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Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the Evidence Base for the PTSD Trials Standardized Data Repository

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This report is based on research conducted by the <to be added for final report> Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. <#>). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

A representative from AHRQ served as a Contracting Officer's Representative and reviewed the contract deliverables for adherence to contract requirements and quality. AHRQ did not directly participate in the literature search, determination of study eligibility criteria, data analysis, interpretation of data, or preparation or drafting of this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The U.S. Department of Veterans Affairs requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: <to be added to final report> Evidence-based Practice Center (Contract Number: xxxx).

The reports and assessments provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies. This evidence report provides an overview of key issues related to the interventions included—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. The report includes data abstracted from published randomized controlled trials on interventions for posttraumatic stress disorder. These data were adapted to support the development of a publicly available repository by the National Center for Posttraumatic Stress Disorder (NCPTSD).

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that EPC evidence reports and technology assessments will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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 with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

Content Technical Expert Panel

The list of Technical Experts who provided input to this report will be added for the final version.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers 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 with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers who reviewed the report will be added for the final version.

Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the Evidence Base for the PTSD Trials Standardized Data Repository

Structured Abstract

Objectives. Identify and abstract data from randomized controlled trials (RCTs) examining treatment for posttraumatic stress disorder (PTSD) and comorbid PTSD/substance use disorder to update the previous Agency for Healthcare Research and Quality (AHRQ) report on this topic and the National Center for PTSD (NCPTSD) PTSD Trials Standardized Data Repository (PTSD-Repository) with newly published trials.

Data sources. We searched PTSDpubs, Ovid® MEDLINE®, Cochrane CENTRAL, PsycINFO®, Embase®, CINAHL®, and Scopus® for eligible RCTs published from August 1, 2021, to June 14, 2022.

Review methods. In consultation with AHRQ and NCPTSD, we updated the evidence tables for the PTSD-Repository by including evidence published after publication of the last update and expanding abstraction of results to include calculated standardized effect sizes. The primary publication for each RCT was abstracted; data and citations from secondary publications (i.e., companion papers) appear in the same record. We assessed risk of bias (RoB) for all newly included studies using the Revised Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials. For studies already in the PTSD-Repository, we will add calculated standardized effect sizes and update RoB using the new RoB 2 tool over the next several annual updates.

Results. We added 39 new RCTs examining treatments for PTSD, for a total of 475 included studies published from 1988 to June 14, 2022. Among all 475 included RCTs, studies of psychotherapy interventions were the most common (49%), followed by pharmacologic interventions (21%). Most studies were conducted in the United States (59%) and had sample sizes ranging from 25 to 99 participants (59%). Approximately half of the studies enrolled community (not specifically military) participants (54%), and most were conducted in outpatient settings (78%). Studies typically enrolled participants with a mix of trauma types (51%).

Among the 39 newly added RCTs, psychotherapy interventions were the most commonly employed (46%), followed by complementary and integrative health (18%). Approximately half of the studies were conducted in the United States (49%); the majority enrolled community participants (59%) and participants with a mix of trauma types (54%). Studies typically had sample sizes ranging from 25 to 99 participants (56%). Of the newly added RCTs, RoB was rated as high for 67 percent of studies, 15 percent were rated as having some concerns, and the remaining 18 percent were rated as low RoB.

Conclusions. This report updates the previous AHRQ report to include 39 recently published RCTs, for a total of 475 studies. This update adds comprehensive data, standardized effect sizes

for PTSD outcomes, and RoB assessment for the newly included RCTs. As with the previous AHRQ update, this report will serve as the updated evidence base for the PTSD-Repository, a comprehensive database of PTSD trials.

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Executive Summary

Main Points

- This update adds 39 newly published randomized controlled trials (RCTs) on posttraumatic stress disorder (PTSD) and comorbid PTSD/substance use disorder (SUD) to the previous Agency for Healthcare Research and Quality (AHRQ) report on this topic[1] and the National Center for PTSD (NCPTSD) PTSD Trials Standardized Data Repository (PTSD-Repository);[2] the new total of included RCTs is 475.
- Across all 475 RCTs:
  - The most commonly studied intervention was psychotherapy (49%), followed by pharmacologic interventions (21%), and complementary and integrative health (8%); 7 percent of studies used both pharmacologic and psychotherapeutic interventions.
  - Overall, most studies were conducted in the United States (59%), and most had sample sizes in the range of 25 to 99 participants (59%), with a relatively small number of studies enrolling more than 200 participants (8%).
  - Almost a third of studies (33%) targeted specific types of trauma; combat-related trauma was the most commonly targeted (15% of all studies), followed by terrorism/political violence/forced displacement (5%) and accidents (3%); 51 percent allowed a mix of trauma types and 16 percent did not provide information on participant trauma types.
- Across the 39 newly added RCTs:
  - The most commonly studied intervention was psychotherapy (46%), followed by complementary and integrative health (18%) and nonpharmacologic biologic interventions (10%); 8 percent of studies used both pharmacologic and psychotherapeutic interventions.
  - Almost half of the newly added RCTs were conducted in the United States (49%), and a majority enrolled community (not specifically military) participants (59%). Most had sample sizes in the range of 25 to 99 participants (56%), with a relatively small number of studies enrolling more than 200 participants (5%).
  - 18 percent of studies targeted a specific trauma type, and about half of studies allowed a mix of trauma types (54%); 28 percent did not provide information on participant trauma types.
- For studies added in this update, we abstracted data to calculate standardized effect sizes for continuous PTSD outcomes, and risk of bias (RoB) using the updated Cochrane RoB 2 tool for randomized trials. Of the 39 newly added RCTs, RoB was rated as low RoB for 18 percent, some concerns for 15 percent, and as high for the remaining studies (67%). For studies included prior to our implementation of RoB 2 (k=388), RoB is being progressively reassessed using RoB 2 and will be provided in a future update, along with calculated standardized effect sizes.

Background and Purpose

PTSD is a disorder that results from being exposed to a traumatic event. People with PTSD have symptoms such as flashbacks, avoidance of trauma-related stimuli, negative beliefs about themselves and/or others, and hypervigilance. These symptoms reduce quality of life and function. The purpose of this report is to update the previous AHRQ report[1] by identifying and

abstracting data from newly published RCTs examining treatment for PTSD and comorbid PTSD/SUD: this project builds upon our previous work.[1,2,3,4] These data will inform the subsequent update and expansion of the PTSD-Repository (a publicly accessible clinical trials database maintained by the NCPTSD).[5] A comprehensive data repository allows future systematic reviews to easily identify includable studies and extract data relevant to their review. The PTSD-Repository can also help identify research gaps to determine future research priorities and encourage researchers to adopt standard data elements in research and reporting. In addition, it can serve as a source for patients, clinicians, and policymakers to search for evidence on the effectiveness of specific interventions and augment existing patient education tools.

Methods

We followed methods outlined in the AHRQ Evidence-based Practice Center Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview) where applicable.[6] For this update, we searched PTSDpubs (formerly PILOTS), Ovid® MEDLINE®, Cochrane CENTRAL, PsycINFO®, Embase®, CINAHL®, and Scopus® for eligible RCTs published from August 1, 2021, to June 14, 2022. We dually reviewed citations from the literature search and potentially includable full-text articles for eligibility, resolving disagreement by consensus. We developed evidence tables for the prior updates[1,2] and for this update; one team member abstracted data from included RCTs into these evidence tables and a second reviewer checked for accuracy and completeness. An investigator assessed RoB for newly added studies using Cochrane's RoB 2: A Revised Tool for Assessing Risk of Bias in Randomized Trials,[7] and a second reviewer checked for accuracy. For studies included prior to our implementation of RoB 2 (k=388), an investigator reassessed a subset of the 388 studies using RoB 2 and a second reviewer checked for accuracy. Note that we do not provide summary statistics for RoB assessment of all 475 studies in this update, since we will not complete updated RoB assessment for all 388 studies from the previous reports in this phase; complete RoB assessment using the updated Cochrane RoB 2 tool and summary statistics will be provided in future annual updates.

Results

In this update, we added 39 RCTs examining treatments for PTSD for a total of 475 included RCTs overall. The updated report now includes 133 pharmacologic studies (trials with at least one medication arm) and 342 nonpharmacologic studies (trials with no medication arms). Across all 475 RCTs, the most commonly studied intervention was psychotherapy (49%), followed by pharmacologic interventions (21%), and complementary and integrative health (8%); 7 percent of studies used both pharmacologic and psychotherapeutic interventions. Overall, most studies were conducted in the United States (59%), and enrolled community (not specifically military) populations (54%). A total of 40,329 participants are represented; sample sizes ranged from 8 to 943 with most studies (59%) enrolling 25 to 99 participants.

Among the 39 newly added RCTs, psychotherapy interventions were the most commonly employed (46%), followed by complementary and integrative health (18%). The 475 trials were published from 1988 to 2022. A majority of studies were conducted in the United States (59%), enrolled community participants (59%), and about half enrolled participants with a mix of trauma types (51%). The newly added studies had sample sizes ranging from 20 to 916, with most studies having a sample size between 25 and 99 participants (56%). The Clinician-Administered PTSD Scale (CAPS) and the PTSD CheckList (PCL) were measures most

frequently used to assess continuous PTSD outcomes, used in 59 percent and 51 percent of studies, respectively. PTSD diagnostic change or clinically meaningful response were assessed in 46 percent of studies. Among non-PTSD outcomes, depression was the most commonly assessed (62% of the newly added studies). Of the 39 newly added RCTs, 67 percent were rated as high RoB, 15 percent were rated as some concerns, and 18 percent were rated as low RoB.

Limitations

Study inclusion was limited to studies published in English. Many data elements were not reported or were reported in an inconsistent manner across the available body of literature. Data elements that were infrequently reported include the number of participants with a history of traumatic brain injuries, SUD, or suicidal ideation/behavior, and mean number of trauma types per participant.

Implications and Conclusions

This report updates the previous AHRQ report on this topic[1] with comprehensive data, calculated standardized effect sizes for PTSD outcomes, and RoB assessment from 39 recently published trials. As with the previous AHRQ reports on this topic,[1,2,3] this update will be used by NCPTSD to inform updates to the PTSD-Repository, a publicly available PTSD trials database (accessible at https://www.ptsd.va.gov/ptsdrepository/index.asp) that allows clinical, research, education, and policy stakeholders to understand current research on treatment effectiveness and harms, and enables these stakeholders to more quickly and accurately make informed decisions about future research, mental health policy, and clinical care priorities. These updates ensure that all available evidence is included and accessible for a broad range of users. Updating RoB assessment to the same scale for all studies and adding standardized effect sizes will allow for more efficient and accurate comparisons across PTSD trials.

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Introduction

Background

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 between 3.4 and 8.0 percent in U.S. civilians and 7.7 to 13.4 percent in U.S. military veterans.[2-5] Individuals with PTSD are often more likely to experience other mental health comorbidities compared to those without, particularly substance use.[3] For example, studies estimate that around one quarter to one half of individuals who have experienced PTSD in their lifetime also met criteria for a substance use disorder.[6,7]

Since PTSD was first included by the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) in 1980, there have been over 400 published randomized controlled trials (RCTs) evaluating a wide range of treatments and treatment modalities (e.g., psychotherapy, psychopharmacotherapy, complementary and integrative approaches, etc.). Many systematic reviews also aim to include nonrandomized comparative studies, which likely number in the thousands. Given the large and varied body of evidence, to make reviews on this topic feasible, 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.[8] 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. In addition, heterogeneity of review methods, scope, and data presentation make it difficult to synthesize across reviews and have led to variation in conclusions.[9,10] Methodological differences, such as data coding approaches and combining treatment categories for analysis, further limit the comparability of findings.

Purpose and Scope

Answering important clinical questions about PTSD treatments requires the examination of all available data, yet existing systematic reviews do not make this logistically easy, and they may intentionally exclude important treatments 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-analysis 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 address this need, the PTSD Trials Standardized Data Repository or "PTSD-Repository" was created to: (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] The Department of Veterans Affairs' National Center for PTSD (NCPTSD) partnered with the

Agency for Healthcare Research and Quality (AHRQ) to develop the evidence tables that form the basis of the PTSD-Repository.

The initial development of the evidence tables and subsequent update have been detailed elsewhere.[13-15] The purpose of this update review, and the three earlier AHRQ reviews, is to search the literature to identify and abstract data from RCTs examining treatment for PTSD and comorbid PTSD/substance use disorder (SUD) to inform the PTSD-Repository.[16] This publicly accessible clinical trials database is maintained by NCPTSD and available at https://www.ptsd.va.gov/ptsdrepository/index.asp. The initial 2018 report[13] identified 318 studies. The second report[15] was an update to the evidence, published in 2020, with expansion of the inclusion criteria (including adding studies focused on treating comorbid PTSD-SUD on the recommendation of the Technical Expert Panel and NCPTSD) and extension of the search dates to include newly published studies, bringing the total number of included studies to 389. The third report, published in 2022 added 48 studies to the database for a total of 437 included studies.[17] This current update builds on the prior AHRQ reports by adding 39 newly published RCTs, as well as making minor updates to the database for all studies such as adding detailed information on inclusion and exclusion criteria for all included studies. Specifically, this report updates the database to include RCTs of PTSD interventions published from August 1, 2021 through June 14, 2022 (studies published since the completion of the last update[17]). Because one trial previously included was found to be ineligible (due to ineligible study design) and removed, the database now includes a total of 475 RCTs.

As in the previous update,[17] this update used the Cochrane RoB 2 tool to assess RoB for the newly included studies and a subset of the previously included studies. Future updates will expand RoB 2 assessment and for all previously included studies.

Key Question

Key Question 1. What interventions have been studied for the treatment of PTSD alone or with comorbid SUD?

