Evidence-based Practice Center Systematic Review Protocol

Project Title: ***Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the PTSD Repository Evidence Base***

I. Background and Objectives for the Systematic Review

Posttraumatic stress disorder (PTSD) is a prevalent disorder with significant negative impacts on health, quality of life, and healthcare utilization.[1] Lifetime prevalence of PTSD is estimated to be 6.1 percent in American civilians and 6.9 percent in Veterans.[2,3] Since PTSD was first included by the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) in 1980, there have been over 300 published randomized controlled trials (RCTs) evaluating a vast number of treatments and treatment modalities (e.g., psychotherapy, psychopharmacotherapy, complementary approaches, etc.). Given the large and varied body of evidence, even some of the most comprehensive systematic reviews on PTSD have excluded some intervention types (e.g., complementary and integrative approaches) due to the prohibitively large number of studies that would have to be reviewed.[4] Without a comprehensive database containing all published RCTs on PTSD, clinicians and researchers may need to consult multiple reviews in order to synthesize evidence across studies and evaluate the effectiveness and comparative effectiveness of treatments. However, heterogeneity of review methods, scope, and data presentation make it difficult to synthesize across reviews and have led to variation in conclusions.[5,6] Methodological differences, such as data coding approaches and combining treatment categories for analysis, further limit the generalizability of findings. Systematic reviews typically abstract a small number of data elements pertinent to the scope of the review due to resource constraints. Furthermore, even when abstracted data are made publicly available, they may be presented in a format that does not readily lend itself to re-analyses without reformatting or re-entry. Hence, there is a need for a single source that provides up-to-date, detailed, comprehensive data on existing PTSD trials to better address current clinical, research, and policy stakeholders' needs.

To meet this need, databases were initially developed in two previous AHRQ reports, a 2019 report (Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: Groundwork for a Publicly Available Repository of Randomized Controlled Trial Data) and subsequent 2020 report (Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the PTSD-Repository Evidence Base).[7,8] These databases were then converted into an online, accessible, interactive data repository disseminated by the National Center for PTSD (NCPTSD), called the PTSD Trials Standardized Data Repository, or "PTSD-Repository."[9] Since then, the database was updated in the 2022 report,[10] and will be updated again through this evidence review. The PTSD-Repository could (1) serve as a data source for future systematic reviews, meta-analyses, or other cross-study comparisons; (2) help identify research gaps to determine future research priorities; (3) encourage researchers to adopt standard data elements in research and reporting; (4) serve as a source for clinicians seeking information on effectiveness of interventions for patients with particular demographics or exposures; (5) provide the public a source to search for

evidence on interventions they or their loved ones are considering; (6) provide policymakers with an up-to-date accounting of evidence to respond to inquiries; and (7) augment and inform the use of existing patient education tools such as PTSD mobile applications[11] or the online PTSD Treatment Decision Aid.[12]

This review will update the literature base and build on the PTSD-Repository by including additional data elements, expanding abstraction of standardized results, and further applying the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[13] As part of the update process, corresponding authors of publications included in the prior report will be notified of their study's inclusion in the report,[10] and invited to submit any corrections to the study team. These data will be available through the resulting report and excel files, as well as the PTSD-Repository.

II. Key Questions

Key Question. What interventions have been studied for the treatment of PTSD alone or with comorbid substance use disorder (SUD)?

