



## Evidence-based Practice Center Program Technical Brief Protocol

### Project Title: *Pharmacologic and Nonpharmacologic Treatments of Post-Traumatic Stress Disorder*

#### I. Background and Objectives for the Technical Briefs

Post-Traumatic Stress Disorder (PTSD) is characterized by group of symptoms such as intrusive thoughts, nightmares, flashbacks, avoidance of trauma-related stimuli, negative beliefs about self and/or others, and hypervigilance due to direct or indirect exposure to trauma such as actual or threatened death, injury, or sexual violence.<sup>1</sup> PTSD has significant negative impacts on quality of life and functioning.<sup>2</sup>

In response to the DSM-5 update of diagnostic criteria for PTSD, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) conducted the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), assessing national prevalence of PTSD and other mental disorders such as anxiety, mood, personality, and substance use disorders.<sup>3,4</sup> PTSD afflicts military personnel and civilians alike. The national civilian 12-month and lifetime prevalence of PTSD are 4.7 percent and 6.1 percent, respectively,<sup>3</sup> compared to the lifetime prevalence of 6.9% in Veterans.<sup>4</sup> Sociodemographic characteristics associated with higher prevalence were: female sex, White or Native American ethnicities, ≤65 years old, previously married, less than high school education, family income ≤\$70,000, and rural residents.<sup>3</sup> The most common traumatic events are personal sexual/physical assault and witnessing a death due to violence, accident, or disaster.<sup>5</sup>

Greater exposure to traumatic events is also associated with increased risk of developing PTSD. Research suggests that slightly higher lifetime prevalence estimates are common among wartime Veterans, particularly from a specific era.<sup>6-8</sup> In a RAND Corporation survey conducted in 2008, point-prevalence of PTSD among service members deployed in Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) was 13.8 percent.<sup>9</sup>

In multivariable models adjusting for age, race/ethnicity, sex, education, income, marital status, urbanicity, geographic region, and additional psychiatric disorders, PTSD was highly associated with comorbid anxiety, mood, and personality disorders in both civilians and veterans.<sup>3,4</sup> PTSD is also associated with cardiovascular disease, arthritis, asthma, chronic pain, diabetes, bone and joint conditions, and gastrointestinal disorders,<sup>3</sup> leading to high utilization of health services.

In 2017, the Department of Veterans Affairs (VA) and the Department of Defense (DoD) released an updated Clinical Practice Guideline (CPG) on treatment of PTSD.<sup>10</sup> This CPG was based on literature available through March 2016, and it addresses pharmacologic, nonpharmacologic, and complementary and integrative health (CIH) interventions for PTSD.<sup>10</sup> The CPG recommended individual, manualized trauma-focused psychotherapy with exposure and/or cognitive restructuring, such as Prolonged Exposure (PE), Cognitive Processing Therapy (CPT), Eye Movement Desensitization and Reprocessing (EMDR), specific cognitive behavioral therapies (CBT) for PTSD, Brief Eclectic Psychotherapy (BEP), Narrative Exposure Therapy

(NET), and written narrative exposure. If trauma-focused psychotherapy is not readily available or not preferred, the CPG recommended individual non-trauma-focused psychotherapy or pharmacotherapy. Currently, only the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine are approved by the Food and Drug Administration (FDA) for treatment of PTSD. However, the CPG recommended the SSRI fluoxetine and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine as well.

While many randomized controlled trials (RCTs) were included in the systematic review used to develop the CPG, newer RCTs examine new populations, combinations with other interventions, or different timeframes or modalities.<sup>10-13</sup> Other recent RCTs address new or emerging interventions, such as pharmacotherapies effective for depression or other mental health disorders associated with PTSD, repetitive transcranial magnetic stimulation (rTMS), and ketamine.<sup>14,15</sup>