The Key Question is based on updating the same body of literature included in Technical Brief No. 32[13] and expanded to include interventions targeting comorbid PTSD/SUD, as examined in CER No. 235.[15] 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 a patient-reported assessment tool
- **Interventions:**
  - Pharmacologic and nonpharmacologic interventions, including complementary and integrative approaches, for treatment of 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

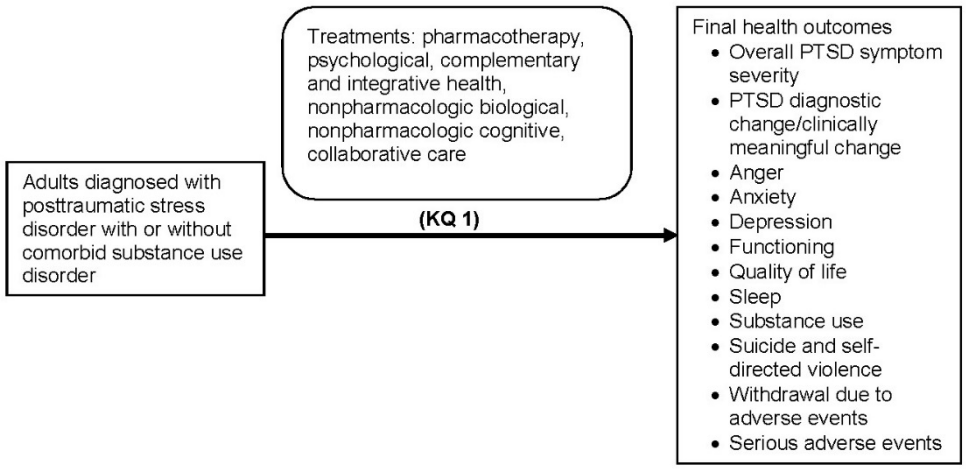
- Other outcomes – Anxiety, anger, depression, function, quality of life, sleep, substance use, suicide- and self-directed violence, withdrawal due to adverse events, serious adverse events

- **Timing:**
  - No limitation on study duration or length of followup
- **Settings:**
  - No limitation on study setting
- **Study Design:**
  - RCTs

Analytic Framework

Figure 1 depicts the Key Question within the context of the PICOTS inclusion and exclusion criteria presented in Table 1 in the Methods chapter. Figure 1 illustrates how PTSD treatments – including pharmacotherapy, psychotherapy, nonpharmacologic biologic treatments (e.g., biofeedback, vagal nerve stimulation), and complementary and integrative approaches – may be associated with health and functional outcomes (such as 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 treatments of posttraumatic stress disorder



Abbreviations: KQ = Key Question; PTSD = posttraumatic stress disorder

Methods

This report follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews[18] where applicable to creating a systematic data repository. Methods were determined *a priori* after discussion with AHRQ and the National Center for PTSD (NCPTSD), and are consistent with methods utilized in our first report[13] and the last update.[17] A protocol was published on the AHRQ website (https://effectivehealthcare.ahrq.gov/products/ptsd-pharm-nonpharm-treatment-update/protocol).

Criteria for Inclusion/Exclusion of Studies in the Review

Detailed inclusion and exclusion criteria for the Key Question are listed in Table 1 following the PICOTS (populations, interventions, comparators, outcomes, timing, settings, study design) criteria identified above (see Key Question). These inclusion and exclusion criteria are the same as those applied in our previous update report.[17] We included treatments for PTSD and comorbid PTSD/substance use disorder (SUD). Treatments targeting PTSD and a comorbid condition other than SUD were included as long as the treatment could be used for PTSD alone (i.e., without the presence of the comorbid condition). For example, treatments for PTSD and insomnia were included because sleep difficulties are often part of a standalone PTSD diagnosis, and therefore these treatments could be used for PTSD without the presence of another diagnosis. Similarly, treatments for comorbid PTSD and depression were included if they were appropriate for individuals with a standalone PTSD diagnosis because of the frequency of mood-related impacts of PTSD even without a comorbid diagnosis of depression.

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 study-defined 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 biologic 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.
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 followup	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)

Abbreviations: PICOTS = populations, interventions, comparators, outcomes, timing, settings, study design; PTSD = posttraumatic stress disorder; RCTs = randomized controlled trials; SUD = substance use disorder

Literature Search

Electronic databases were searched for evidence from August 1, 2021, to June 14, 2022. An updated literature search will be conducted concurrently with the peer review process and public

comment period, and any new literature identified that meets inclusion criteria will be incorporated into the final report.

Literature databases searched included PTSDpubs (formerly PILOTS), Ovid® MEDLINE®, Cochrane CENTRAL, Embase®, the Cumulative Index to Nursing and Allied Health Literature (CINAHL®), SCOPUS, and PsycINFO®. Search strategies are provided in Appendix A. The search strategies were developed and conducted by the Pacific Northwest Evidence-based Practice Center (EPC) librarian and peer reviewed by a NCPTSD librarian. A gray literature search was not conducted. Due to the nature of the project, a portal for submission of Supplemental Evidence And Data for Systematic review (SEADS) was not opened for this project.

PICOTS (Table 1) were used to determine eligibility for inclusion and exclusion of abstracts. One reviewer determined eligibility at the title/abstract review stage and a second investigator reviewed excluded records. For records included at the title/abstract review stage, full-text articles were retrieved and reviewed independently for eligibility by two reviewers. Disagreements were resolved by consensus of the team of investigators. A record of included studies is available in Appendix B and studies excluded at the full-text level with reasons for exclusion appear in Appendix C.

Data Abstraction

After studies were screened and deemed to meet inclusion criteria, study data were abstracted, including study design, year, setting, country, sample size, eligibility criteria, source(s) of funding, study characteristics, population characteristics, intervention characteristics, and study results (see Appendix D for a complete list of data elements abstracted). Data were abstracted into detailed evidence tables in Microsoft® Excel developed for the first report[13] and revised for the 2020 and 2022 reports[15,17] to include additional data elements such as study inclusion/exclusion criteria related to suicide and psychosis, proportion of participants with comorbidities at baseline (e.g., suicidal ideation/behavior, psychotic, personality, and anxiety disorder, and prior hospitalization), results for secondary PTSD outcomes at treatment arm-level, and results for suicide- or self-directed violence-related outcomes including suicidal ideation/behavior. In this current update, detailed data on inclusion and exclusion criteria were added to the database, including quoted inclusion/exclusion criteria sections pasted directly from the published, included studies.

For the last update,[17] the evidence tables were restructured to ensure that future updates to the PTSD-Repository no longer required any hand searching and editing when transforming data from the Microsoft® Excel data tables into the PTSD-Repository online database, and that most, if not all, data integration processes could be automated using replicable syntax. The last update also added calculation of standardized effect sizes for newly included studies, provided the study reported the necessary data, and newly added studies from this current update also include these standardized effect size data. Previously included studies will be updated to include standardized effect size data in future updates. All abstracted data were dual reviewed for accuracy and completeness. Evidence tables are available in Appendix E and Appendix F.

A separate evidence table was constructed to record RoB assessments, described below. All studies regardless of overall RoB rating were incorporated in the summarized results presented below. Results from studies were not synthesized, but characteristics of included studies including number of publications by year, study sample size, proportion of studies enrolling

community versus military/veteran populations, and distribution of studies by PTSD assessment method, were summarized using simple counts and proportions.

Standardized Effect Size Calculation

Standardized effect sizes were calculated for continuous PTSD outcomes for newly included studies, provided the necessary data was reported in the study. Future updates will add calculated standardized effect sizes for all previously included studies. To facilitate comparison across studies and across outcomes, a within-arm effect size was calculated using formula (Figure 2), as an analog of Cohen's *d*. Hedge's *g* was used as the standardized effect size for between-arm comparisons. Hedge's *g* was calculated based on adjusted mean difference, if reported. Otherwise, it was calculated based on followup scores or change scores, with followup scores preferred. We preferred followup scores because they have been shown to be more conservative when combining RCTs compared to placebo, when baseline scores show some evidence of imbalance. When baseline scores are balanced, the followup score and change score provide similar results.[19] For studies not reporting standard deviation, it was calculated from 95 percent confidence interval whenever reported. All analyses were performed using R (version 4.1.0).

Figure 2. Within-arm effect size formula

$$d = \frac{Mean_{folow\ -up} - Mean_{baseline}}{s}$$

$$\text{Where, } s = \sqrt{s^2_{baseline} + s^2_{follow\ -up} - 2 \times corr \times s_{baseline} \times s_{follow\ -up}}$$

$$\text{Assuming correlation} = 0.5 \text{ and } N_{baseline} = N_{follow\ -up}$$

Assessment of Methodological Risk of Bias of Individual Studies

Risk of bias was assessed for all new randomized controlled trials (RCTs) added in this update using Cochrane's RoB 2 system. To augment and clarify aspects of the RoB assessments to ensure transparency and ease of future updating, we included detailed definitions related to how RoB was assessed. We also abstracted RoB-related data into additional columns to document the overall percent of primary PTSD outcome assessment data that was missing (i.e., overall attrition from measurement) and the percent primary PTSD outcome data in each arm of the study of missing that was missing (i.e., differential attrition from measurement). Because previously-included studies from prior reports[15] were assessed with an earlier version of Cochrane's RoB assessment tool based on the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Review,[20] we updated RoB assessments for a subset of RCTs previously included the PTSD-Repository in this report and plan to complete the transition to the Cochrane RoB 2 system for the remaining studies in future updates. Appendix G contains RoB assessments: 39 newly included studies assessed using RoB 2 (Appendix Table G-1); 231 studies included in prior reports and not yet updated to RoB 2 (Appendix Table G-2); and 244 studies assessed using RoB 2 (Appendix Table G-3).

Grading the Strength of Evidence for Major Comparisons and Outcomes

Strength of evidence was not assessed for this review.

Assessing Applicability

Applicability was not assessed for this review.

Peer Review and Public Commentary

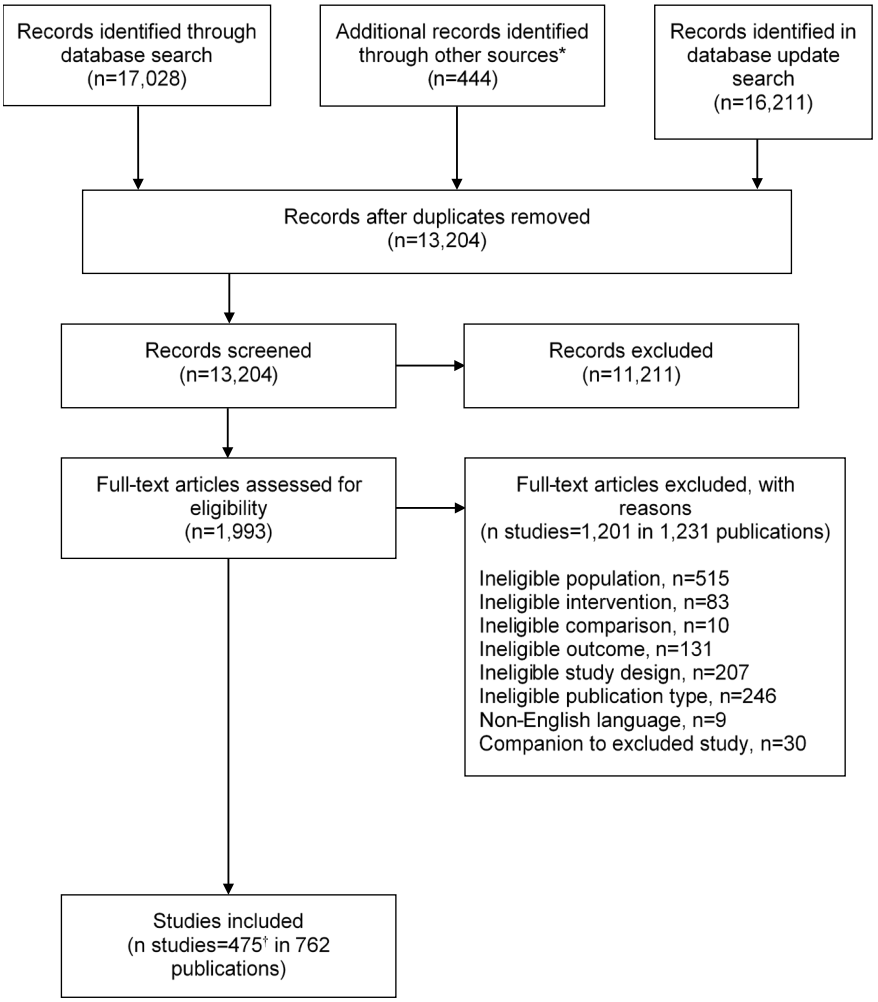
Experts in the field of PTSD will be invited to provide external peer review of this review and evidence tables. Comments and editorial review were also sought from the AHRQ Task Order Officer, an associate editor, and partners at NCPTSD. The draft report will be posted on the AHRQ website for 4 weeks to elicit public comment. In response to reviewers' comments, we will revise text as needed and address all relevant reviewer comments in an associated disposition of comments report with the authors' individual responses. This report will be posted after the publication of the final evidence report on the AHRQ website.

Results

Results of Literature Search

In this update we included 39 new studies[21-59] published through June 14, 2022, bringing the total number of included studies in this report to 475 (in 762 publications). The literature flow diagram (Figure 3) summarizes the search and selection of articles performed previously in prior reports in addition to this update to provide a comprehensive overview of all included studies. Combining all database searches and other sources yielded 13,205 unique records. After review of abstracts and titles, 1,993 articles were selected for full-text review, and 475 studies were determined to meet inclusion criteria and were designated for data abstraction. Reasons for exclusion of studies were ineligible population, intervention, outcomes, study design, publication type, and foreign language articles. Appendix B contains the list of studies that met inclusion criteria; Appendix C lists studies excluded upon full-text review and reasons for exclusion.