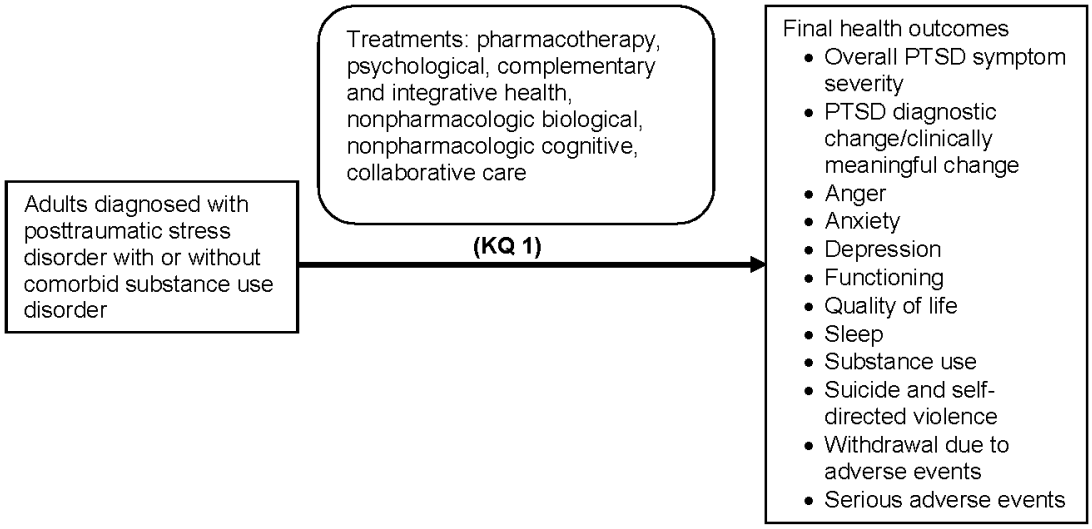
This review will update the literature for this Key Question from previous reviews.[7,8,10] The PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings, Study Design) criteria are:

- **Population(s):**
  - Adults (≥18 years old) diagnosed with PTSD by a clinician or through patient-reported assessment tool
- **Interventions:**
  - Pharmacologic and nonpharmacologic interventions, including complementary and integrative approaches, for PTSD or comorbid PTSD/SUD
- **Comparators:**
  - Any comparator, including another intervention, waitlist/minimal attention, usual care, or placebo
- **Outcomes:**
  - Overall PTSD outcome, PTSD diagnostic change, PTSD clinically meaningful change
  - Other outcomes - anxiety, anger, depression, functioning, quality of life, sleep, substance use, suicide and self-directed violence, withdrawal due to adverse events, serious adverse events
- **Timing:**
  - No limitation on study duration or length of follow up
- **Settings:**
  - No limitation on study setting
- **Study Design:**
  - Randomized controlled trials

III. Analytic Framework

The analytic framework (Figure 1) illustrates how PTSD treatments may be associated with health and functional outcomes including PTSD symptoms and diagnosis, substance use, anxiety, depression, and quality of life; as well as how these interventions may be associated with harms.

Figure 1. Analytic Framework for Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder



IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

Detailed inclusion and exclusion criteria for the Key Question are listed in Table 1 and are consistent with the PICOTS described above in Section II. This is unchanged from the previous review protocol.[14]

Table 1. PICOTS: Inclusion and exclusion criteria

PICOTS	Include	Exclude
Populations	• Adults (mean age ≥18 years old) with PTSD diagnosed by a clinician or through the administration of a validated clinician-administered or patient-reported assessment tool	• Children (mean age <18 years old) • Diagnosis of acute stress disorder • Studies that do not specify criteria used to diagnose PTSD • Sample population with <80% of participants diagnosed with PTSD (i.e., >20% with subthreshold PTSD), or if include comorbid SUD, <80% of participants diagnosed with comorbid PTSD/SUD
Interventions	• Pharmacologic and/or nonpharmacologic interventions for PTSD or comorbid PTSD/SUD in adults. Interventions can include any pharmacologic component, whether singly, in combination with other treatment categories, or compared with another intervention category, or complementary and integrative approaches, nonpharmacologic biological treatments, and psychotherapeutic treatments • Interventions designed to treat insomnia and nightmares related to PTSD	• Interventions designed to simultaneously target PTSD and comorbid conditions other than SUD if they cannot be standalone PTSD interventions (i.e., interventions targeting PTSD and a comorbidity such as depression are included if the intervention can be a treatment for PTSD alone). Interventions designed to prevent PTSD, treat self-stigma, or facilitate posttraumatic growth are excluded unless they are designed to treat PTSD directly as well. • Interventions with no provider interaction
Comparators	• No limitations applied. Direct head-to-head comparison of PTSD interventions were included. • Interventions such as waitlist/minimal attention, usual care, placebo, or other minimally-active treatment (e.g., education or attention control) are categorized as "Controls"	None
Outcomes	• Any overall PTSD outcome	• Studies reporting only individual symptoms or symptom clusters without overall PTSD outcome
Timing	• Any study duration and length of follow up	None
Setting	• All study settings	None
Study Design	• RCTs	• Non-RCTs • Selected systematic reviews will be considered as reference check sources of studies to be reviewed for possible inclusion (data will be abstracted from individual studies rather than from systematic reviews) • Partial studies (limited course of treatment), outcome studies (lower dose), experimental treatment manipulations (dismantling)

