress Disorder

A Systematic Review

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Background: Cannabis is available from medical dispensaries for treating posttraumatic stress disorder (PTSD) in many states of the union, yet its efficacy in treating PTSD symptoms remains uncertain.

Purpose: To identify ongoing studies and review existing evidence regarding the benefits and harms of plant-based cannabis preparations in treating PTSD in adults.

Data Sources: MEDLINE, the Cochrane Library, and other sources from database inception to March 2017.

Study Selection: English-language systematic reviews, trials, and observational studies with a control group that reported PTSD symptoms and adverse effects of plant-based cannabis use in adults with PTSD.

Data Extraction: Study data extracted by 1 investigator was checked by a second reviewer; 2 reviewers independently assessed study quality, and the investigator group graded the overall strength of evidence by using standard criteria.

Data Synthesis: Two systematic reviews, 3 observational studies, and no randomized trials were found. The systematic reviews reported insufficient evidence to draw conclusions about benefits and harms. The observational studies found that compared with nonuse, cannabis did not reduce PTSD symptoms. Studies had medium and high risk of bias, and overall evidence was judged insufficient. Two randomized trials and 6 other studies examining outcomes of cannabis use in patients with PTSD are ongoing and are expected to be completed within 3 years.

Limitation: Very scant evidence with medium to high risk of bias.

Conclusion: Evidence is insufficient to draw conclusions about the benefits and harms of plant-based cannabis preparations in patients with PTSD, but several ongoing studies may soon provide important results.

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Cannabis use has become more common in the United States–the number of persons reporting past-year cannabis use nearly doubled between 2001 and 2013 to 1 in 10 adults (1). Cannabis has been legalized for recreational purposes in 8 states of the union and the District of Columbia and for medical use in 28 states and the District of Columbia (2–4). Many states list posttraumatic stress disorder (PTSD) as an indication for cannabis use (5). More than one third of patients seeking cannabis for medical purposes in states where it is legal list PTSD as the primary reason for their request (6–8). However, little comprehensive and critically appraised information is available about the benefits and harms of cannabis use for treating PTSD. The objectives of this systematic review were to assess the benefits and harms of plant-based cannabis use in patients with PTSD and to identify ongoing studies in this area.

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METHODS

This article is part of a larger report commissioned by the Veterans Health Administration (8). The review plan was posted to a publicly accessible Web site before the study was initiated (9).