Figure 3. Literature flow diagram (summary of all included studies)



*Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
†In this update report, 39 new studies were included and 1 prior report included study[60] was excluded.

Characteristics of Included Studies

Treatments were classified by the intervention categories described in Table 2. These categories included pharmacologic treatments and five nonpharmacologic treatment categories, which are psychotherapy, nonpharmacologic biologic treatments, nonpharmacologic cognitive therapy, complementary and integrative health, and collaborative care. Each treatment arm was classified; an arm could have more than one intervention category because a treatment could include interventions falling into different categories. For example, a study that evaluated a combined psychotherapy and pharmacotherapy intervention versus control intervention would have the first arm classified as both psychotherapy and pharmacotherapy, and the second arm as control.

Table 2. Intervention categories with examples*

Category	Definition	Examples
Pharmacotherapy	Medication	Antiadrenergic drugs Antidepressants Antipsychotics Benzodiazepines Cannabinoids Mood Stabilizers
Nonpharmacologic Biologic	Interventions that use a medical device or procedure of some kind.	Electroconvulsive therapy Hyperbaric oxygen therapy Repetitive transcranial magnetic stimulation Stellate ganglion block Vagal nerve stimulation Neurofeedback
Complementary and Integrative Health	Wide category of approaches that are considered to be outside the standard in the current practice of Western medicine.	Acupuncture Clinical hypnosis Meditation Massage therapy Tai chi/qi gong Yoga
Psychotherapy	Talk therapy with a licensed provider	Cognitive Processing Therapy Eye Movement Desensitization and Reprocessing Cognitive Behavioral Therapy Narrative Exposure Therapy Present-centered therapy Prolonged Exposure
Nonpharmacologic Cognitive	Interventions that teach cognitive skills to improve attention.	Attention bias modification Attention control training
Collaborative Care	Interventions in which integrated medical and mental health treatment is delivered in primary care, often by nurse managers.	Centrally assisted collaborative telecare Three component model Trauma-informed collaborative care
Other	Treatments that don't fit into another category	Animal-assisted Other physical activity and recreational therapies Digital interventions not delivered by a licensed provider
Control	Comparison conditions such as a placebo pill, waitlist, and treatment as usual.	Placebo Psychoeducation Sham Treatment as Usual Waitlist

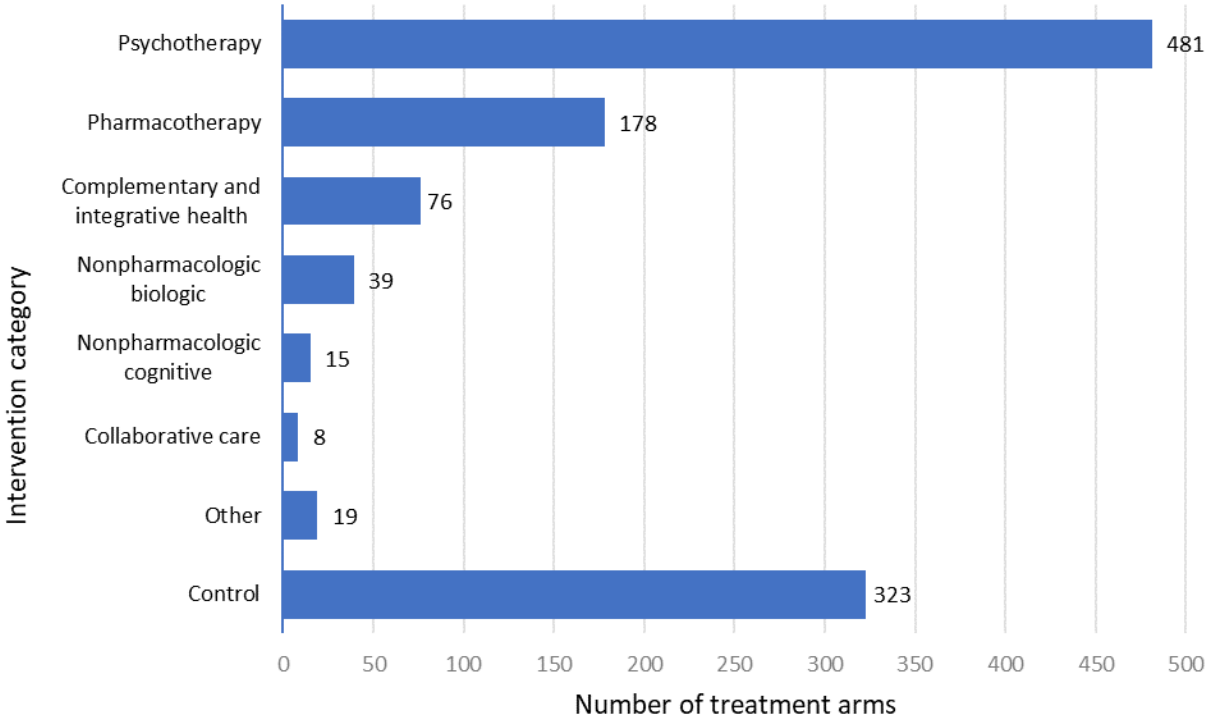
*Table 2 intervention lists and categories adapted from the 2017 Department of Veterans Affairs/Department of Defense clinical practice guideline.[61]

Overall Studies Included in the Evidence Tables

The data abstraction evidence tables (Appendix E and Appendix F) for this report presents detailed information on study and population characteristics for the 475 total included studies.

The distribution of treatment arms by intervention category is shown in Figure 4. Psychotherapy was the most frequently studied treatment, employed in 46 percent of total treatment arms, followed by pharmacotherapy in 17 percent of treatment arms.

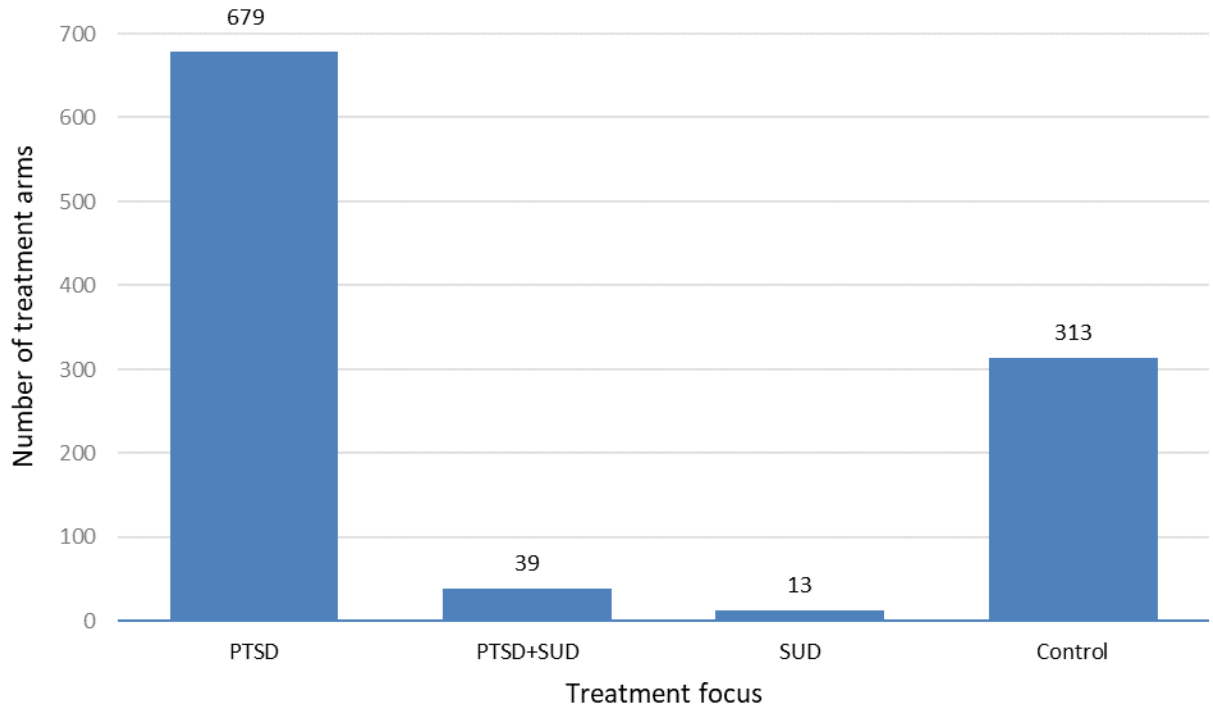
Figure 4. Summary of all included studies: distribution of treatment arms by intervention category[a]



[a] Studies have more than one treatment arm, and a treatment arm may include multiple intervention categories.

Treatment arms were also classified by treatment focus (e.g., PTSD, PTSD and SUD, SUD or control) as shown in Figure 5. In this classification, each arm was classified into a single category. Across included studies, comorbid PTSD/SUD was the focus for 4 percent of treatment arms and 1 percent focused on SUD. Sixty-five percent of treatment arms addressed PTSD and 30 percent were non-therapeutic control arms.

Figure 5. Summary of all included studies: distribution of treatment arms by treatment focus[a]

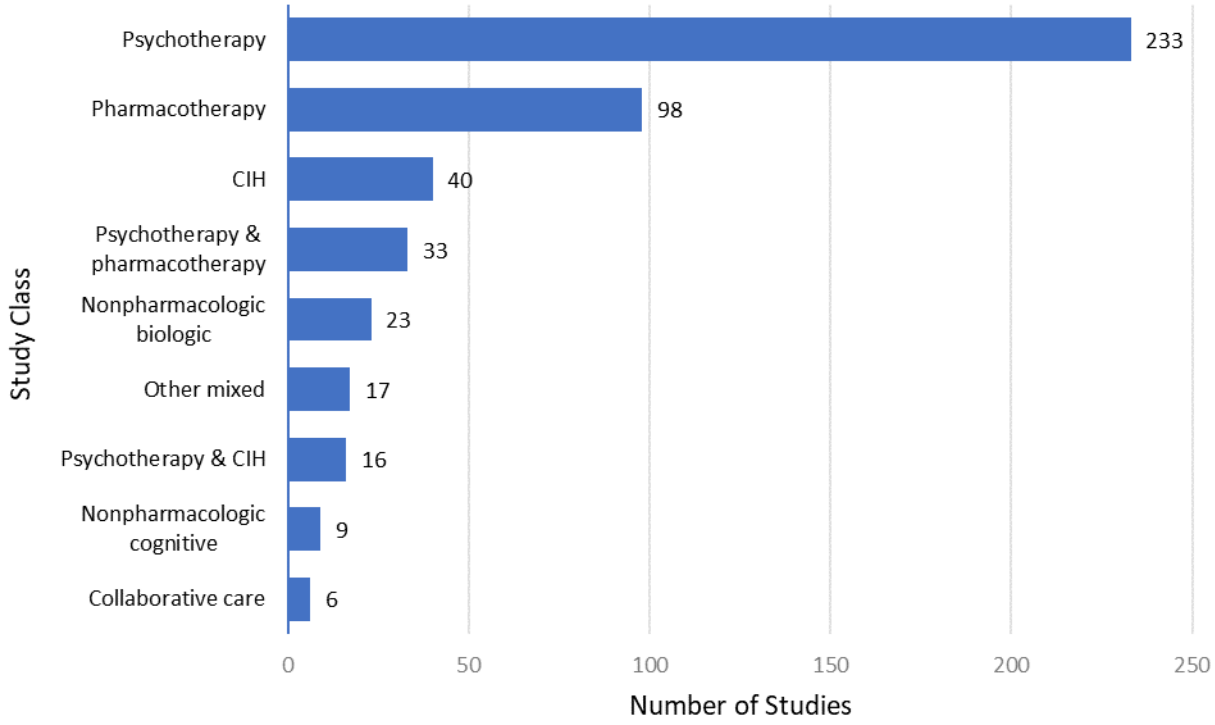


[a] Studies have more than one treatment arm.
Abbreviations: PTSD = posttraumatic stress disorder; SUD = substance use disorder

Studies were grouped into nine study classes based on interventions studied. For studies in which the treatment arms were all the same category, or compared with a treatment arm categorized as control, then the study was categorized as the study class of the active treatment(s). For example, a study of prolonged exposure (psychotherapy) versus waitlist (control) would be categorized as psychotherapy for the study class. Studies in which the treatment arms were of different intervention categories were classified into a combination category for study class, for the most common combinations (i.e., psychotherapy and pharmacotherapy, and psychotherapy and CIH). Other combinations were grouped in the other mixed study class.

Most studies examined interventions within a single category versus a control (409 studies, 86%), predominantly psychotherapy or pharmacotherapy treatments (49% and 21% of all studies, respectively) (Figure 6).