PTSD = posttraumatic stress disorder; RCTs = randomized controlled trials; SUD = substance use disorder

Literature Search Strategies to Identify Relevant Studies to Answer the Key Questions:

Publication Date Range: Electronic databases will be searched for evidence from October 15, 2021, to present, with three months of overlap with the last database search for the prior update report.[10] An updated literature search will be conducted concurrently with the peer review and public comment process and any new literature identified that meets inclusion criteria will be incorporated into the report.

Literature Databases: PTSDpubs (formerly PILOTS), Ovid® MEDLINE®, Cochrane CENTRAL, Embase®, the Cumulative Index to Nursing and Allied Health Literature (CINAHL®), SCOPUS, and PsycINFO®. Search strategies are in Appendix A.

Grey Literature: A gray literature search will not be conducted. Due to the nature of the project, a portal for submission of Supplemental Evidence And Data for Systematic review (SEADS) will not be opened for this project.

Hand Searching: Reference lists of relevant, recent, high-quality systematic reviews or meta-analysis identified in the search will be reviewed to identify RCTs eligible for inclusion.

Process for Selecting Studies: PICOTS described in Section II and criteria in Table 1 will be used to determine eligibility for inclusion and exclusion of abstracts. One investigator will determine eligibility at the title/abstract review stage and a second investigator will review excluded studies. For studies included at the title/abstract review stage, the full-text will be retrieved and reviewed independently for eligibility by two investigators. Any disagreements will be resolved by consensus of the team of investigators.

Contacting study authors: The EPC will send an email to the list of corresponding authors for all new studies included in the prior update report,[10] notifying them of the inclusion of their study and providing the report public link on the AHRQ website **[PLACEHOLDER FOR LINK TO PTSD3 UPDATE]**. If study authors respond and report missing study data, corrections, or other study information relevant to evidence table variables, the EPC will document this information in the updated evidence tables, including information obtained from published materials in the evidence table, and reporting unpublished information provided by study authors in evidence table notes or other sections of the final report indicating the unpublished source(s).

Data Abstraction and Data Management:
After studies are screened and determined to meet inclusion criteria, study design, year, setting, country, sample size, eligibility criteria, source(s) of funding, study characteristics, population characteristics, intervention characteristics, and results will be abstracted using a revised version of the evidence table developed for the 2019 report, expanded in the 2020 report, and updated in the 2022 report.[7,8,10] The evidence table will be in Microsoft® Excel (see Appendix B for detailed list of data elements). Data elements added to this update will be incorporated into the existing evidence table with guidance from the NCPTSD partner and Technical Expert Panel (TEP). All study data will be verified for accuracy and completeness by a senior investigator. A record of studies excluded at the full-text level with reasons for exclusion will be maintained.