Data Sources and Searches

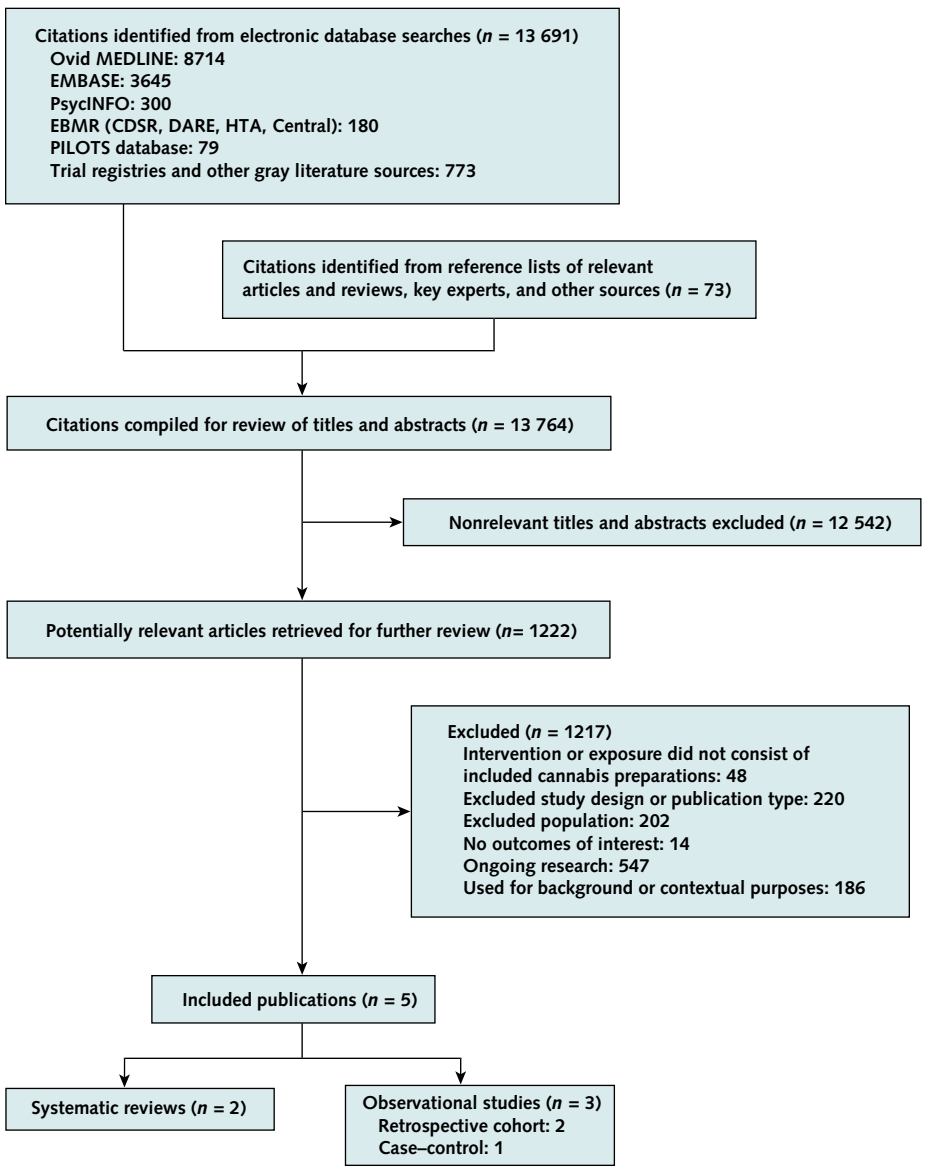
We searched Ovid MEDLINE, EMBASE, PubMed, PsycINFO, the Published International Literature on Traumatic Stress database, Evidence-Based Medicine Reviews (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment Database, and Cochrane Central Register of Controlled Trials), and gray literature sources from database inception through March 2017. We obtained additional articles from systematic reviews, reference lists, and experts and also searched for ongoing, unpublished, or recently completed studies at ClinicalTrials.gov, the International Clinical Trials Registry Platform, the International Standard Randomised Controlled Trials Number registry, the National Institutes of Health Reporter, and the Agency for Healthcare Research and Quality Grants On-Line Database. The searches, developed in consultation with a research librarian, were limited to English-language literature (Appendix A of the **Supplement**, available at Annals.org).

Study Selection

We included studies (systematic reviews, controlled clinical trials, and observational studies using control groups) of nonpregnant adults with PTSD that assessed the effects of plant-based cannabis preparations or whole-plant extracts, such as nabiximols, a nonsynthetic pharmaceutical product with a standard composition and dosage. (For selection criteria, see Appendix B of the Supplement, available at Annals.org). We did not include synthesized, pharmaceutically prepared cannabinoids, such as dronabinol and nabilone, because they are not available in dispensaries, and the efficacy of synthetic cannabinoid preparations was examined in a recent review (10, 11). We broadly defined plant-based cannabis preparations to include any preparation of the plant or its extracts to capture the wide variety of products available in U.S. dispensaries (12).

We dual-screened 5% of identified abstracts and all full-text articles; disagreements were resolved by a third reviewer. We included only systematic reviews that reported their search strategy, inclusion and exclusion criteria, and risk-of-bias assessment of included studies (13). We included all individual studies meeting inclusion criteria that either were published after the end search date of a selected review or had not been included in a previous systematic review. We also identified all ongoing studies (trials and observational and

Figure. Literature flow diagram.



Central = The Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = The Database of Abstracts of Reviews of Effects; EBMR = Evidence-Based Medicine Reviews; HTA = Health Technology Assessments; PILOTS = Published International Literature on Traumatic Stress.