There are several challenges to reviewing existing PTSD RCT literature. First, many PTSD trials evaluate complex (multicomponent) interventions (e.g., patients receiving multiple types of psychotherapy components comprising one intervention arm, or receiving both medication and psychotherapy).<sup>16</sup> These multicomponent interventions present many challenges: (a) some multicomponent interventions are referred to by the same name (e.g., cognitive behavioral therapy or trauma-focused therapy), yet often times include different combinations of components, (b) depending on the study design, comparisons may not be possible, and (c) additional heterogeneity is introduced if specific techniques used for each component differ across studies or treatment arms. Second, high dropout rate in some intervention arm(s) may jeopardize the validity of findings.<sup>17-19</sup> Third, there are numerous methods of diagnosing PTSD that are not always consistent or validated; only some (primarily structured clinical interviews such as the Clinician Administered PTSD Scale [CAPS]<sup>20</sup>) are designed to diagnose PTSD, while self-report questionnaires often use cutoffs as a proxy for diagnosis.<sup>21</sup> Different versions of the same tool (e.g., CAPS-5 versus CAPS for DSM-IV) add complexity when comparing results across studies. Fourth, outcomes reported may be statistically significant but not clinically meaningful, may not correlate with functional improvements or loss of PTSD diagnosis, or may obscure clinically significant effects that occur in a subgroup of patients who respond well to treatment. Fifth, heterogeneity in populations impacts applicability and is a challenge in this body of literature, as inadequate reporting of inclusion criteria is unfortunately common. In many cases, determining whether participants met criteria for PTSD, or other related disorders such as acute stress disorder, is often impossible based on published data. Similarly, studies often do not report detailed information on demographics, comorbidities, or other population characteristics that are important in determining the applicability or generalizability of the study, such as percentages of civilian versus Veteran participants. This is particularly important when comparing interventions with heterogeneous treatment techniques (e.g., session number, frequency, intensity, homework) and heterogeneity in and definitions of comparators (e.g., usual care, waitlist, attention control, placebo).

The purpose of this project is to systematically abstract data from RCTs of PTSD interventions and develop a new database. This data, when made available in a publicly accessible database (e.g., through the National Center for PTSD [NCPTSD] website), could serve multiple stakeholders and purposes such as: (1) provide policymakers with an up-to-date accounting of

evidence to facilitate quick and accurate responses to urgent government or media inquiries; (2) serve as a data source for future systematic reviews or meta-analyses; (3) identify research gaps to determine future research priorities on intervention harms or effectiveness; (4) provide the public with a place to search for evidence on interventions they or their loved ones are considering, and augment and inform the use of existing tools to assist in patient decision-making such as “AboutFace” videos on PTSD treatments,<sup>22</sup> PTSD apps,<sup>23</sup> or online decision aids available on the National Center for PTSD website;<sup>24</sup> and (5) serve as a resource on effectiveness of interventions for PTSD in patients with particular demographics or exposures.

## II. Guiding Questions

The Guiding Questions for the technical briefs are:

1. What pharmacologic interventions have been studied for the treatment of PTSD (since 1980)?
2. What nonpharmacologic interventions have been studied for the treatment of PTSD (since 1980)?

Studies of PTSD interventions will be included according to criteria based on the following PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings, Study Designs).

- Populations—Adults ( $\geq 18$  years old) with PTSD (*DSM-III*, *DSM-IV*, or *DSM-5*); subthreshold PTSD will be included if there are fewer than 400 eligible studies on adults with PTSD. Subpopulations based on trauma type and mental health comorbidity.
- Interventions—Pharmacologic treatments (defined as any drug used to treat PTSD, whether approved by the FDA for any use in the United States or not, including DEA Schedule I drugs), nonpharmacologic treatments including complementary and integrative approaches, and combination of pharmacologic and nonpharmacologic treatments.
- Comparators—Waitlist/minimal attention, usual care, placebo, or other active treatment including education or attention control.
- Outcomes—Any reported PTSD outcome, including outcomes related to overall PTSD symptoms (e.g., change in total PTSD symptom severity score, diagnostic change, meaningful/reliable/clinically significant change); functional outcomes (e.g., social, family, vocational, education); return to school/work; prevention or reduction of comorbid psychiatric or medical diagnoses; remission; quality of life; loss of diagnosis; change in scale scores of self-reported/clinician-reported outcomes; and adverse effects and other harms (e.g., sleep disturbance, agitation, mortality, and other serious adverse events, including harm to self or others); number who completed treatment; percent of total sessions attended; number who completed measurement, how missing data is handled.

- Timing—No restriction by length of intervention or length of followup.
- Settings—No restriction by location of either the provider or patient (e.g., military base, Veterans Affairs clinic, community clinic, intervention delivered via telehealth).
- Study Design—randomized controlled trials (RCTs) published from January 1, 1980 through present.