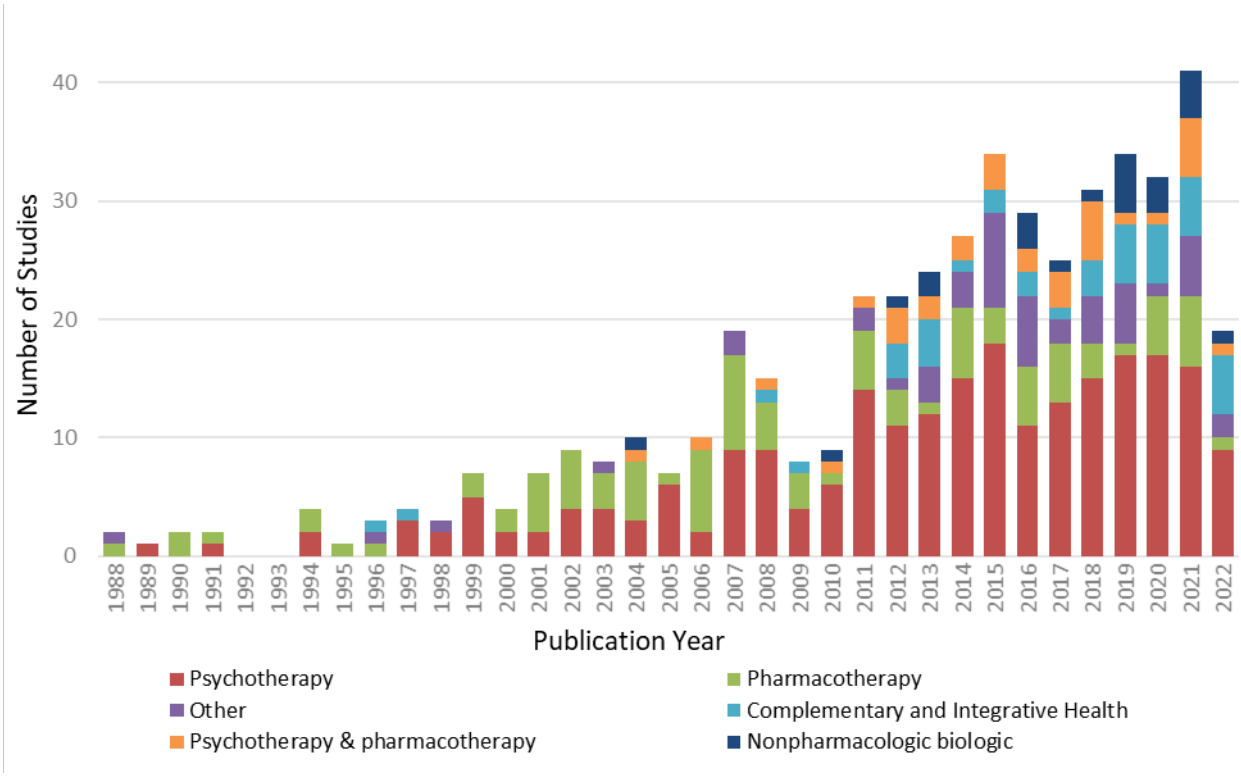
Figure 6. Summary of all included studies: distribution of included publications by study class



Other mixed includes studies in which the interventions studied were classified as "Other", or were a combination other than psychotherapy & pharmacotherapy or psychotherapy & CIH (e.g. nonpharmacologic biologic & psychotherapy)
Abbreviations: CIH = complementary and integrative health

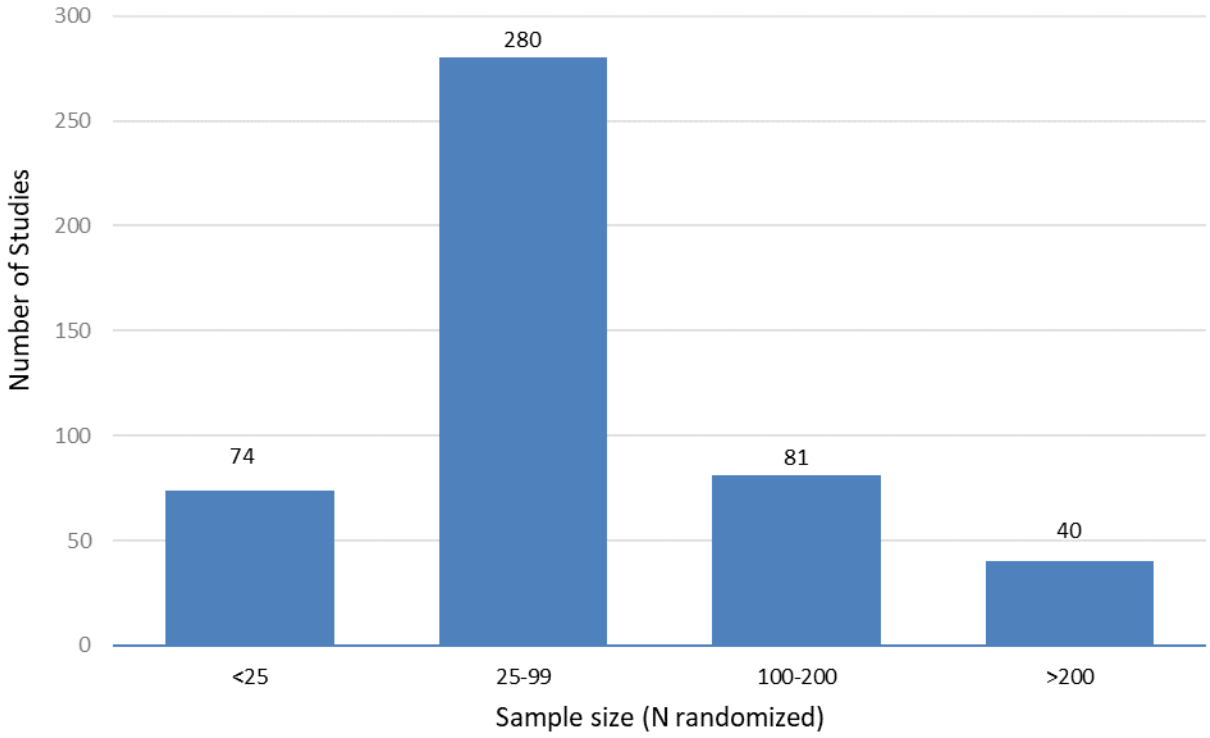
The publication dates of the included studies ranged from 1988 to partway through 2022 (Figure 7). Forty-one studies were published in 2021, the highest amount of any year. The number of studies published per year increased in the 2000s. This increase was seen particularly with psychotherapy treatment studies—24 studies of psychotherapy interventions were published in 2015, compared with six pharmacologic studies. Most studies of CIH interventions were published in the last ten years, a trend also observed with studies of nonpharmacologic biologic and nonpharmacologic cognitive interventions.

Figure 7. Summary of all included studies: distribution of included publications by year



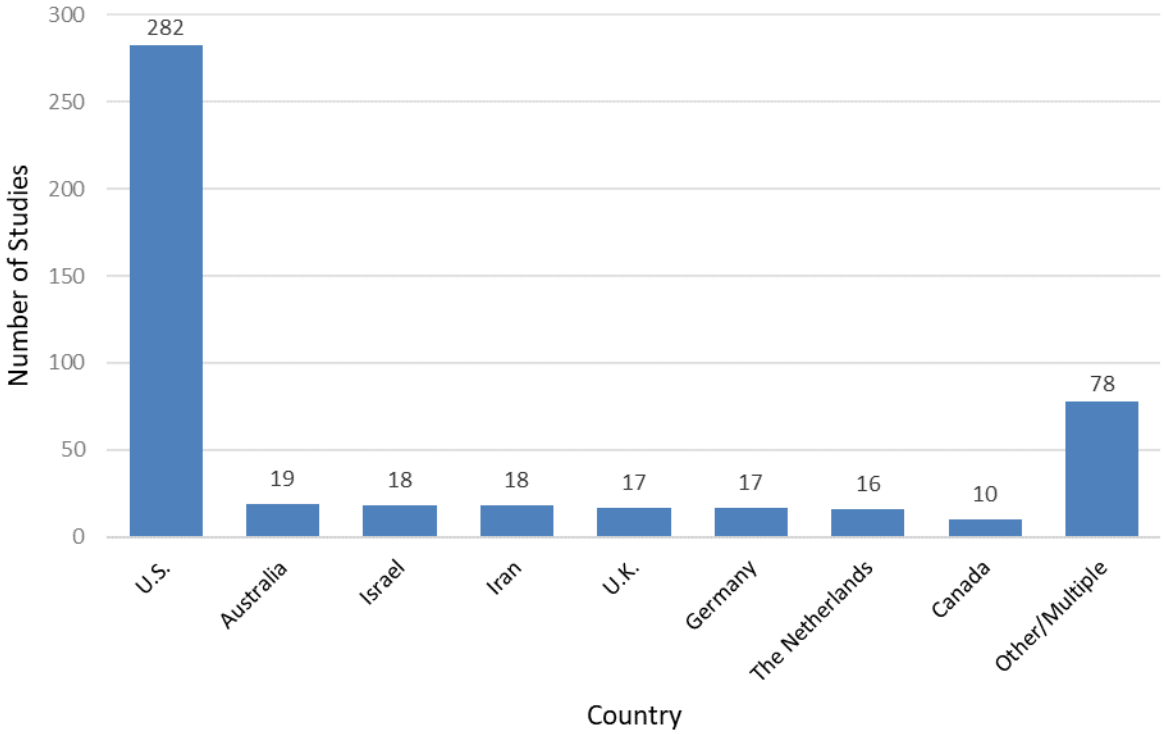
Sample sizes across included studies ranged from eight to 943 participants, with a total of 40,329 participants included in the database. The median sample size was 55 (interquartile range [IQR] 30 to 100). A little over half of studies (59%) had sample sizes in the range of 25 to 99 participants and a relatively small number of studies (17%) enrolled fewer than 25 participants (Figure 8).

Figure 8. Summary of all included studies: studies by sample size



The majority of studies (59%) were conducted in the United States (Figure 9), though it is important to note that inclusion eligibility required that the study was published in English.

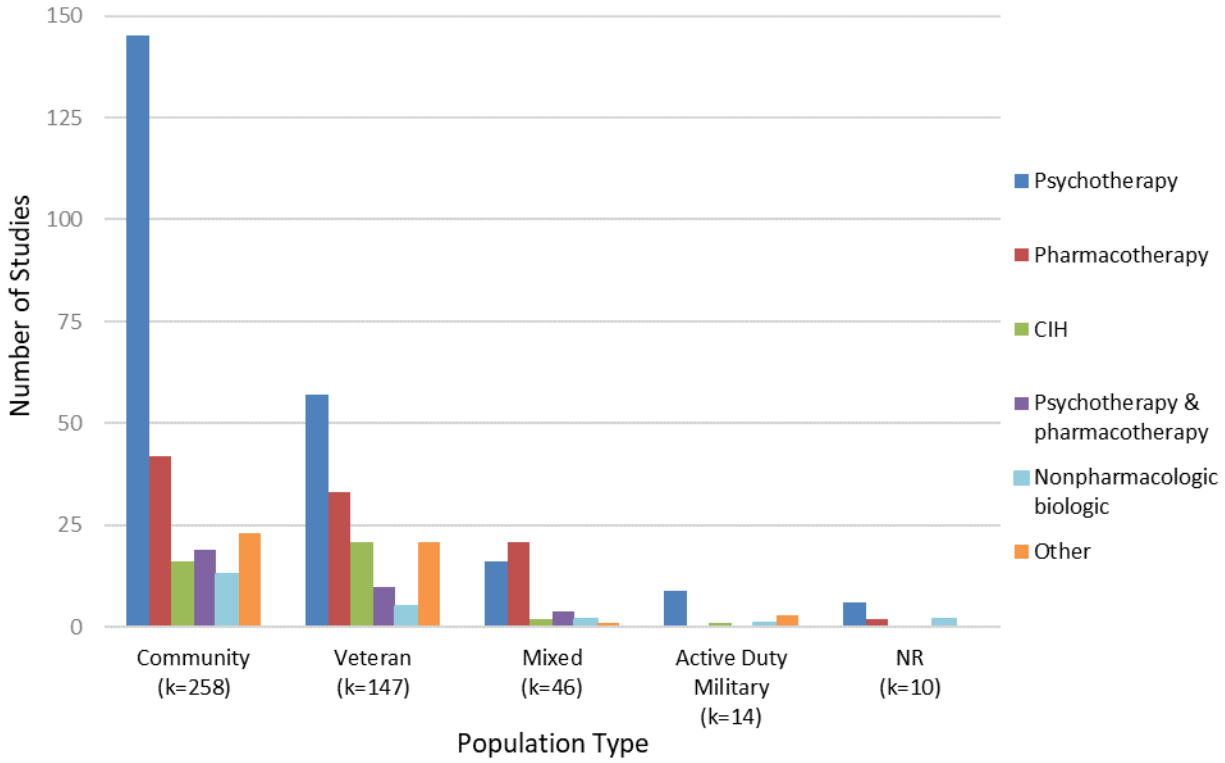
Figure 9. Summary of all included studies: distribution of included studies by country



Multiple = study conducted in multiple countries. Only the eight countries with largest number of studies were included in this graph, studies conducted in the remaining countries are counted in "Other/Multiple".
Abbreviations: U.K. = United Kingdom; U.S. = United States

Slightly more studies enrolled participants from a community population (54% of studies) than from a military, veteran, or mixed population (Figure 10). Community samples may or may not include Active Duty Military or veteran participants, as many studies did not clarify these variables when describing community samples. The community population was predominant across trials of most treatment types (psychotherapy, pharmacologic, and nonpharmacologic biologic RCTs); however, for CIH, most studies (53%; 21 of 40 studies) were among veterans.