Table 1. Studies of the Effects of Cannabis on PTSD Symptoms

Study, Year (Reference)	Setting and Design	Patients, *n*	Risk of Bias	Funding Source	Sample Description
Wilkinson et al, 2015 (20)	VA retrospective cohort study	2276	Medium	National Institute of Mental Health	All veterans referred for intensive PTSD treatment, excluding those with prior drug or alcohol use Mean age: 51.7 y Male: 96.7%
Johnson et al, 2016 (21)	VA matched, case–control, cross-sectional study	700	High	NR	All veterans with a probable PTSD diagnosis referred for a primary care/mental health integration program based on clinical need after depression, PTSD, and alcohol use screening or clinical judgment Mean age: 47.1 y Male: 91.0%
Ruglass et al, 2017 (22)	Retrospective cohort study	136	High	National Institute on Drug Abuse; National Institute on Alcohol Abuse and Alcoholism	All participants had substance use disorder and PTSD and were from 2 clinical trials comparing interventions for comorbid PTSD and substance use disorders Mean age: 43.4 y Male: 47.8%

NR = not reported; PTSD = posttraumatic stress disorder; VA = U.S. Department of Veterans Affairs.
* Use at admission but not at 4 mo after baseline.
† Use at admission and 4 mo after baseline.
‡ No use at admission but use at 4 months after baseline.

mixed-methods studies) examining the benefits or harms of cannabis use in patients with PTSD.

Data Extraction and Quality Assessment

One investigator extracted study details (such as design, setting, patient population, intervention, follow-up, co-interventions, health outcomes, health care use, and harms), whereas a second investigator reviewed the accuracy of the data extracted. Two reviewers independently assessed study quality as low, medium, or high risk of bias, considering the potential sources of bias most relevant to this evidence base by adapting an existing assessment tool (14, 15) (Appendix C of the Supplement, available at Annals.org). Disagreements were resolved by consensus.

Data Synthesis and Analysis

We qualitatively synthesized the evidence and did not conduct a meta-analysis because of the small number of studies and their marked clinical heterogeneity. Our main outcome of interest was effects on PTSD symptoms and severity. Secondary outcomes of interest included quality of life, mental health, and health care use. After group discussion, we classified the overall strength of evidence for each outcome as high, moderate, low, or insufficient on the basis of the consistency, coherence, and applicability of the body of evidence as well as the internal validity of individual studies (16, 17).

Role of the Funding Source

The U.S. Department of Veterans Affairs (VA) Quality Enhancement Research Initiative supported the review but had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

Of 13 764 screened titles and abstracts, 2 systematic reviews (18, 19) and 3 primary studies (20–22) were selected (Figure). Most individual studies of cannabis use in patients with PTSD that were excluded were cross-sectional or did not include a comparison group.

Benefits and Harms of Cannabis for Treating PTSD

Systematic Reviews

The authors of the 2 selected systematic reviews searched the literature to March 2015 and September 2015, respectively (18, 19). In the first review, Wilkinson and colleagues (18) looked at 3 studies of nabilone (a synthetic cannabis) (23–25) and 3 studies of plant-based cannabis that reported on PTSD symptoms; of the latter group, 2 studies were prospective, open-label trials without a control group (26, 27) and 1 was a case series ([28], as cited in [18]). The authors considered the evidence insufficient to determine whether cannabis (in either plant-based or synthetic form) is effective in treating PTSD. In the second review, Walsh and colleagues (19) evaluated 4 observational studies of synthetic and nonsynthetic cannabis preparations that reported on PTSD symptoms (20, 24, 27, 29). Although