Assessment of Methodological Risk of Bias of Individual Studies:
The EPC will conduct a risk of bias (RoB) assessment for each of the new studies identified in this update using RoB 2.[13] To ensure transparency and ease of future updating, the EPC will include detailed definitions related to how RoB was assessed, and abstract RoB-related data into additional columns focused on documenting the analysis type (e.g., intent to treat, per protocol), the overall percent of missing primary PTSD outcome assessment data (i.e., overall attrition from measurement), and the percent of missing primary PTSD outcome data in each of the arms of the study (i.e., differential attrition from measurement). Because studies included in prior reports were assessed with a different RoB assessment tool,[7,8] we will update RoB assessments for a subset of RCTs previously included in this report and plan to complete the transition to the Cochrane RoB 2 system for the remaining studies in future updates.

Data Synthesis:
For each included study, data will be abstracted into a detailed evidence table. Characteristics of included studies, such as number of publications by year, study sample size, proportion of studies enrolling community versus military population, and distribution of studies by PTSD assessment method, will be summarized in descriptive tables and text, though no formal data synthesis will be completed as part of this project. All studies, regardless of overall RoB rating, will be incorporated in the descriptive summaries. Results from studies will not be synthesized quantitatively.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: Strength of evidence will not be assessed as a part of this project, nor will assessing applicability.

V. References

1. Giacco D, Matanov A, Priebe S. Symptoms and subjective quality of life in post-traumatic stress disorder: a longitudinal study. PLoS One. 2013;8(4):e60991. doi: 10.1371/journal.pone.0060991. PMID: 23585868.
2. Kilpatrick DG, Resnick HS, Milanak ME, et al. National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria. Journal of traumatic stress. 2013 Oct;26(5):537-47. doi: 10.1002/jts.21848. PMID: 24151000.
3. Pietrzak RH, Goldstein RB, Southwick SM, et al. Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. J Anxiety Disord. 2011 Apr;25(3):456-65. doi: 10.1016/j.janxdis.2010.11.010. PMID: 21168991.
4. Forman-Hoffman V, Middleton JC, Feltner C, et al. Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder: A Systematic Review Update. Comparative Effectiveness Review No. 207. (Prepared by the RTI International-University of North Carolinaat Chapel Hill Evidence-based Practice Center under Contract No. 290-2015-00011-I for AHRQ and PCORI.) AHRQ Publication No. 18-EHC011-EF. PCORI Publication No. 2018-SR-01. Rockville, MD: Agency for Healthcare Research and Quality; 2018. PMID: 30204376.
5. Cipriani A, Williams T, Nikolakopoulou A, et al. Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis. Psychol Med. 2018 Sep;48(12):1975-84. doi: 10.1017/s003329171700349x. PMID: 29254516.
6. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2006 Jan 25;2006(1):Cd002795. doi: 10.1002/14651858.CD002795.pub2. PMID: 16437445.
7. O'Neil ME, Cheney TP, Hsu FC, et al. Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the PTSD-Repository Evidence Base. Comparative Effectiveness Review No. 235. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20(21)-EHC029. Rockville, MD: Agency for Healthcare Research and Quality; November 2020. doi: 10.23970/AHRQEPCCER235.
8. O'Neil M, McDonagh M, Hsu F, et al. Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: Groundwork for a Publicly Available Repository of Randomized Controlled Trial Data. Technical Brief No. 32. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ

Publication No. 19-EHC018-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2019. doi: 10.23970/AHRQEPCTB32.
9. National Center for PTSD. PTSD-Repository. https://ptsd-va.data.socrata.com. Accessed September 1, 2021.
10. O'Neil ME, Cheney TP, Yun Y, et al. Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the PTSD Repository Evidence Base. Evidence Report. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) AHRQ Publication No. 22(23)-EHC040. Rockville, MD: Agency for Healthcare Research and Quality; October 2022. doi: 10.23970/AHRQEPCPTSD.
11. National Center for PTSD. PTSD Mobile Applications (for Veterans, General Public, Family and Friends. Washington, DC: U.S. Department of Veterans Affairs; 2017. https://www.ptsd.va.gov/public/materials/apps/. Accessed June 21, 2019.
12. National Center for PTSD. PTSD Treatment Decision Aid: The Choice is Yours. U.S. Department of Veterans Affairs. https://www.ptsd.va.gov/apps/decisionaid/. Accessed June 21, 2019.
13. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
14. Research Protocol: Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the PTSD Repository Evidence Base. Rockville, MD: Agency for Healthcare Research and Quality; June 2021. https://effectivehealthcare.ahrq.gov/products/ptsd-repository-update/protocol.

VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

If the EPC needs to amend the protocol, we will give the date of each amendment, describe the change, and provide rationale in this section. Changes will not be incorporated into the protocol.

VIII. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any

other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

IX. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

X. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

XI. Role of the Funder

This project was funded under Contract No. 75Q80120D00006 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by either the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XII. Registration

Because this is a data abstraction and evidence base expansion project and not a systematic review, this protocol will not be registered in the international prospective register of systematic reviews (PROSPERO).

APPENDIX A. SEARCH STRATEGIES

Database: Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations

Pharmacologic interventions

1. stress disorders, post-traumatic/
2. ("posttraumatic stress disorder" or "post traumatic stress disorder" or PTSD).ti,ab.
3. 1 or 2
4. exp Drug Therapy/ or dt.fs. or (medication* or pharmacologic* or pharmaco-therap* or pharmacotherap*).ti,ab.
5. (drug* adj2 (therap* or treatment*)).ti,ab. or exp Adrenergic alpha-Antagonists/ or Sympatholytics/ or Doxazosin/ or Prazosin/
6. ("adrenergic alpha antagonist*" or "adrenergic receptor block*" or "alpha adrenergic antagonist*" or "alpha block*" or antiadrenergic* or doxazosin or prazosin or sympatholytic* or terazosin).ti,ab. or exp Antipsychotic Agents/
7. exp Benzodiazepines/ or ("anti-psychotic*" or antipsychotic* or FGA* or SGA* or aripiprazole or asenapine or brexpiprazole or cariprazine or chlorpromazine or clozapine or fluphenazine or haloperidol or iloperidone or loxapine or lurasidone or olanzapine or paliperidone or perphenazine or pimozide or quetiapine or risperidone or thioridazine or thiothixene or trifluoperazine or ziprasidone).ti,ab.
8. (alprazolam or benzodiazepine* or benzodiazepinone* or chlordiazepoxide or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or midazolam or oxazepam or quazepam or temazepam or triazolam).ti,ab. or exp Monoamine Oxidase Inhibitors/
9. (("monoamine oxidase" adj2 inhibitor*) or MAOI or isocarboxazid or phenelzine or selegiline or tranylcypromine).ti,ab
10. carbamazepine/ or clonidine/ or lithium/ or pregabalin/ or valproic acid/ or exp Anticonvulsants/ or exp Antimanic Agents/
11. exp Cyclohexanecarboxylic Acids/ or (anticonvuls* or carbamazepine or clonidine or divalproex or gabapentin or lamotrigine or lithium or oxcarbazepine or pregabalin or tiagabine or topiramate or valproate or "valproic acid").ti,ab.
12. exp "hypnotics and sedatives"/ or exp anti-anxiety agents/ or ("anti anxiety" or antianxiety or buspirone or diphenhydramine or eszopiclone or guanfacine or hydroxizine or hypnotic* or ramelteon or sedative* or suvorexant or tasimelteon or zaleplon or zolpidem or zopiclone).ti,ab.
13. (antidepressant* or "anti-depressant*" or "selective serotonin" or (serotonin adj3 reuptake) or SNRI* or SSRI* or tricyclic or amitriptyline or amoxapine or bupropion or citalopram or clomipramine or desipramine or desvenlafaxine or doxepin or duloxetine or escitalopram or fluoxetine or fluvoxamine or hydroxizine or imipramine or levomilnacipran or maprotiline or milnacipran or mirtazapine or nefazodone or nortriptyline or paroxetine or protriptyline or sertraline or trazadone or trimipramine or venlafaxine or vilazodone or vortioxetine).ti,ab. or exp Antidepressive Agents/
14. exp Amphetamines/ or (amphetamine or armodafanil or atomoxetine or dexmethylphenidate or dextroamphetamine or lisdexamphetamine or MDMA or methamphetamine or methylphenidate or modafanil).ti,ab.
15. exp Steroids/ or (DHEA or hydrocortisone or steroid*).ti,ab. or exp Cannabinoids/
16. Cannabis/ or Medical Marijuana/ or (cannabi* or marijuana or tetrahydrocannabinol or THC).ti,ab.
17. ketamine/ or ketamine.ti,ab. or Propranolol/ or propranolol.ti,ab.
18. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. 3 and 18
20. exp Randomized Controlled Trials as Topic/ or exp Randomized Controlled Trial/
21. double-blind method/ or random allocation/ or single-blind method/ or Placebos/
22. (random* or control* or trial or sham or placebo* or blind* or dumm* or mask*).ti,ab,kw.
23. 20 or 21 or 22
24. 19 and 23