Figure 10. Summary of all included studies: distribution of included studies by population type

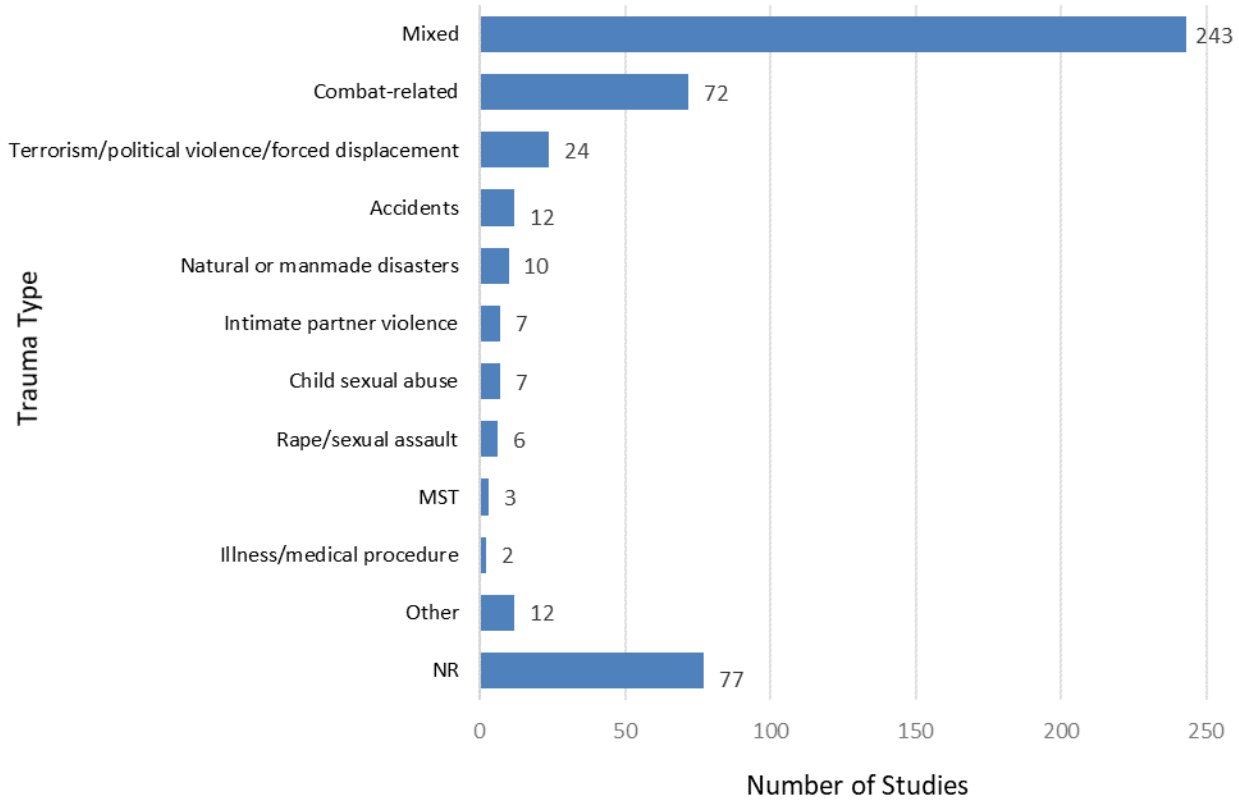


Mixed = Any combination of Active Duty Military, veteran, and Community based samples.
Abbreviations: CIH = complementary and integrative health; k = number of studies; NR = not reported

Only a small proportion of studies (k=36, 8%) included any participants with subthreshold PTSD. However, studies including more than 20 percent of participants with subthreshold PTSD were excluded from the database according to inclusion/exclusion criteria (i.e., only those with more than 80% of participants with PTSD were included in the database and in this calculation). Most studies (78%) were conducted in the outpatient setting.

Some studies targeted specific types of trauma (e.g., required participants to have experienced combat-related trauma or sexual assault), though in most cases other additional trauma types were allowed (i.e., most studies did not target specific types of trauma and included participants with a mix of trauma types). The distribution of included studies by trauma type are shown in Figure 11, with mixed trauma types being most prevalent among these study populations (51%), followed by combat-related trauma (15%).

Figure 11. Summary of all included studies: distribution of included studies by trauma type



Notes: Active Duty member reporting sexual assault outside of military was categorized as rape/sexual assault. Intimate partner violence includes domestic violence. Accidents includes motor vehicle accidents, transportation-related accidents, and accidents due to construction. Natural or manmade disasters includes tornadoes, hurricanes, wildfires, earthquake, drought, and chemical spills. Mixed indicates multiple trauma types were targeted/included (e.g., a study which included participants with either child sexual abuse or rape/sexual assault would be classified as mixed).
Abbreviations: NR = not reported; MST = military sexual trauma

Studies Added in this Update

Key characteristics for the 39 studies added in this update are described in Tables 3-5. Table 3 provides study and sample characteristics. Table 4 details characteristics of the interventions. Table 5 provides a list of outcomes for each of the studies. Additional information about these studies are included in the detailed data abstraction evidence tables in Appendix E.

Table 3. Summary of newly included studies: study and sample characteristics

Author, Year	Study Class	Sample Size	Countries	Clinical Setting	Military Status	Race/Ethnicity Reported	Trauma Type
Abdallah, 2022[21]	Pharmacotherapy	158	U.S.	Outpatient clinic	Mixed	Race and Ethnicity data reported	NR
Abraham, 2022[22]	CIH	29	U.S.	NR	Mixed	Race and Ethnicity data reported	NR
Acierno, 2021[23]	Psychotherapy	136	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	MST
Alon, 2022[24]	Nonpharmacologic cognitive	60	Israel	Telehealth	Community	Not reported	Mixed
Baig, 2022[25]	Psychotherapy and Pharmacotherapy	20	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	Combat-related
Brady, 2021[26]	Psychotherapy	25	U.K.	Outpatient clinic	Community	Not reported	Terrorism/political violence/forced displacement
Bremner, 2021[27]	Nonpharmacologic Biological	20	U.S.	Mixed	NR	Race data reported	Mixed
Dell, 2022[28]	Psychotherapy	138	Australia	Mixed	Mixed	Not reported	Mixed
Devilly, 1999[29]	Psychotherapy	23	Australia	Outpatient clinic	Community	Not reported	Mixed
Doenyas-Barak, 2022[30]	Nonpharmacologic Biological	35	Israel	NR	Veteran	Not reported	Combat-related
Echiverri-Cohen, 2021[31]	Nonpharmacologic cognitive	49	U.S.	Outpatient clinic	Community	Race data reported	NR
Fruchtman-Steinbok, 2021[32]	CIH	59	Israel	Outpatient clinic	Community	Not reported	Mixed
Gibert, 2022[33]	CIH	34	France	Other	Community	Not reported	Terrorism/political violence/forced displacement
Isserles, 2021[34]	Nonpharmacologic biological	125	Israel, Canada, U.S., Europe	Outpatient clinic	Community	Race and Ethnicity data reported	Mixed
Jahanpour, 2019[35]	CIH	60	Iran	Inpatient	Community	Not reported	NR
Jamshidi, 2020[36]	Psychotherapy	30	Iran	Residential inpatient	Community	Not reported	Mixed
Khan, 2021[37]	Psychotherapy	30	Pakistan	Other	Community	Not reported	NR
Kobayashi, 2021[38]	Psychotherapy and Pharmacotherapy	27	U.S.	Outpatient clinic	Community	Race and Ethnicity data reported	Mixed
Koebach, 2021[39]	Psychotherapy	448	Democratic Republic of Congo	Unclear/NR	Veteran	Not reported	Mixed

Author, Year	Study Class	Sample Size	Countries	Clinical Setting	Military Status	Race/Ethnicity Reported	Trauma Type
Leem, 2021[40]	Nonpharmacologic Biological	22	South Korea	Outpatient clinic	Community	Not reported	Mixed
Lehrner, 2021[41]	Psychotherapy and Pharmacotherapy	60	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	Other
Meredith, 2022[42]	Collaborative Care	40	U.S.	Primary care clinic	Community	Race data reported	NR
Morland, 2022[43]	Psychotherapy	137	U.S.	Mixed	Veteran	Race and Ethnicity data reported	NR
Norman, 2022[44]	Psychotherapy	145	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	Mixed
Pigeon, 2022[45]	Psychotherapy	110	U.S.	Outpatient clinic	Community	Race data reported	NR
Ramakrishnan, 2021[46]	Pharmacotherapy	24	U.S.	Outpatient clinic	Mixed	Race data reported	Mixed
Rudstam, 2022[47]	CIH	45	Sweden	Outpatient clinic	Community	Not reported	Mixed
Schnurr, 2022[48]	Psychotherapy	916	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	Mixed
Sloan, 2022[49]	Psychotherapy	169	U.S.	Outpatient clinic	Active Duty Military	Race and Ethnicity data reported	NR
Somohano, 2022[50]	Psychotherapy	83	U.S.	Mixed	Community	Race and Ethnicity data reported	NR
Stein, 2021[51]	Pharmacotherapy	149	U.S.	Outpatient Clinic	Mixed	Race data reported	Mixed
Steuwe, 2021[52]	Psychotherapy	58	Germany	Residential inpatient	Community	Not reported	Mixed
Susanty, 2022[53]	Psychotherapy	91	Indonesia	Mixed	Community	Not reported	Mixed
Thierree, 2021[54]	Other mixed	38	France	Other	Community	Not reported	Mixed
van Vliet, 2021[55]	Psychotherapy	121	The Netherlands	Outpatient clinic	Community	Not reported	Mixed
Vera, 2021[56]	Psychotherapy	98	U.S.	Outpatient clinic	Community	Ethnicity data reported	Mixed
Wallace, 2022[57]	CIH	30	U.S.	Other	Veteran	Race and Ethnicity data reported	NR
Yi, 2022[58]	CIH	94	China	NR	Community	Not reported	Accidents
Zemestani, 2022[59]	Psychotherapy	48	Iraq	Outpatient clinic	Community	Not reported	Mixed

Abbreviations: CIH = complementary and integrative health; MST = military sexual trauma; NR = not reported; U.K. = United Kingdom; U.S. = United States.

Table 4. Summary of newly included studies: intervention characteristics

Author, Year	Intervention Group*	Treatment Name	Treatment Focus	Intervention Categorization	Intervention Format	Intervention Delivery Method
Abdallah, 2022[21]	A	Standard dose ketamine	PTSD	Pharmacotherapy	Individual	In Person
Abdallah, 2022[21]	B	Low dose ketamine	PTSD	Pharmacotherapy	Individual	In Person
Abdallah, 2022[21]	C	Placebo	Control	Control	Individual	In Person
Abraham, 2022[22]	A	Service dog training program	PTSD	Other	Individual	In Person
Abraham, 2022[22]	B	Waitlist	Control	Control	NA	NA
Acierno, 2021[23]	A	PE delivered via telehealth	PTSD	Psychotherapy	Individual	Video
Acierno, 2021[23]	B	PE delivered in person	PTSD	Psychotherapy	Individual	In Person
Alon, 2022[24]	A	Attention control training	PTSD	Nonpharmacologic cognitive	Individual	Technology assisted
Alon, 2022[24]	B	Attention bias modification	PTSD	Nonpharmacologic cognitive	Individual	Technology assisted
Baig, 2022[25]	A	Quetiapine + PE	PTSD	Psychotherapy & pharmacotherapy	Individual	In Person
Baig, 2022[25]	B	TAU + PE	PTSD	Psychotherapy & control	Individual	In Person
Brady, 2021[26]	A	NET	PTSD	Psychotherapy	Individual	In Person
Brady, 2021[26]	B	Waitlist	Control	Control	NA	NA
Bremner, 2021[27]	A	Transcutaneous cervical vagal nerve stimulation	PTSD	Nonpharmacologic biologic	Individual	In Person
Bremner, 2021[27]	B	Sham transcutaneous cervical vagal nerve stimulation	Control	Control	Individual	In Person
Dell, 2022[28]	A	Massed PE	PTSD	Psychotherapy	Individual	Mixed
Dell, 2022[28]	B	Standard PE	PTSD	Psychotherapy	Individual	Mixed
Devilly, 1999[29]	A	Trauma Treatment Protocol	PTSD	Psychotherapy	Individual	In Person
Devilly, 1999[29]	B	EMDR	PTSD	Psychotherapy	Individual	In Person
Doenyas-Barak, 2022[30]	A	Hyperbaric oxygen therapy	PTSD	Nonpharmacologic biologic	Individual	In Person
Doenyas-Barak, 2022[30]	B	TAU	Control	Control	Individual	In Person
Echiverri-Cohen, 2021[31]	A	Response inhibition training	PTSD	Nonpharmacologic cognitive	Individual	Technology assisted
Echiverri-Cohen, 2021[31]	B	Waitlist	Control	Control	NA	NA
Fruchtman-Steinbok, 2021[32]	A	Trauma-focused neurofeedback	PTSD	Nonpharmacologic biologic	Individual	In Person

Author, Year	Intervention Group*	Treatment Name	Treatment Focus	Intervention Categorization	Intervention Format	Intervention Delivery Method
Fruchtman-Steinbok, 2021[32]	B	Neutral neurofeedback	Control	Nonpharmacologic biologic	Individual	In Person
Fruchtman-Steinbok, 2021[32]	C	Control	Control	Control	Individual	In Person
Gibert, 2022[33]	A	Meditative scuba diving	PTSD	Other	Group	In Person
Gibert, 2022[33]	B	Multisport activities	PTSD	Other	Group	In Person
Isserles, 2021[34]	A	Deep TMS	PTSD	Nonpharmacologic biologic	Individual	In Person
Isserles, 2021[34]	B	Sham TMS	Control	Control	Individual	In Person
Jahanpour, 2019[35]	A	Poetry therapy	PTSD	CIH	Individual	In Person
Jahanpour, 2019[35]	B	Control	Control	Control	NA	NA
Jamshidi, 2020[36]	A	EMDR	PTSD	Psychotherapy	Individual	In Person
Jamshidi, 2020[36]	B	Waitlist	Control	Control	NA	NA
Khan, 2021[37]	A	CBT	PTSD	Psychotherapy	Individual	In Person
Khan, 2021[37]	B	TAU	Control	Control	Individual	In Person
Kobayashi, 2021[38]	A	Suvorexant + written narrative exposure	PTSD	Psychotherapy & pharmacotherapy	Individual	In Person
Kobayashi, 2021[38]	B	Placebo + written narrative exposure	PTSD	Psychotherapy & control	Individual	In Person
Koebach, 2021[39]	A	Revised adaptation of FORNET	PTSD	Psychotherapy	Mixed	In Person
Koebach, 2021[39]	B	TAU	Control	Control	Individual	In Person
Leem, 2021[40]	A	Neurofeedback + psychotherapy	PTSD	Nonpharmacologic biologic & psychotherapy	Individual	In Person
Leem, 2021[40]	B	Waitlist	Control	Control	NA	NA
Lehrner, 2021[41]	A	Hydrocortisone + PE	PTSD	Psychotherapy & pharmacotherapy	Individual	In Person
Lehrner, 2021[41]	B	Placebo + PE	PTSD	Psychotherapy & control	Individual	In Person
Meredith, 2022[42]	A	Trauma-Informed Collaborative Care	PTSD	Collaborative care	Individual	Mixed
Meredith, 2022[42]	B	Enhanced Usual Care	Control	Control	Individual	In person
Morland, 2022[43]	A	Office-based brief conjoint CBT	PTSD	Psychotherapy	Couples	In person
Morland, 2022[43]	B	Home-based brief conjoint CBT	PTSD	Psychotherapy	Couples	Video