Table 1–Continued

Description and Duration of Cannabis Use and Comparators	Primary Findings	Other Findings
Self-reported cannabis use during 4-mo follow-up: Never-users: 850 Stoppers: 299* Continuing users: 296† Starters: 831‡ Concomitant medications: Usual medical care, including psychotropic medications and psychotherapy, provided to all participants	Continuing users and starters had significantly worse PTSD symptoms than never-users and stoppers ($P < 0.0001$)	Violent behavior: Starters had significantly more violent behavior than continuing users, never-users, and stoppers ($P < 0.0001$) Alcohol abuse: Starters had significantly more alcohol abuse than continuing users, never-users, and stoppers; continuing users had significantly more alcohol abuse than stoppers ($P < 0.0001$) Drug abuse: Continuing users and starters had significantly more drug abuse than never-users and stoppers ($P < 0.0001$) Employment status: No significant differences among groups ($P = 0.58$)
Self-reported cannabis use within 3 mo of assessment ($n = 350$) compared with no lifetime cannabis use reported at assessment ($n = 350$). Users were matched to nonusers by age and sex. Analyses were adjusted for confounders, including severity of symptoms of PTSD and depression, suicidal ideation, alcohol use, marital status, race, and financial status.	Nonsignificant differences in PTSD symptoms in cannabis users compared with nonusers ($P = 0.91$)	Users vs. nonusers: Employed: 23% vs. 40% ($P < 0.0001$) Financially stable: 61% vs. 71% ($P < 0.0001$) Depression symptoms: No significant differences between groups ($P = 0.07$) Suicidal ideation: 33% vs. 26% ($P = 0.04$) Alcohol use: Users had significantly more alcoholic drinks per day than nonusers: 6.3% vs. 3.1% ($P < 0.0001$)
Self-reported cannabis use within 7 d of baseline assessment for the clinical trial ($n = 32$) vs. no cannabis use within 7 d of baseline ($n = 104$)	Baseline days of cannabis use were not a significant predictor of PTSD symptom severity at the end of treatment ($P = 0.30$)	Baseline days of cannabis use were not a significant predictor of substance use at the end of treatment ($P = 0.84$) Higher weekly cannabis use was associated with greater weekly PTSD symptom severity early in treatment but lower weekly PTSD symptom severity later in treatment

cannabis was associated with less severe PTSD symptoms in 3 cross-sectional studies (24, 27, 29), 1 retrospective cohort study (described in detail later) found that cannabis was associated with worsening PTSD symptoms (20). This review (19) also included 3 prospective studies of potential harms associated with cannabis use in patients with PTSD (7, 30, 31) and noted that cannabis use disorder in these patients was associated with negative treatment and cessation outcomes. Of note, none of those 3 studies met our selection criteria for individual study review, and strength of evidence was not formally rated in the second review.

Individual Studies

Table 1 provides a summary of the 3 individual studies that met our inclusion criteria. One was a retrospective cohort study (20) that was included in 1 of the systematic reviews (19). This large observational study examined data from 47 000 veterans in VA intensive PTSD programs from 1992 to 2011. Veterans who reported consuming more than 2 alcoholic drinks on 1 occasion or using any other drug 30 days before admission or who were referred from a drug or alcohol treatment program were excluded from the study. The remaining participants were grouped into "never-users"; "stoppers," who used cannabis before but not after admission; "continuing users"; and "starters," who did not use cannabis before admission but started afterward. After balancing sample sizes across groups and adjusting for sociodemographic features and baseline clinical, community adjustment, and program participation variables, the investigators compared 4-month outcomes for 2276 veterans. Adjusted analyses found that continuing users and starters had worse PTSD symptoms than never-users and stoppers at 4 months of follow-up, although the absolute differences were small (mean score on the short form of the Mississippi Scale for Combat-Related PTSD was 36.64 for stoppers and 39.67 for starters; $P < 0.01$ [20]). Continuing users and starters also had a higher level of drug abuse (mean Addiction Severity Index [ASI] score, 0.128 and 0.130, respectively) than never-users (mean ASI score, 0.037) and stoppers (mean ASI score, 0.034; $P < 0.01$ for paired comparisons). Starters had a higher level of alcohol abuse (mean ASI score, 0.229) than the other groups (mean ASI score: 0.129 for continuers, 0.079 for stoppers, and 0.096 for never-users; $P < 0.01$), and continuing users had a higher level of alcohol abuse than stoppers ($P < 0.01$). Starters had a higher level of violent behavior at follow-up than the other groups; mean score based on a 4-item questionnaire from the National Vietnam Veterans Readjustment Study ([32], as cited in reference 20) was 1.25 among starters, 0.93 among continuing users, 0.76 among stoppers, and 0.87 among never-users ($P < 0.01$). No differences were found in employment status.