### III. Methods

#### 1. Criteria for Inclusion/Exclusion of Studies in the Technical Briefs

The criteria for inclusion and exclusion of studies (Table 1) are based on the Guiding Questions and are consistent with the PICOTS in Section II.

**Table 1. Inclusion and exclusion criteria**

Category	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years old) with a PTSD diagnosis (DSM-III, DSM-IV, or DSM-5)	Children (<18 years old) Diagnosis of acute stress disorder Studies that do not specify criteria used to diagnose PTSD Partial studies (limited course of treatment), outcome studies (lower dose), experimental treatment manipulations (dismantling)
Interventions	Pharmacologic treatments Nonpharmacologic treatments, including complementary and integrative approaches Combinations of pharmacologic and nonpharmacologic treatments	Interventions designed to simultaneously target PTSD and comorbid conditions Interventions designed to prevent PTSD
Comparators	Waitlist/minimal attention, usual care, placebo, or other active treatment, including education or attention control	None
Outcomes	Any reported PTSD outcome	Individual symptoms or symptom clusters
Timing	Any study duration and length of followup	None
Settings	All	None
Study Design	Randomized controlled trials	Studies that do not have a randomized controlled trial design. Selected systematic reviews will be considered as reference check sources of studies to be reviewed for possible inclusion; however, data will be abstracted from individual studies, rather than from systematic reviews.
Publication Language and Dates	English language articles 1980 to present	Non-English language articles Unpublished data Publication date prior to 1980

DSM = Diagnostic and Statistical Manual of Mental Disorders; PTSD = Post-Traumatic Stress Disorder

Up to 400 studies will be included in the evidence tables for the two technical briefs. If the final list of included studies exceeds 400, additional exclusion criteria will be applied, such as

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restriction of settings to outpatient or restriction to single-diagnosis PTSD interventions (as opposed to treatment simultaneously targeting both PTSD and a co-occurring condition, such as a substance use disorder).

## **2. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

Literature Databases: Published International Literature on Traumatic Stress (PILOTS), Ovid<sup>®</sup> MEDLINE<sup>®</sup>, Cochrane CENTRAL, Embase<sup>®</sup>, the Cumulative Index to Nursing and Allied Health Literature (CINAHL<sup>®</sup>), SCOPUS, and PsycINFO<sup>®</sup>. Preliminary search strategies are in Appendix A.

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

Gray 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.

Peer Review: The search strategy will be peer reviewed by NCPTSD librarians.

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 pulled. Each full-text article will be independently reviewed for eligibility by two investigators, including articles suggested by peer reviewers, or that arise from the public posting. Any disagreements will be resolved by consensus of the team of investigators.

## **3. Data Abstraction and Data Management**

After studies are deemed to meet inclusion criteria, study design, year, setting, country, sample size, eligibility criteria, study characteristics, population characteristics, intervention characteristics, results relevant to the Guiding Questions, and sources of funding will be abstracted. See Appendix B for detailed study characteristics, population characteristics, and results data that will be abstracted. All study data will be verified for accuracy and completeness by a second team member. A record of studies excluded at the full-text level with reasons for exclusion will be maintained.

Risk of bias (quality) assessment will not be conducted.

We will construct an evidence table identifying the study characteristics (as described above) and results of interest for all included studies. The evidence table will be developed using Microsoft<sup>®</sup> Excel and will include all components in the Statement of Work (see Appendix B). The Excel spreadsheet will be developed with guidance from the NCPTSD partner, and the NCPTSD will review and approve updates and changes to the Excel spreadsheet at weekly meetings.