Author, Year	Intervention Group*	Treatment Name	Treatment Focus	Intervention Categorization	Intervention Format	Intervention Delivery Method
Morland, 2022[43]	C	PTSD family education	Control	Control	Couples	In person
Norman, 2022[44]	A	Trauma-Informed Guilt Reduction	PTSD	Psychotherapy	Individual	In Person
Norman, 2022[44]	B	Supportive Care Therapy	PTSD	Psychotherapy	Individual	In Person
Pigeon, 2022[45]	A	CBTi	PTSD	Psychotherapy	Individual	In person
Pigeon, 2022[45]	B	Waitlist control	Control	Control	NA	NA
Ramakrishnan, 2021[46]	A	Lanicemine	PTSD	Pharmacotherapy	Individual	In Person
Ramakrishnan, 2021[46]	B	Placebo	Control	Control	Individual	In Person
Rudstam, 2022[47]	A	Trauma-focused group music and imagery	PTSD	CIH	Group	In Person
Rudstam, 2022[47]	B	Waitlist	Control	Control	NA	NA
Schnurr, 2022[48]	A	PE	PTSD	Psychotherapy	Individual	In Person
Schnurr, 2022[48]	B	CPT	PTSD	Psychotherapy	Individual	In Person
Sloan, 2022[49]	A	CPT	PTSD	Psychotherapy	Individual	In Person
Sloan, 2022[49]	B	Written exposure therapy	PTSD	Psychotherapy	Individual	In Person
Somohano, 2022[50]	A	Trauma-integrated mindfulness-based relapse prevention	PTSD+SUD	Psychotherapy	Group	In Person
Somohano, 2022[50]	B	Mindfulness-based relapse prevention	SUD	Psychotherapy	Group	In Person
Stein, 2021[51]	A	Losartan	PTSD	Pharmacotherapy	Individual	In Person
Stein, 2021[51]	B	Placebo	Control	Control	Individual	In Person
Steuwe, 2021[52]	A	NET	PTSD	Psychotherapy	Individual	In Person
Steuwe, 2021[52]	B	Dialectic behavior therapy	PTSD	Psychotherapy	Mixed	In Person
Susanty, 2022[53]	A	Eye Movement Desensitization	PTSD	Psychotherapy	Individual	In Person
Susanty, 2022[53]	B	Retrieval only	PTSD	Psychotherapy	Individual	In Person
Thierree, 2021[54]	A	High frequency rTMS and exposure therapy	PTSD	Psychotherapy & nonpharmacologic biologic	Individual	In Person
Thierree, 2021[54]	B	Sham rTMS and exposure therapy	Control	Psychotherapy & control	Individual	In Person
van Vliet, 2021[55]	A	STAIR-EMDR	PTSD	Psychotherapy	Individual	In Person

Author, Year	Intervention Group*	Treatment Name	Treatment Focus	Intervention Categorization	Intervention Format	Intervention Delivery Method
van Vliet, 2021[55]	B	EMDR	PTSD	Psychotherapy	Individual	In Person
Vera, 2021[56]	A	PE	PTSD	Psychotherapy	Individual	In Person
Vera, 2021[56]	B	Applied Relaxation	PTSD	CIH	Individual	In Person
Wallace, 2022[57]	A	Diaphragmatic breathing with BreatheWell Wear + TAU	PTSD	CIH	Mixed	In Person
Wallace, 2022[57]	B	Diaphragmatic breathing + TAU	Control	CIH	Mixed	In Person
Yi, 2022[58]	A	Yoga	PTSD	CIH	Group	In Person
Yi, 2022[58]	B	Control	Control	Control	Group	In Person
Zemestani, 2022[59]	A	Culturally adapted TF-CBT	PTSD	Psychotherapy	Individual	In Person
Zemestani, 2022[59]	B	Waitlist	Control	Control	NA	NA

*Each intervention group (study arm) is listed in a separate row, therefore studies are listed in multiple rows.
Abbreviations: CBT = cognitive behavioral therapy; CBTi = cognitive behavioral therapy for insomnia; CIH = complementary and integrative health; CPT = cognitive processing therapy; EMDR = eye movement desensitization and reprocessing; FORNET = Forensic Offender Rehabilitation narrative exposure therapy; NA = not applicable; NET = narrative exposure therapy; PE = prolonged exposure; PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; STAIR = Skills Training in Affect and Interpersonal Regulation; TAU = treatment as usual; TF-CBT = trauma-focused cognitive behavioral therapy; TMS = transcranial magnetic stimulation

Table 5. Newly included studies: Type of PTSD outcomes and other reported outcomes

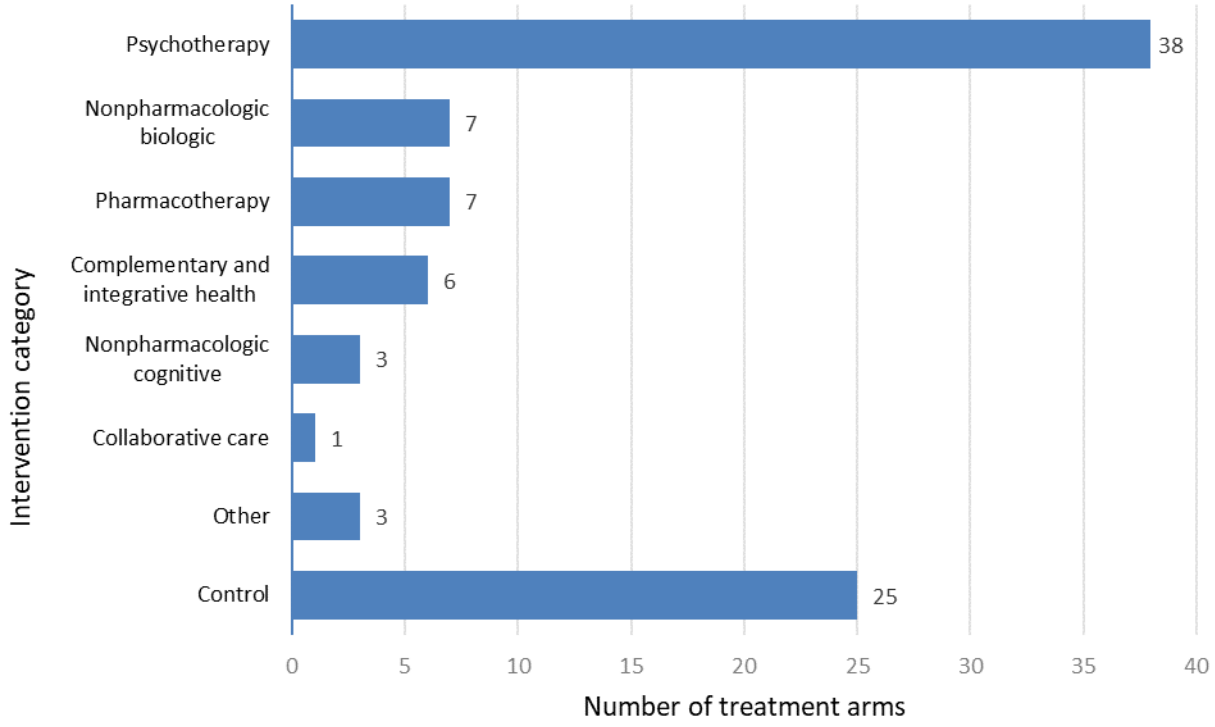
Author, Year	PTSD Continuous Outcome Measure(s)	PTSD Diagnostic Change	PTSD Clinically Meaningful Response	Anger	Anxiety	Depression	Function	Quality of Life	Sleep	Substance Use	Suicide
Abdallah, 2022[21]	CAPS, PCL	Y	Y	N	N	Y	N	N	N	N	Y
Abraham, 2022[22]	PCL	N	N	N	Y	Y	N	N	Y	N	N
Acierno, 2021[23]	PCL	N	N	N	N	Y	N	N	N	N	N
Alon, 2022[24]	CAPS, PCL	Y	N	N	N	Y	N	N	N	N	N
Baig, 2022[25]	CAPS, PCL	N	N	N	N	N	N	N	Y	N	N
Brady, 2021[26]	CAPS, PCL	N	N	N	Y	Y	N	N	N	N	N
Bremner, 2021[27]	CAPS, PCL	N	N	N	N	N	N	N	N	N	N
Dell, 2022[28]	CAPS	Y	N	N	N	N	N	N	N	N	N
Devilly, 1999[29]	PTSD-I, PSS-SR, IES, CMS	Y	Y	N	Y	Y	N	N	N	N	N
Doenyas-Barak, 2022[30]	CAPS	N	N	N	Y	Y	N	N	N	N	N
Echiverri-Cohen, 2021[31]	PDS	N	N	N	N	N	N	N	N	N	N
Fruchtman-Steinbok, 2021[32]	CAPS, PCL	Y	N	N	Y	Y	N	N	N	N	N
Gibert, 2022[33]	PCL	N	N	N	N	N	N	N	N	N	N
Isserles, 2021[34]	CAPS, MPSS	N	Y	N	N	N	N	N	N	N	Y
Jahanpour, 2019[35]	PCL	N	N	N	Y	N	N	N	N	N	N
Jamshidi, 2020[36]	CMS	N	N	N	N	Y	N	N	N	N	Y
Khan, 2021[37]	CAPS	N	N	N	N	N	N	N	N	N	N
Kobayashi, 2021[38]	CAPS	N	N	N	N	N	N	N	Y	N	N
Koebach, 2021[39]	PSS-I	N	Y	Y	N	Y	N	N	N	Y	N
Leem, 2021[40]	PCL, IES	N	N	Y	Y	Y	N	Y	Y	N	N
Lehrner, 2021[41]	CAPS, PDS	N	N	N	N	Y	N	N	N	N	N

Author, Year	PTSD Continuous Outcome Measure(s)	PTSD Diagnostic Change	PTSD Clinically Meaningful Response	Anger	Anxiety	Depression	Function	Quality of Life	Sleep	Substance Use	Suicide
Meredith, 2022[42]	PCL	Y	N	N	N	N	N	N	N	N	N
Morland, 2022[43]	CAPS	Y	Y	N	N	N	Y	N	N	N	N
Norman, 2022[44]	CAPS	Y	Y	N	N	Y	N	Y	N	N	N
Pigeon, 2022[45]	CAPS	N	N	N	N	Y	N	N	Y	N	N
Ramakrishnan, 2021[46]	CAPS	N	N	N	N	N	N	N	N	N	Y
Rudstam, 2022[47]	PCL	Y	Y	N	Y	Y	N	N	N	N	N
Schnurr, 2022[48]	CAPS, PDS	Y	Y	N	Y	Y	Y	N	N	Y	N
Sloan, 2022[49]	CAPS	N	Y	N	N	N	N	N	N	N	N
Somohano, 2022[50]	PCL	N	N	N	N	N	N	N	N	Y	N
Stein, 2021[51]	CAPS, PCL	N	Y	N	N	Y	N	N	N	N	N
Steuwe, 2021[52]	CAPS, PDS	Y	Y	N	N	Y	N	Y	N	N	N
Susanty, 2022[53]	PCL	N	N	N	Y	Y	N	Y	N	N	N
Thierree, 2021[54]	CAPS, PCL	Y	N	N	Y	Y	N	N	N	N	N
van Vliet, 2021[55]	CAPS, PSS-SR	Y	Y	N	N	N	N	N	N	N	N
Vera, 2021[56]	CAPS, PCL	Y	N	N	Y	Y	N	N	N	N	N
Wallace, 2022[57]	PCL	N	N	N	Y	Y	N	N	N	N	N
Yi, 2022[58]	IES	N	N	N	Y	Y	N	N	N	N	N
Zemestani, 2022[59]	PCL	N	N	N	Y	Y	N	Y	N	N	N

Abbreviations: CAPS = Clinician-Administered PTSD Scale; CMS = Civilian Mississippi Scale for PTSD; IES = Impact of Event Scale; MPSS = Modified PTSD Symptom Scale; N = No, data element was not reported for the study; PCL = PTSD Checklist; PDS = Posttraumatic Diagnostic Scale; PSS-I = PTSD Symptom Scale-Interview; PSS-SR = PTSD Symptom Scale-Self-Report; PTSD = posttraumatic stress disorder; Y = Yes, outcome was reported for the study.