Two studies (21, 22) not included in either of the systematic reviews met our inclusion criteria. One study of age- and sex-matched patients entering a VA-based primary care and mental health integration program (21) included 350 patients with PTSD who used cannabis and 350 who did not. Compared with cannabis users, nonusers were more likely to be married, white, employed, and financially stable. After these and other potential confounding variables, such as alcohol use, depression symptom severity, and suicidal ideation, were controlled for, no association was found between frequency of cannabis use and PTSD symptom severity

Table 2. Ongoing Studies of Cannabis for PTSD*

Principal Investigator/ Study Director	ClinicalTrials.gov Identifier	Study Design	Sponsor	Estimated Study Completion Date	Study Title
Kimberly Babson	NCT02102230	Double-blind RCT	VA Clinical Science Research and Development CDA-2	August 2019	The Impact of CBT-I on Cannabis Cessation Outcomes
Michele Bedard-Gilligan	NCT02874898	Single-group assignment	National Institute on Drug Abuse	April 2019	Marijuana Use, Extinction Learning, and Exposure Therapy in Individuals With PTSD
Marcel Bonn-Miller	NCT02759185	Crossover RCT	Colorado Department of Public Health and Environment	April 2019	Placebo-Controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans With Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)
		Observational study	None	June 2017	Evaluation of Veteran Cannabis Use and Impact on Sleep and PTSD
	–	Observational study	Colorado Department of Public Health and Environment	September 2018	Treating PTSD With Marijuana: Clinical and Functional Outcomes
Kendall Browne	–	Mixed-methods observational study	University of Washington Alcohol and Drug Abuse Institute and VA Puget Sound Health Care System Research and Development	September 2017	Characterizing Cannabis Use in Veterans With PTSD
Joshua Eades	NCT02517424	Crossover RCT	Tilray and University of British Columbia	December 2018	Placebo-Controlled, Triple-Blind, Crossover Study of the Safety and Efficacy of Three Different Potencies of Vaporized Cannabis in 42 Participants With Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)
Christine A. Rabinak	NCT03008005	Parallel-group RCT	Wayne State University	December 2019	Effects of THC on Retention of Memory for Fear Extinction Learning in PTSD: R61 Study

CAPS = Clinician-Administered PTSD Scale; CBD = cannabidiol; CBT = cognitive behavioral therapy; CBT-I = Cognitive Behavioral Therapy for Insomnia; CDA-2 = VA Career Development Award-2; CUD = cannabis use disorder; IVR = interactive voice response; MINI = Mini International Neuropsychiatric Interview; MPS = Marijuana Problems Scale; PCL-5 = Posttraumatic Stress Disorder Checklist for *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; PSQI = Pittsburgh Sleep Quality Index; PSS-I = Posttraumatic Stress Disorder Symptom Scale–Interview Version; PTSD = posttraumatic stress disorder; QIDS = Quick Inventory of Depressive Symptomatology; RCT = randomized controlled trial; THC = tetrahydrocannabinol; TLFB = timeline followback; VA = U.S. Department of Veterans Affairs.
* Unpublished studies completed in June 2015 or later are included in the table in order to allow time for publication.