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## IV. References

1. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. 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.
3. Goldstein RB, Smith SM, Chou SP, et al. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *Soc Psychiatry Psychiatr Epidemiol*. 2016;51(8):1137-48. PMID: 27106853.
4. Smith SM, Goldstein RB, Grant BF. The association between post-traumatic stress disorder and lifetime DSM-5 psychiatric disorders among veterans: data from the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III). *J Psychiatr Res*. 2016;82:16-22. PMID: 27455424.
5. 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. *J Trauma Stress*. 2013 Oct;26(5):537-47. doi: 10.1002/jts.21848. PMID: 24151000.
6. LeardMann CA, Smith TC, Smith B, et al. Baseline self reported functional health and vulnerability to post-traumatic stress disorder after combat deployment: prospective US military cohort study. *BMJ*. 2009 Apr 16;338:b1273. doi: 10.1136/bmj.b1273. PMID: 19372117.
7. Smith TC, Ryan MA, Wingard DL, et al. New onset and persistent symptoms of post-traumatic stress disorder self reported after deployment and combat exposures: prospective population based US military cohort study. *BMJ*. 2008 Feb 16;336(7640):366-71. doi: 10.1136/bmj.39430.638241.AE. PMID: 18198395.
8. Wisco BE, Marx BP, Wolf EJ, et al. Posttraumatic stress disorder in the US veteran population: results from the National Health and Resilience in Veterans Study. *J Clin Psychiatry*. 2014 Dec;75(12):1338-46. doi: 10.4088/JCP.14m09328. PMID: 25551234.
9. Schell T, Marshall G. Chapter 4: Survey of Individuals Previously Deployed for OEF/OIF. In: Tanielian T, Jaycox LH, eds. *Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery*. Sponsored by the California Community Foundation. Santa Monica, CA: RAND Center for Military Health Policy Research; 2008.
10. VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder, Version 3.0. Prepared by The Management of Posttraumatic Stress Disorder Work Group with support from The Office of Quality, Safety and Value, Office of Evidence Based Practice, U.S. Army Medical Command. Washington, DC: Department of Veterans Affairs and Department of Defense; 2017. <https://www.healthquality.va.gov/guidelines/MH/ptsd/>. Accessed May 18, 2018.
11. Chen S, Spry C. Group Cognitive Processing Therapy for Adults with Post-Traumatic Stress Disorder, Anxiety, or Mood Disorders: A Review of Clinical Effectiveness and Guidelines. Rapid Response Summary with Critical Appraisal. Project Number: RC0891-000. Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health; June 12, 2017.
12. Gobin RL, Mackintosh MA, Willis E, et al. Predictors of Differential PTSD Treatment Outcomes Between Veteran and Civilian Women After Cognitive Processing Therapy. *Psychol Trauma*. 2017 Apr 17doi: 10.1037/tra0000266. PMID: 28414493.
13. Levi O, Wald I, Svetlitsky V, et al. Combat-Related Multifaceted Trauma-Focused Group Therapy: A Pilot Study. *J Nerv Ment Dis*. 2017 Feb;205(2):133-9. doi: 10.1097/NMD.0000000000000619. PMID: 27861458.
14. Pradhan B, Kluewer D'Amico J, Makani R, et al. Nonconventional interventions for chronic post-traumatic stress disorder: Ketamine, repetitive trans-cranial magnetic stimulation (rTMS), and alternative approaches. *J Trauma Dissociation*. 2016;17(1):35-54. doi: 10.1080/15299732.2015.1046101. PMID: 26162001.

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15. Rasmussen AM, Marx CE, Jain S, et al. A randomized controlled trial of ganaxolone in posttraumatic stress disorder. *Psychopharmacology (Berl)*. 2017 Aug;234(15):2245-57. doi: 10.1007/s00213-017-4649-y. PMID: 28667510.
16. Hien DA, Morgan-Lopez AA, Campbell AN, et al. Attendance and substance use outcomes for the Seeking Safety program: sometimes less is more. *J Consult Clin Psychol*. 2012 Feb;80(1):29-42. doi: 10.1037/a0026361. PMID: 22182262.
17. Hoge CW, Grossman SH, Auchterlonie JL, et al. PTSD treatment for soldiers after combat deployment: low utilization of mental health care and reasons for dropout. *Psychiatr Serv*. 2014 Aug 01;65(8):997-1004. doi: 10.1176/appi.ps.201300307. PMID: 24788253.
18. Imel ZE, Laska K, Jakupcak M, et al. Meta-analysis of dropout in treatments for posttraumatic stress disorder. *J Consult Clin Psychol*. 2013 Jun;81(3):394-404. doi: 10.1037/a0031474. PMID: 23339535.
19. Watts BV, Shiner B, Zubkoff L, et al. Implementation of evidence-based psychotherapies for posttraumatic stress disorder in VA specialty clinics. *Psychiatr Serv*. 2014 May 01;65(5):648-53. doi: 10.1176/appi.ps.201300176. PMID: 24430622.
20. National Center for PTSD. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Department of Veterans Affairs. <https://www.ptsd.va.gov/PTSD/professional/assessment/adult-int/caps.asp>. Accessed May 18, 2018.
21. National Center for PTSD. PTSD Checklist for DSM-5 (PCL-5). Washington, DC: U.S. Department of Veterans Affairs; 2017. <https://www.ptsd.va.gov/PTSD/professional/assessment/adult-sr/ptsd-checklist.asp>. Accessed March 16, 2018.
22. National Center for PTSD. PTSD Videos for Veterans, General Public, Family & Friends. Washington, DC: U.S. Department of Veterans Affairs; 2016. <https://www.ptsd.va.gov/PTSD/public/materials/videos/index.asp>. Accessed May 18, 2018.
23. 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 May 18, 2018.
24. 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/>. May 18, 2018.