Nonpharmacologic interventions

1. stress disorders, post-traumatic/ or ("posttraumatic stress disorder" or "post traumatic stress disorder" or PTSD).ti,ab.
2. nlpx "query=th.fs. OR exp Psychotherapy/ OR exp Complementary Therapies/ OR exp Convulsive Therapy","desiredResults=10000","minHitsDivisor=7","permitHyponyms=NO","lowestVocabularySearchLevel=none","phrasesBroken=NO","speedWanted=Fastest","comment=No Related Terms","elimEnable=NO","constraintMinTerms=2"
3. Hyperbaric Oxygenation/ or Transcranial Magnetic Stimulation/ or exp Rehabilitation/
4. exp Dietary Supplements/
5. exp "Delivery of Health Care, Integrated"/ or exp Self-Help Groups/ or exp peer group/
6. exp social support/ or exp Telemedicine/ or telephone/ or exp cell phone/
7. (therap* or psychotherap* or counsel* or nonpharma* or non-pharma* or ("alternative medicine" or acupuncture or "animal assist*" or art or "cell phone" or "cognitive behavior*" or CBT or complementary or dance or drama or electroconvulsive or ECT or exercise or "eye movement desensitization and reprocessing" or EMDR or family or "hyperbaric oxygen*" or integrated or meditation or "mind body" or mindfulness or music or "prolonged exposure" or relaxation or "seeking safety" or "self help" or "tai chi" or "tai ji" or "text messag*" or "transcranial magnetic stimulation" or TMS or yoga)).ti,ab.
8. or/2-7
9. 1 and 8
10. exp Randomized Controlled Trials as Topic/ or exp Randomized Controlled Trial/ or double-blind method/ or random allocation/ or single-blind method/ or Placebos/ or (random* or control* or trial or sham or placebo* or blind* or dumm* or mask*).ti,ab,kw.
11. 9 and 10

Database: APA PsycInfo

1. exp posttraumatic stress disorder/ or ("post traumatic stress disorder" or "posttraumatic stress disorder" or PTSD).ti,ab.
2. exp treatment/ or exp stimulation/ or exp electroconvulsive shock/ or exp TELEMEDICINE/ or exp counseling/ or exp support groups/ or (therap* or psychotherap* or counsel* or nonpharma* or non-pharma*).ti,ab. or ("alternative medicine" or acupuncture or "animal assist*" or art or "cell phone" or "cognitive behavior*" or CBT or complementary or dance or drama or electroconvulsive or ECT or exercise or "eye movement desensitization and reprocessing" or EMDR or family or "hyperbaric oxygen*" or integrated or meditation or "mind body" or mindfulness or music or "prolonged exposure" or relaxation or "seeking safety" or "self help" or "tai chi" or "tai ji" or "text messag*" or "transcranial magnetic stimulation" or TMS or yoga).ti,ab.
3. treatment effectiveness evaluation/ or Treatment Outcomes/ or followup studies/ or (random* or control* or trial or sham or placebo* or blind* or dumm* or mask*).ti,ab