Table 2–Continued

Purpose of Study	Participants and Intervention/Comparator	Primary Outcome and Timing
To examine the role of a behavioral intervention for sleep on cannabis use frequency and insomnia symptoms among veterans with CUD and insomnia.	200 veterans with CUD and insomnia randomly assigned to 1 of the following conditions: CBT for insomnia CBT for insomnia + CBT-I Coach (mobile application) Placebo control (quasi-desensitization)	Change in cannabis use frequency, point-prevalence abstinence, and change in sleep quality at multiple time points up to 6 mo after treatment
To examine the effects of cannabis use on extinction learning by using both a standard discriminative conditioning and extinction task at pretreatment and response to an exposure treatment protocol. Also to examine the ability of a brief protocol to decrease PTSD in and retain in treatment patients with and without cannabis use.	72 men and women aged 18–65 y with chronic PTSD (≥3 mo), 50% of whom are heavy cannabis smokers (≥5 d/wk) and 50% of whom are cannabis nonusers (no use in the past 3 mo). Brief imaginal exposure protocol (6 daily sessions) for PTSD is provided to all participants.	PTSD severity (PSS-I severity) at posttreatment and 12-wk follow-up; treatment dropout (completion of <5 imaginal exposure sessions). Other outcomes: Depression symptoms (QIDS) and cannabis use and problems (MPS and Marijuana Frequency and Quantity Scale) assessed at posttreatment and 12-wk follow-up
To evaluate the safety and efficacy of smoked cannabis of 4 different concentrations among participants with chronic, treatment-resistant, combat-related PTSD.	76 veterans with service-related PTSD (≥6 mo duration and moderate severity at baseline) who smoke ≥1.8 g of cannabis per day in the following concentrations for 3 wk: High THC (more THC than CBD) High CBD (more CBD than THC) High THC/high CBD (equal amounts) Placebo cannabis (low levels of THC/CBD) Participants receive 2 of the 4 types of cannabis during 2 stages, each lasting 3 wk (2-wk washout).	Change in CAPS Global Severity Score at 3 wk and 8 wk after randomization. Other outcomes: Depression and anxiety symptoms, general and psychosocial functioning, sleep quality, suicidal ideation, responses to cannabis, withdrawal, and results of blood and urine tests
To fill a large gap in the literature by providing an a priori test of the effect of cannabis, including variations in cannabinoids, on individual sleep, PTSD, and psychosocial functioning.	150 veterans currently using cannabis who are members of the Santa Cruz Veterans Alliance. Data are collected through repeated survey assessments every other week. All products provided to veterans by the Santa Cruz Veterans Alliance are tested for cannabinoid content by an independent laboratory.	The association between cannabinoid concentration and symptoms of PTSD, sleep, and psychosocial functioning over time among cannabis-using veterans.
To determine whether, among a sample of Colorado residents (veterans and nonveterans), persons with PTSD who obtain and use cannabis from a medical or recreational dispensary compared with a matched sample of persons with PTSD who report no current cannabis use at study baseline (control) will exhibit lower PTSD symptom severity.	150 adult Colorado residents with PTSD, 50% of whom use cannabis from a medical or recreational dispensary in Colorado and 50% of whom report no recent (within the past 6 mo) cannabis use. Assessment at baseline and at 3, 6, 9, and 12 mo after baseline. Measures include interview (MINI, CAPS-5, and TLFB), self-report, computerized neuropsychological assessments, and results of actigraphy for 1 wk after each assessment point and urine tests for objective verification of use status. Furthermore, those using cannabis report on the cannabis used and the dispensary from which it is obtained, and a sample is procured and tested for cannabinoid and terpene content.	PTSD symptom severity, as indexed by self-reported overall symptom severity at each time point as assessed by the CAPS-5, self-reported and objective sleep quality at each time point as assessed by the PSQI and actigraphy, and interview-based diagnosis at 12-mo follow-up as assessed by the CAPS-5. Secondary outcomes (assessed at each time point): Self-reported and objective psychosocial functioning, suicidal ideation, and engagement in medical and psychological services
To build understanding of cannabis use in veterans with PTSD by characterizing cannabis use patterns and motives in veterans with PTSD symptoms, conducting a prospective examination of the day-to-day relations between PTSD symptoms and cannabis use, and conducting the first effort to qualitatively describe the perspective of veterans with PTSD who use cannabis.	Veterans diagnosed with PTSD who report at least weekly cannabis use are invited to participate in an anonymous online survey (n = 200), daily symptom and use monitoring (i.e., IVR; n = 48), in-depth qualitative interviews (n = 30), and blood draws for cannabis biomarkers (n = 48).	Characterize cannabis use patterns and replicate previous findings related to PTSD symptoms, cannabis use, motives for use, and craving through use of an online survey. Examine (via IVR) day-to-day relations between cannabis use and PTSD symptoms along with a 1-time assessment of cannabis use motives. Characterize veterans' beliefs about the relations between cannabis use and mental health symptoms and treatment, including the role of cannabis in PTSD symptom management, treatment for cannabis use, and PTSD treatment through key informant interviews.
To evaluate the safety and efficacy of vaporized cannabis of 3 different concentrations among participants with chronic, treatment-resistant PTSD.	42 adults with PTSD (≥6 mo duration and a PCL-5 score ≥40 at baseline). Approximately 50% police/military veterans, 33%–50% female, and 8%–12% Aboriginal (First Nations, Metis, and Inuit). ≥2 g of cannabis per day administered via vaporization in the following concentrations: High THC/low CBD High THC/high CBD Low THC/low CBD	Change in CAPS Global Severity Score at 3 wk and 8 wk after randomization. Other outcomes: Anxiety and depression symptoms, psychosocial functioning, preference, sleep quality, problems associated with cannabis use, and suicidal thoughts or behaviors
To examine how cannabinoids are related to the processing of fear signals, the experience of emotions and fear, and the pattern of brain activity involved in these processes and in the development of PTSD.	78 adults with PTSD randomly assigned to a 1-time oral dose of the following: Dronabinol, 5.0 mg Dronabinol, 10.0 mg Placebo	Baseline, approximately 2 h after oral dose, and ≥1 wk after oral dose: Brain measures (functional magnetic resonance imaging), skin conductance response, and aversive cue expectancy ratings Other outcomes: Measures of distress, mood, drug effects, anxiety, heart rate, and blood pressure