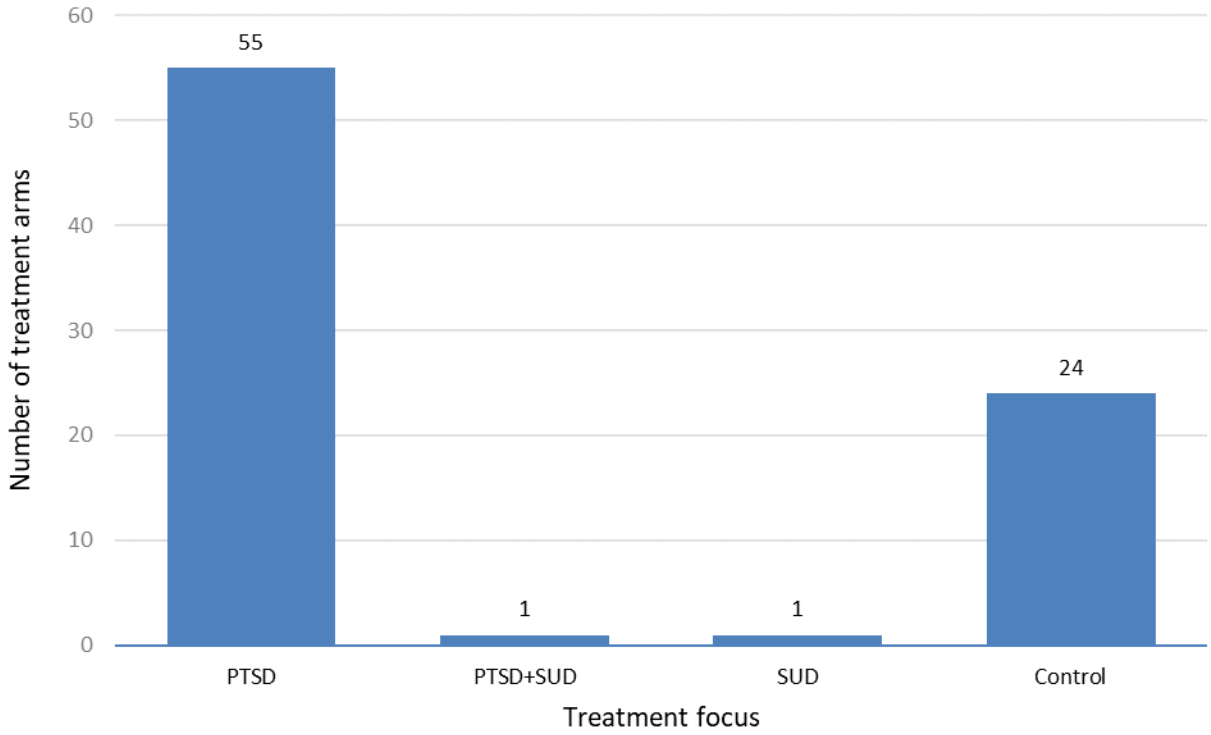
The distribution of treatment arms by intervention category is shown in Figure 12. Psychotherapy was employed in almost half of the treatment arms (47%); other treatments employed were pharmacotherapy (9%), nonpharmacologic biologic interventions (9%), and CIH (7%). The treatment focus of the interventions was mostly posttraumatic stress disorder (PTSD) (68% of treatment arms); comorbid PTSD/substance use disorder (SUD) was the focus for one treatment arm (1%) and 30 percent were non-therapeutic control arms (Figure 13).

Figure 12. Summary of newly included studies: distribution of treatment arms by intervention category*



*Studies have more than one treatment arm, and a treatment arm may include multiple intervention categories.

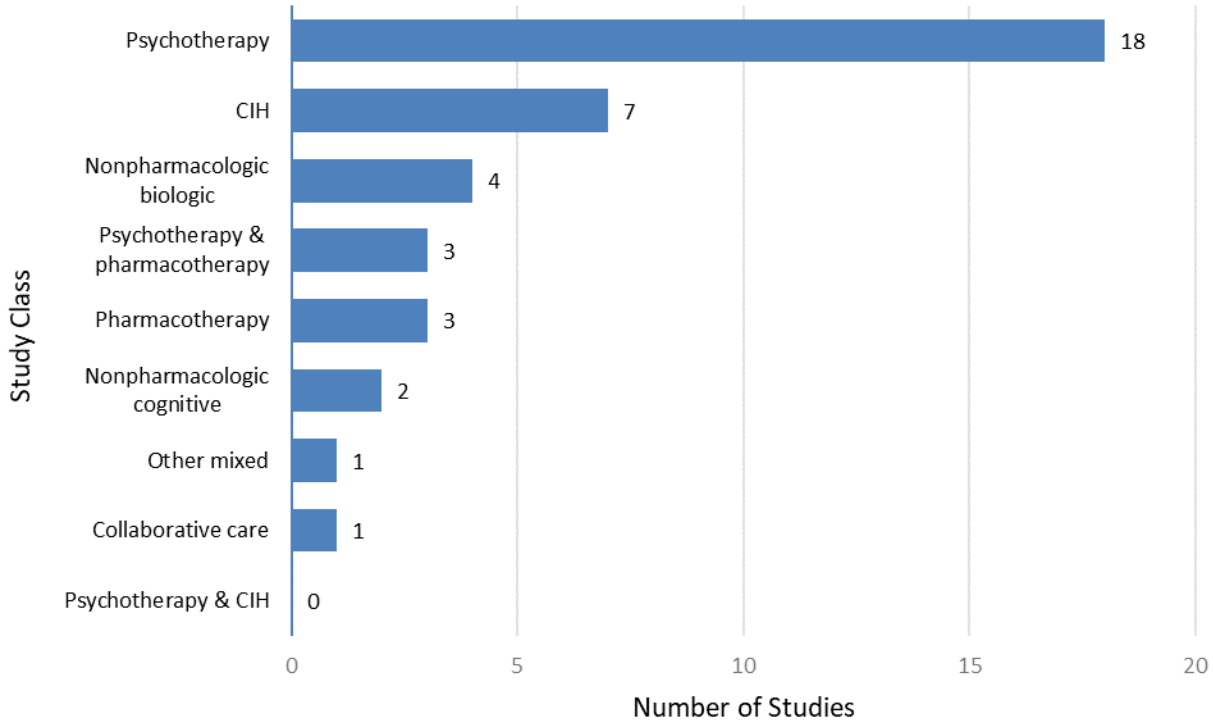
Figure 13. Summary of newly included studies: distribution of treatment arms by treatment focus*



*Studies have more than one treatment arm.
Abbreviations: PTSD = posttraumatic stress disorder; SUD = substance use disorder.

Almost all the studies (35/39, 90%) examined interventions within a single category versus a control. The predominant intervention studied was psychotherapy treatments (46%), with the remainder of studies classified as CIH (18%), nonpharmacologic biologic (10%), pharmacotherapy (8%), psychotherapy & pharmacotherapy (8%), nonpharmacologic cognitive (5%), collaborative care (3%), and other mixed (3%) (Figure 14).

Figure 14. Summary of newly included studies: distribution of study class*



Abbreviations: CIH = complementary and integrative health.

A total of 3,984 participants were enrolled in the newly included studies, with sample sizes ranging from 20 to 916. The median sample size was 59 (IQR 30 to 118) and most studies (56%) had sample sizes between 25 and 99 participants (Figure 15). There were two studies with over 200 participants. Participants were drawn from the community population in 59 percent of studies, veterans in 23 percent of studies, and Active Duty military in one study (3%); five studies (13%) were in a mixed population (Figure 16). Nearly half of the studies (49%) were conducted in the U.S. Other countries in which more than one study was conducted are Israel (3 studies), Australia (2 studies), France (2 studies), and Iran (2 studies).

Figure 15. Summary of newly included studies: distribution of studies by sample size*

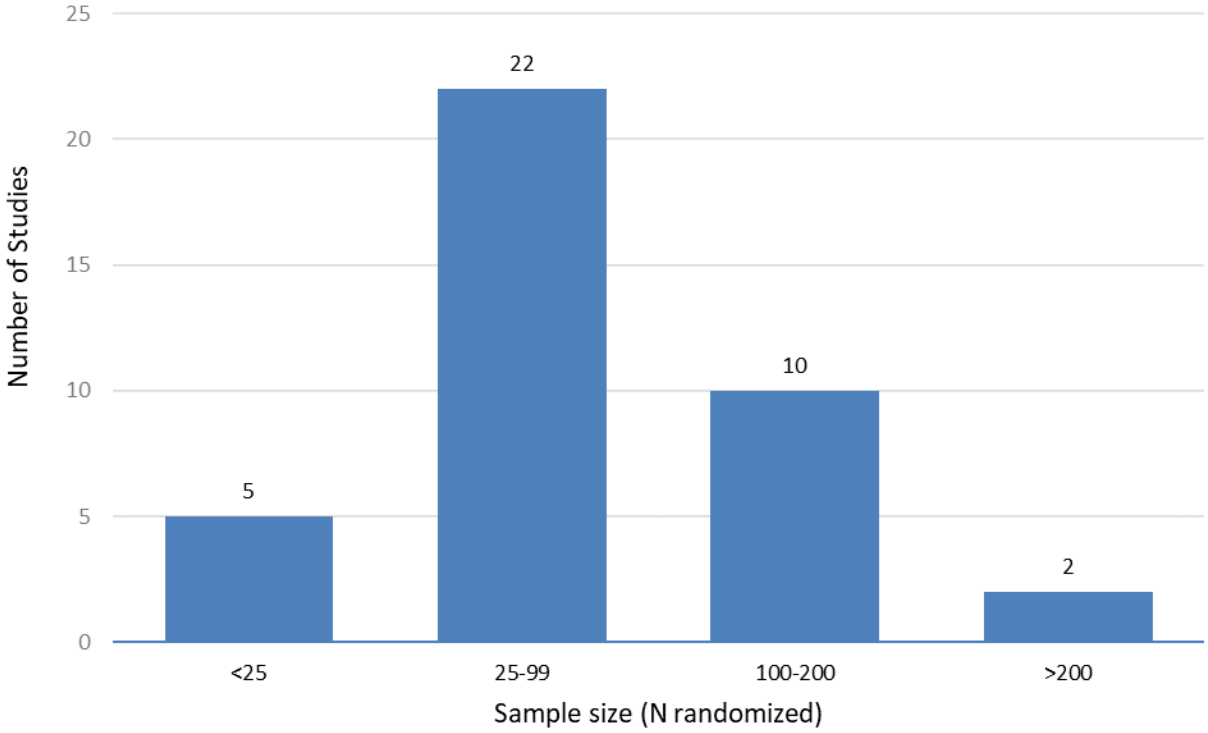
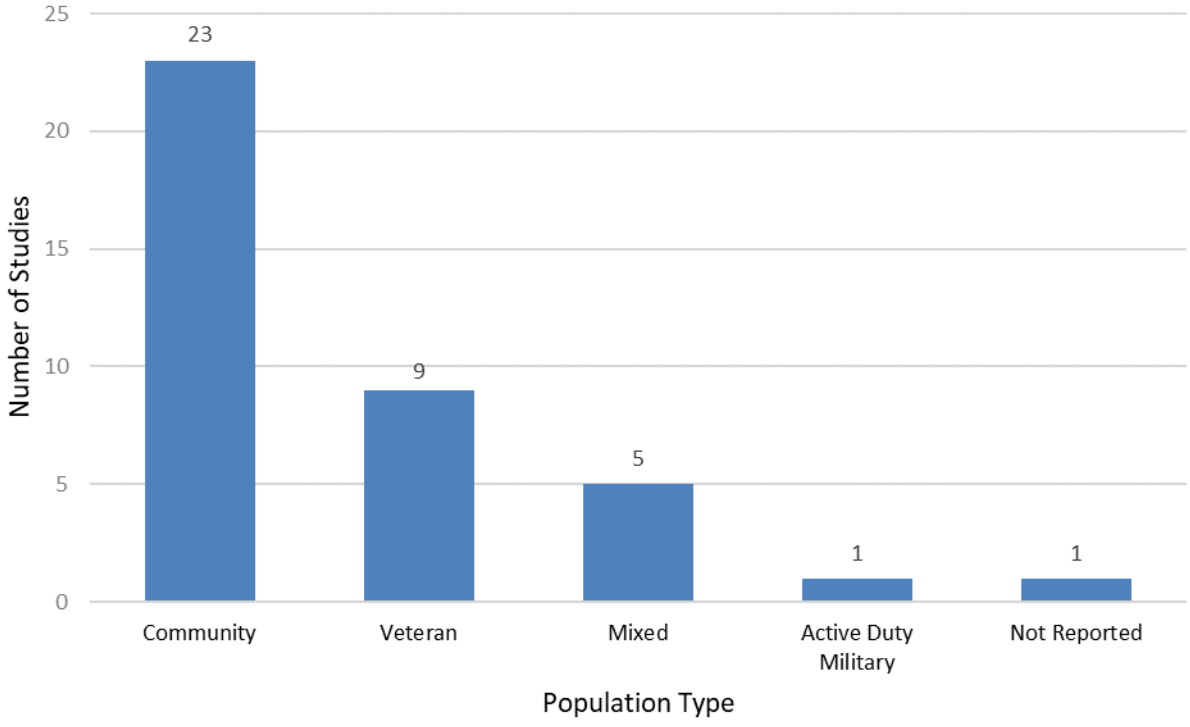
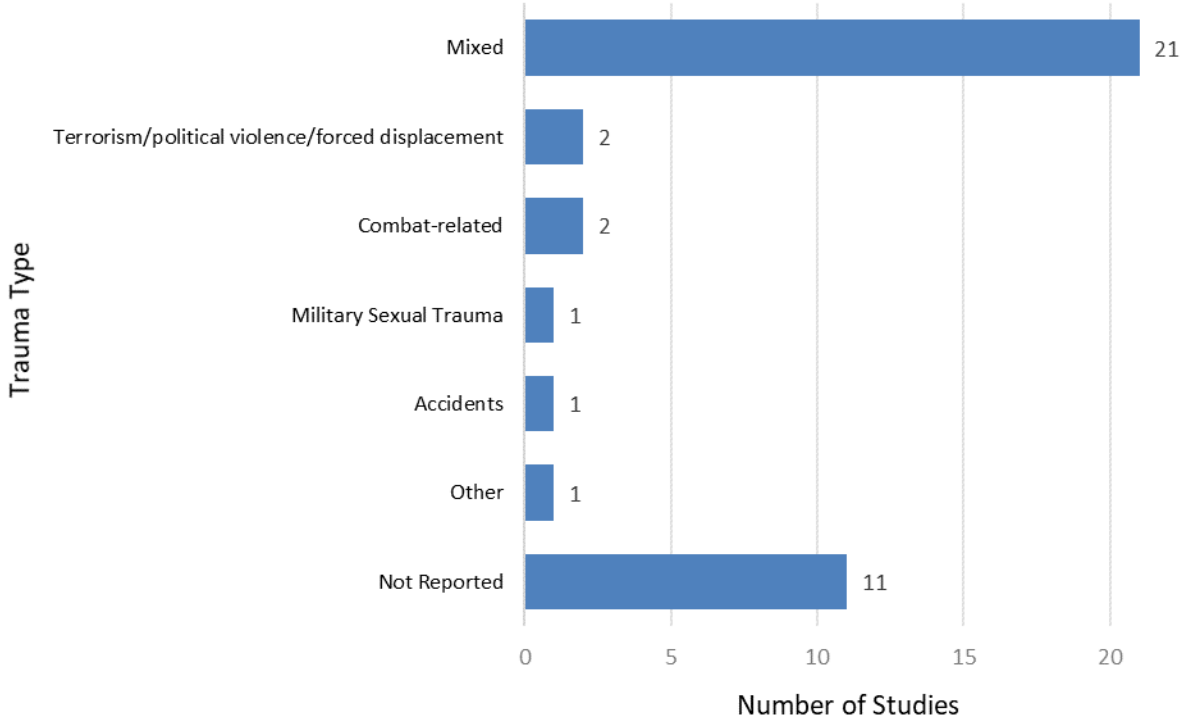