4. 1 and 2 and 3

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1. Stress Disorders, Post-Traumatic/ or ("posttraumatic stress disorder" or "post traumatic stress disorder" or "ptsd").ti,ab.
2. (dt or pc or rh or th).fs. or exp treatment outcome/ or exp therapeutics/ or (treatment or therap* or intervention*).ti,ab,kw
3. 1 and 2
4. limit 3 to medline records
5. 3 not 4

Database: PTSDpubs (formerly PILOTS)

(MAINSUBJECT.EXACT("PTSD") OR MAINSUBJECT.EXACT("PTSD (DSM-III-R)") OR MAINSUBJECT.EXACT("PTSD (DSM-III)") OR MAINSUBJECT.EXACT("PTSD (DSM-IV)") OR MAINSUBJECT.EXACT("PTSD (DSM-5)") OR MAINSUBJECT.EXACT("Complex PTSD") OR MAINSUBJECT.EXACT("PTSD (ICD-11)") OR MAINSUBJECT.EXACT("PTSD (ICD-10)") OR MAINSUBJECT.EXACT("PTSD (ICD-9)") OR (ptsd OR "posttraumatic stress disorder" OR "post-traumatic stress disorder")) AND (MAINSUBJECT.EXACT("Randomized Clinical Trial") OR ti(random* OR control* OR trial))
Additional limits: Scholarly Journals

APPENDIX B. DATA ABSTRACTION ELEMENTS

Study Characteristics

a. Author
b. Year of publication
c. Bibliographic citation
d. PubMed ID
e. PTSDpubs (formerly PILOTS) ID number, if available
f. ClinicalTrials.gov identifier
g. Funding source
h. Country/Countries of study sites
i. Site Type (VA/DoD, non-VA/DoD, Mixed, MIL, Non-MIL)
j. Clinical setting
k. Study design
l. Indicate if subscale or symptom cluster data is reported (Y/N)
m. Indicate if subgroup analyses are reported (Y/N)
n. Indicate if psychotherapy providers have graduate degree (Y/N)
o. Indicate if treatment includes group therapy (Y/N)
p. Indicate if allowed PTSD psychotherapy, other psychotherapy, and psychotropic medication co-intervention (Y/N)
q. Diagnostic instrument(s)
r. Operational definition of PTSD (i.e., score or cutoff required for inclusion)
s. Suicide- and self-directed violence-related inclusion/exclusion criteria
t. Psychotic disorder- and symptom-related inclusion/exclusion criteria

Population Characteristics

a. Number of randomized participants
b. Proportion of participants meeting study-defined criteria for PTSD at baseline
c. Mean PTSD severity at baseline
d. Duration of PTSD symptoms
e. % Active duty military
f. % Veteran
g. % Community
h. Mean age
i. % Female
j. Gender and sexual orientation, if reported
k. Race % (by U.S. Census categories)
l. Ethnicity (by U.S. Census categories)
m. % Treatment-naïve
n. % with depression
o. % with substance use disorder
p. % with history of traumatic brain injury
q. Indicate if patients with suicidality were excluded (Y/N)
r. Participants' trauma type(s)
s. Mean number of trauma types and traumatic events experienced per participant
t. % with suicidal ideation/intent/plan/attempt(s) or self-directed violence
u. % with psychotic disorder
v. % with personality disorder
w. % with anxiety disorder
x. % with prior inpatient hospitalization
y. % service connected Veterans