(odds ratio, 0.99 [95% CI, 0.97% to 1.01%]). In unadjusted analyses, depression symptom severity was similar between cannabis users and nonusers, whereas users were more likely to have suicidal ideation and reported more alcohol use than nonusers (approximately 6 vs. approximately 3 drinks per week).

The other study examined how baseline and ongoing cannabis use was associated with PTSD symptom

severity after cognitive behavioral treatment for comorbid PTSD and substance use (22). In this study, 32 of 136 participants reported cannabis use up to 1 week before treatment. In analyses that adjusted for age, sex, and baseline symptom severity, the authors found no statistically significant association between baseline cannabis use and PTSD symptom severity. More frequent ongoing cannabis use was associated with more severe PTSD symptoms earlier in treatment but with less severe symptoms later in therapy (22). The association between baseline cannabis use and days of substance use during treatment was not statistically significant.

Overall Strength of Evidence

Overall, we found insufficient evidence regarding the benefits and harms of plant-based cannabis preparations for patients with PTSD. The body of literature currently available is limited by small sample sizes, lack of adjustment for important potential confounders, cross-sectional study designs, and a paucity of studies with non–cannabis-using control groups.

Ongoing Studies of Cannabis Use in Persons with PTSD

Recently, 2 randomized controlled trials (RCTs) were initiated that were designed to evaluate the benefits and harms of cannabis therapy for PTSD. The Colorado Department of Public Health and Environment has funded a triple-blind, crossover, placebo-controlled trial to determine the effects of smoking 4 different types of cannabis with various tetrahydrocannabinol and cannabidiol concentrations on PTSD symptoms in veterans (M. Bonn-Miller, study director; ClinicalTrials.gov: NCT02759185). The anticipated completion date of the trial is April 2019. Eades and colleagues are conducting a study sponsored by Tilray and the University of British Columbia (ClinicalTrials.gov: NCT02517424). This study is a crossover RCT of 42 adults with PTSD who will be administered different amounts of tetrahydrocannabinol and cannabidiol (high–low, high–high, and low–low) to compare PTSD, mental health, and physical health outcomes. Other studies of cannabis and PTSD are ongoing that are not RCTs or that are investigating cannabis-related outcomes but are not specifically testing the effectiveness of cannabis in reducing PTSD symptoms. These studies are expected to be completed within the next 3 years; their details are presented in Table 2.