## **V. Definition of Terms**

Important terms will be added as needed.

## **VI. Summary of Protocol Amendments**

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

## **VII. 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. They are 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 results in a thoughtful, relevant

report. 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 Evidence-based Practice Center (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 nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts 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 Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

### **VIII. 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 preparation of 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 three months after the publication of the technical brief 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 may not have any financial conflict of interest greater than \$5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

### **IX. 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. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

### **X. Role of the Funder**

This project was funded under Contract No. HHS 290-2015-00009-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed 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 the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## 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. exp Drug Therapy/
4. dt.fs.
5. (medication\* or pharmacologic\* or pharmaco-therap\* or pharmacotherap\*).ti,ab.
6. (drug\* adj2 (therap\* or treatment\*)).ti,ab.
7. exp Adrenergic alpha-Antagonists/ or Sympatholytics/ or Doxazosin/ or Prazosin/
8. ("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.
9. exp Antipsychotic Agents/
10. ("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.
11. exp Benzodiazepines/
12. (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.
13. exp Monoamine Oxidase Inhibitors/
14. (("monoamine oxidase" adj2 inhibitor\*) or MAOI or isocarboxazid or phenelzine or selegiline or tranylcypromine).ti,ab.
15. carbamazepine/ or clonidine/ or lithium/ or pregabalin/ or valproic acid/
16. exp Anticonvulsants/
17. exp Antimanic Agents/
18. exp Cyclohexanecarboxylic Acids/
19. (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.
20. exp "hypnotics and sedatives"/ or exp anti-anxiety agents/
21. ("anti anxiety" or antianxiety or buspirone or diphenhydramine or eszopiclone or guanfacine or hydroxyzine or hypnotic\* or ramelteon or sedative\* or suvorexant or tasimelteon or zaleplon or zolpidem or zopiclone).ti,ab.
22. exp Antidepressive Agents/
23. (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 hydroxyzine 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.
24. exp Amphetamines/

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25. (amphetamine or armodafanil or atomoxetine or dexmethylphenidate or dextroamphetamine or lisdexamphetamine or MDMA or methamphetamine or methylphenidate or modafanil).ti,ab.
26. exp Steroids/
27. (DHEA or hydrocortisone or steroid\*).ti,ab.
28. exp Cannabinoids/
29. Cannabis/
30. Medical Marijuana/
31. (cannabi\* or marijuana or tetrahydrocannabinol or THC).ti,ab.
32. ketamine/
33. ketamine.ti,ab.
34. Propranolol/
35. propranolol.ti,ab.
36. exp Randomized Controlled Trials as Topic/
37. exp Randomized Controlled Trial/
38. double-blind method/ or random allocation/ or single-blind method/
39. Placebos/
40. (random\* or control\* or trial or sham or placebo\* or blind\* or dumm\* or mask\*).ti,ab,kw.
41. (1 or 2) and (or/3-35)
42. 41 and (or/36-40)

*Nonpharmacologic interventions*

1. stress disorders, post-traumatic/
2. ("posttraumatic stress disorder" or "post traumatic stress disorder" or PTSD).ti,ab.
3. th.fs.
4. exp Psychotherapy/
5. exp Complementary Therapies/
6. exp Convulsive Therapy/
7. Hyperbaric Oxygenation/
8. Transcranial Magnetic Stimulation/
9. exp Rehabilitation/
10. exp Dietary Supplements/
11. exp "Delivery of Health Care, Integrated"/
12. exp Self-Help Groups/
13. exp peer group/
14. exp social support/
15. exp Telemedicine/
16. telephone/ or exp cell phone/
17. (therap\* or psychotherap\* or counsel\* or nonpharma\* or non-pharma\*).ti,ab.
18. ("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.
19. exp Randomized Controlled Trials as Topic/
20. exp Randomized Controlled Trial/