Interventions

a. Intervention classification (pharmacologic, psychotherapy, nonpharmacologic biological, complementary and integrative, mixed, control)
b. Treatment conditions (interventions)
c. Number of participants randomized to each study arm
d. Treatment dose and/or session length
e. Frequency of treatment
f. Duration of treatment
g. Definition of treatment completion and/or adherence
h. Proportion of participants who completed and/or adhered to treatment
i. Mean number of psychotherapy sessions completed or dose of pharmacotherapy
j. Intervention type (PTSD-only, SUD-only, PTSD+SUD, PTSD+other, Control)

Outcomes

a. Primary PTSD outcome measure
b. Method for handling missing data for primary PTSD outcome measure
c. Analysis type of primary PTSD outcome measure (ITT, completer)
d. Statistical analysis method for primary PTSD outcome
e. Assessment time point(s) for primary PTSD outcome
f. Number of participants who completed the primary PTSD outcome assessment
g. Results for primary PTSD outcome (measure score and within-group effect size)
h. Between-group effect size for primary PTSD outcome
i. Proportion of participants who achieved study-defined PTSD diagnostic change
j. Proportion of participants who achieved study-defined clinically meaningful change
k. Results for other PTSD outcome measure(s) for studies that used a clinician-administered measure abstracted as primary PTSD outcome measure
l. Between-group effect sizes for all reported depression outcomes
m. Between-group effect sizes for all reported anxiety outcomes
n. Between-group effect sizes for all reported sleep outcomes
o. Between-group effect sizes for all reported anger outcomes
p. Between-group effect sizes for all reported quality of life outcomes
q. Between-group effect sizes for all reported functioning outcomes
r. Results for all reported substance use outcomes
s. Results for all suicide- or self-directed violence-related outcomes
t. Harms outcomes (withdrawals due to adverse events, serious adverse events)

APPENDIX C. RoB 2, A REVISED TOOL FOR ASSESSING RISK OF BIAS IN RANDOMISED TRIALS: ASSESSMENT ELEMENTS

1.1) Was the allocation sequence random?
1.2) Was the allocation sequence concealed until participants were enrolled and assigned to interventions?
1.3) Did baseline differences between intervention groups suggest a problem with the randomization process?
2.1) Were participants aware of their assigned intervention during the trial?
2.2) Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?
2.3) (If Yes, Probably Yes, or No Information to masking carers or participants) Were there deviations from the intended intervention that arose because of the trial context?
2.4) (If Yes, Probably Yes to previous question) Were these deviations likely to have affected the outcome?
2.5) (If Yes, Probably Yes, No Information to previous question) Were these deviations from intended intervention balanced between groups?
2.6) Was an appropriate analysis used to estimate the effect of assignment to intervention?
2.7 Detail) List type of analysis
2.7) (If No, Probably No, No Information to previous question) Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized
3.1) Were data for this outcome available for all, or nearly all, participants randomized?
3.1 Detail) List overall % of missing outcome (i.e., overall attrition) data
3.2) (If No/Probably No/No Information to previous question) Is there evidence that the result was not biased by missing outcome data?
3.3) (If No/Probably No to previous question) Could missingness in the outcome depend on its true value?
3.4) (If Yes, Probably Yes, No Information to previous question) Is it likely that missingness in the outcome depended on its true value?
3.4 Detail) List % of missing outcome data (i.e., differential attrition) in each group
4.1) Was the method of measuring the outcome inappropriate?
4.2) Could measurement or ascertainment of the outcome have differed between intervention groups?
4.3) (If No/Probably No/No Information to both previous questions) Were outcome assessors aware of the intervention received by study participants?
4.4) (If Yes/Probably Yes/No Information to previous question) Could assessment of the outcome have been influenced by knowledge of intervention received?
4.5) (If Yes/Probably Yes/No Information to previous question) Is it likely that assessment of the outcome was influenced by knowledge of intervention received?
5.1) Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?
5.2) Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?
5.3) Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?