DISCUSSION

In this systematic review, we found insufficient evidence to draw conclusions about potential benefits and harms of cannabis use in patients with PTSD. Two recent systematic reviews came to similar conclusions, and these reviews, along with 3 additional observational studies, do not provide enough rigorous data to comment on the potential benefits and harms of cannabis use in patients with PTSD. No trials have been completed and few observational studies have been done comparing outcomes between cannabis users and nonusers.

Our findings are similar to those of other recently published reviews identified in our literature searches (18, 19, 33). The National Academy of Sciences (NAS) examined the health effects of cannabis (33) and similarly concluded that more rigorous study is necessary to determine the effectiveness of cannabis in treating PTSD. The NAS noted that results from a crossover clinical trial of nabilone, a synthetic form of cannabis (25), in 10 Canadian military personnel indicate that it may have potential as an effective treatment for PTSD symptoms, such as nightmares, but that further study is necessary. The report also described limited evidence based on observational studies that plant-based cannabis is associated with increased severity of PTSD symptoms.

Although we found insufficient evidence, cannabis is commonly available. Despite the limited research on benefits and harms, many states allow medicinal use of cannabis for PTSD (5). The popular press has reported many stories about individuals who had improvement in their PTSD symptoms with cannabis use, and cross-sectional studies have been done in which patients with more severe PTSD reported cannabis use as a coping strategy (34). However, it is impossible to determine from these reports whether cannabis use is a marker for more severe symptoms or is effective at reducing symptoms, or whether the perceived beneficial effects are the result of the cannabis, placebo effects, or the natural course of symptoms.

Clinicians will need to engage in evidence-informed discussions with patients who have PTSD and choose to use or request cannabis. Potential mental health–related harms may exist that are particularly relevant for patients with PTSD. Our full evidence synthesis report and another article describe in greater detail the potential harms of cannabis use in general populations (8, 35). We found low- to moderate-strength evidence that cannabis use is associated with an increased risk for psychotic symptoms, psychosis, mania, and—in active users—short-term cognitive dysfunction.

Patients with PTSD or those with serious mental illness, especially those who already have hypervigilance, agitation, or anger management issues, might be at greater risk for serious consequences if they have any adverse effects. Although clinicians do not have adequate data to quantify risks and benefits for patients with PTSD, they might consider discussing potentially serious adverse effects related to mental health, cognition, and cannabis use disorder during shared decision-making conversations. Clinicians also should discuss other evidence-based interventions recommended by the 2010 VA and Department of Defense Clinical Practice Guidelines for Management of Posttraumatic Stress (36), the Institute of Medicine (37), or the National Center for PTSD (38).

The primary limitation to this body of evidence is the lack of efficacy trials. Additional methodological issues of included studies are detailed in the quality assessment tables (Appendix C of the Supplement). Our

approach to evidence synthesis also has limitations. We excluded studies of synthetic, prescription cannabinoids, because these agents were included in recent reviews and are not available in dispensaries. Including these studies would not have changed our overall findings, because the studies were few and all were small and methodologically limited. A systematic review including studies of both synthetic and plant-based cannabis concluded that evidence from examining its effects in PTSD is insufficient (18).

Virtually no conclusive information exists regarding the benefits of cannabis use in patients with PTSD and information on harms is limited, so methodologically strong research in almost any area likely would add to the strength of evidence. Of particular importance are studies with a longer follow-up and those including cannabis-naive patients. Research is needed to compare cannabis preparations to determine effects of potency of cannabidiol versus tetrahydrocannabinol content. Comparative effectiveness research of cannabis versus evidence-based pharmacologic and psychotherapy interventions for treating PTSD symptoms is warranted. Research is needed on the potential for mental health and cognitive harms of cannabis use in populations with PTSD, because other mental health disorders and impaired cognitive functioning are common in patients with PTSD (39). Of note, the recent NAS report highlighted regulatory barriers to cannabis research as a primary impediment (33).

Although cannabis is increasingly available for treating PTSD, evidence examining its benefits and harms in patients with this disorder is insufficient. Findings from RCTs are needed to help determine whether and to what extent cannabis may improve PTSD symptoms, and further studies also are needed to clarify harms in patients with PTSD.

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