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21. double-blind method/ or random allocation/ or single-blind method/
22. (random\* or control\* or trial or sham or blind\* or dumm\* or mask\*).ti,ab,kw.
23. (1 or 2) and (or/3-18)
24. 23 and (or/19-22)

**Database: ProQuest Published International Literature On Traumatic Stress (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\*

\*Based on discussion with the Technical Expert Panel and the Veterans Affairs National Center for Post-Traumatic Stress Disorder, some changes and additions were made to the data abstraction elements described in the Statement of Work. These are indicated with an asterisk.

### Study Characteristics

- a. Authors
- b. Year of publication
- c. Complete bibliographic citation for the study, including the PubMed ID\*
- d. PILOTS ID number, if available
- e. ClinicalTrials.gov number
- f. Funding source\*
- g. Country/Countries of study sites
- h. Setting (site type, clinical setting)\*
- i. Study design\*
- j. Number of enrolled participants
- k. Diagnostic instrument(s)
- l. Operational definition of PTSD (i.e., score or cutoff required for inclusion); DSM or ICD with version
- m. Proportion of sample meeting DSM-III, DSM-IV, or DSM-5 PTSD criteria at baseline
- n. Treatment conditions (interventions)
- o. Intervention classification (pharmacologic, nonpharmacologic, complementary and integrative, mixed)
- p. Providers have graduate degree\*
- q. Number of enrolled participants as well as the number of participants randomized to each study arm
- r. % meeting criteria for PTSD at baseline
- s. Duration of treatment (number of sessions and number of weeks), per study arm
- t. Number of sessions, per study arm
- u. Allowed/excluded co-interventions (text field)
- v. Primary PTSD outcome measure (if not reported, assume clinician-rated PTSD measure)
- w. All other outcome measures (list)
- x. Assessment time points for primary PTSD outcome
- y. Definition of treatment completion and/or adherence
- z. Indicate (Y/N) if subscale or symptom cluster data is reported\*
- aa. Indicate if subgroup analyses are reported\*

### Population Characteristics

- a. Trauma type required for study entry, if applicable
- b. Number of trauma types and traumatic events experienced per patient\*
- c. Duration of PTSD symptoms\*
- d. % Veteran
- e. % Active Duty Military
- f. % Civilian
- g. % Female

Source: <https://effectivehealthcare.ahrq.gov/>

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- h. Gender and sexual orientation if reported\*
- i. Age (M, range if available)
- j. Race % (by U.S. Census categories)\*
- k. Ethnicity (by U.S. Census categories)\*
- l. % with PTSD diagnosis
- m. Comorbid diagnoses required for study entry
- n. % Treatment naïve\*
- o. % with depression\*
- p. % with history of traumatic brain injury\*
- q. Exclusion of patients with suicidality\*

## Outcomes

- a. Number of participants who completed the treatment
- b. Number of participants who completed measurement for primary PTSD outcome measure at each time point
- c. Method for handling missing data for primary PTSD outcome measure
- d. Results for primary PTSD outcome measure
- e. Analysis type of primary PTSD outcome measure (ITT vs. completer)
- f. Statistical analysis method for primary outcome\*
- g. Results for other PTSD outcome measure
- h. Within group effect size on primary PTSD outcome measure, by condition at posttreatment and each available follow up time point
- i. Between group effect size for primary PTSD outcome at posttreatment and each available follow up time point, for each comparison
- j. Within group effect size for primary PTSD outcome at posttreatment and followup time points\*
- k. Proportion who achieved PTSD diagnostic change (loss of diagnosis), by condition
- l. Other reported cutoff for meaningful change (e.g., reliable change index, clinically significant change, 30% reduction in symptoms, remission of PTSD)
- m. Proportion who achieved other reported cutoff for meaningful change, by condition
- n. Results for all reported depression outcomes
- o. Results for all reported anxiety outcomes
- p. Results for all reported sleep outcomes
- q. Results for all reported anger outcomes
- r. Results for all reported quality of life outcomes
- s. Results for all reported functioning (social/interpersonal, occupational/school, sexual; parental) outcomes
- t. Results for all report substance use outcomes\*
- u. Harms (serious adverse events, study-related serious adverse events), by intervention