Figure 16. Summary of newly included studies: distribution of studies by population type



Seven studies limited inclusion to participants who had experienced specific trauma types, and 11 did not provide information on trauma types (Figure 17). The largest number of studies allowed mixed trauma types (21 studies, 54%).

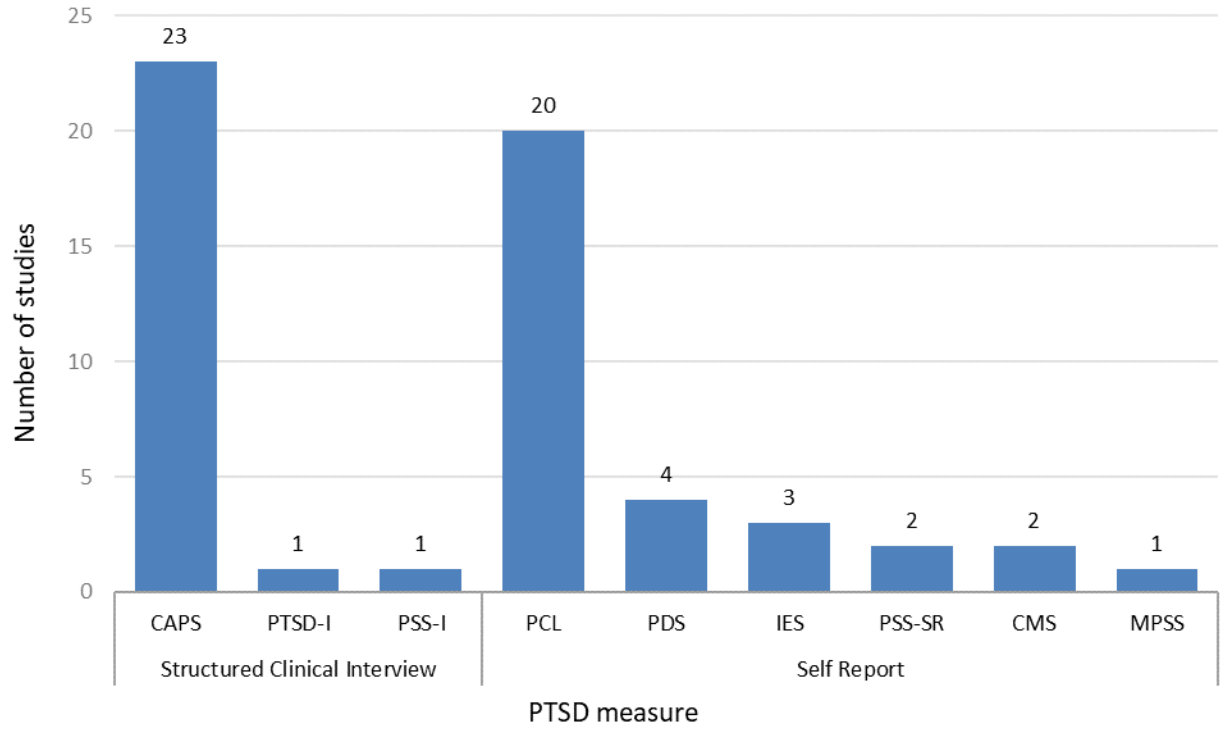
Figure 17. Summary of newly included studies: distribution of studies by trauma type



Notes: Active Duty member reporting sexual assault outside of military was categorized as rape/sexual assault. Accidents include motor vehicle accidents, transportation-related accidents, and accidents due to construction. Mixed indicates multiple trauma types were targeted/included (e.g., a study which included participants with either child sexual abuse or rape/sexual assault would be classified as mixed).

The measure most frequently used to assess continuous PTSD outcomes was the Clinician-Administered PTSD Scale (CAPS), used in 59 percent of studies (Figure 18). Approximately half of studies used the PTSD Checklist (PCL) (51%), 10 percent assessed outcomes using the Posttraumatic Diagnostic Scale (PDS), and 8% used the Impact of Event Scale (IES) (Figure 18).

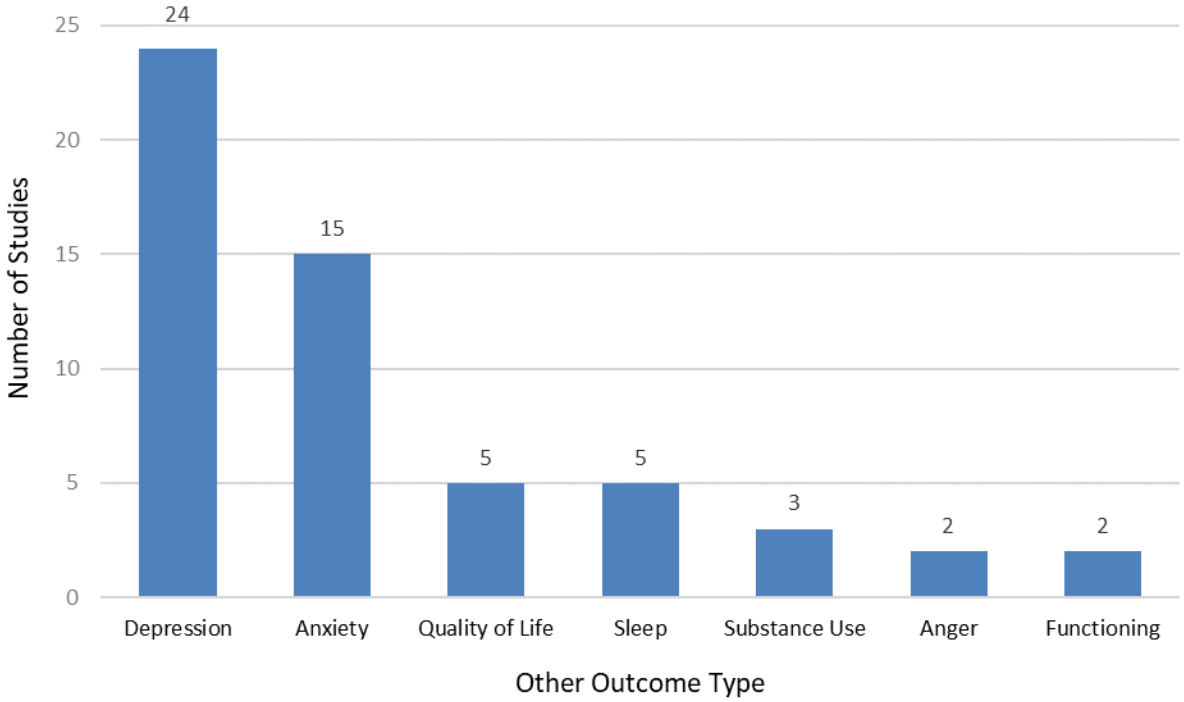
Figure 18. Summary of newly included studies: PTSD measures used to assess continuous PTSD outcomes*



*Studies may have used more than one measure to assess PTSD outcomes.
Abbreviations: CAPS = Clinician-Administered PTSD Scale; CMS = Civilian Mississippi Scale for PTSD; IES = Impact of Event Scale; MPSS = Modified PTSD Symptom Scale; PCL = PTSD Checklist; PDS = Posttraumatic Diagnostic Scale; PSS-I = PTSD Symptom Scale - Interview; PSS-SR = PTSD Symptom Scale – Self-Report; PTSD = posttraumatic stress disorder.

Among other (non-PTSD) outcomes (Figure 19), depression was the most commonly assessed (62% of studies), followed by anxiety (38%), quality of life (13%) and sleep (13%).

Figure 19. Summary of newly included studies: non-PTSD outcomes reported*



Abbreviations: PTSD = posttraumatic stress disorder

Risk of Bias Assessment

Risk of bias (RoB) was assessed for newly included studies and a subset of previously included studies using Cochrane's RoB 2 tool, as described in the Methods section. Detailed RoB ratings from prior reports[15] that used the Agency for Healthcare Research and Quality (AHRQ) Risk of Bias tool are presented separately from RoB 2 ratings to differentiate the assessment tools used for each subgroup of studies (Appendix G).

In this update, 39 newly included studies were assessed using Cochrane's RoB 2 tool for trials (Table 6). The overall risk of bias was assessed as high for 67 percent of studies, some concerns for 15 percent of studies, and low for 18 percent (Figure 20). Studies were rated as high risk of bias mainly due to missing outcome data or measurement of the outcome.

Figure 20. Risk of bias rating for newly included studies (RoB 2 methods)

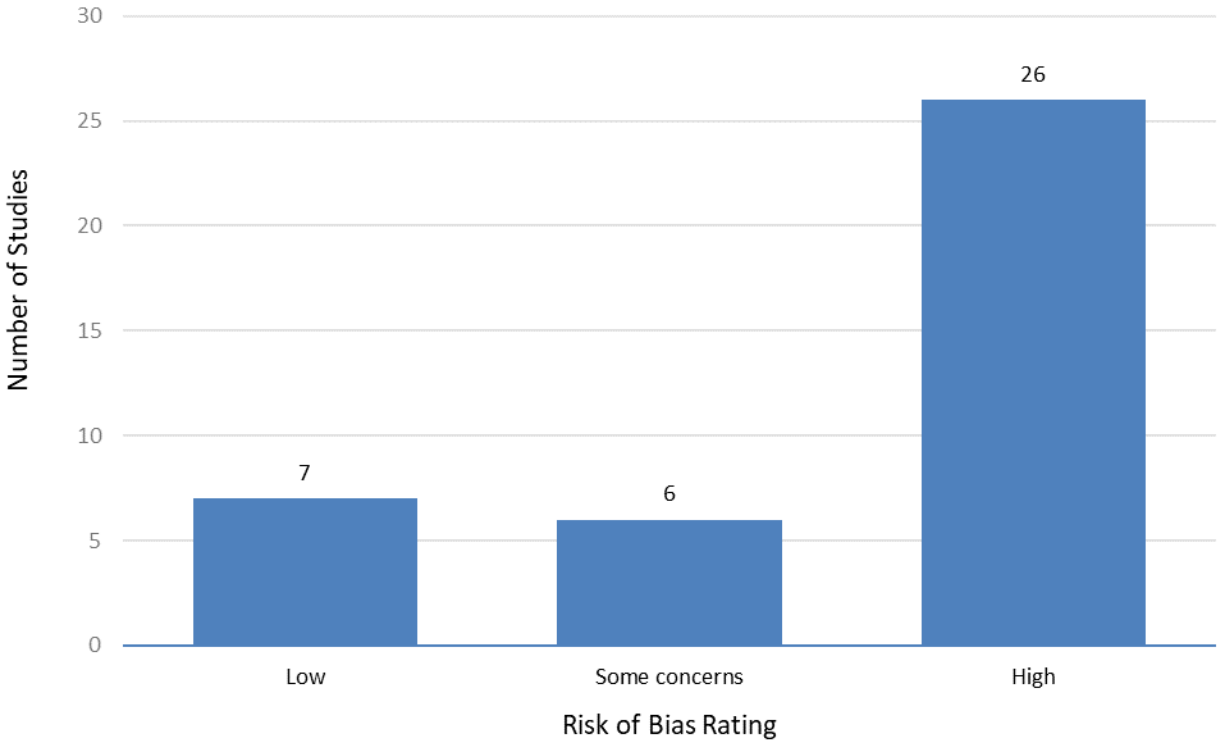


Table 6. Newly included studies: risk of bias ratings using Cochrane RoB 2 methods (k=39)

Category of Bias	Bias Due to Randomization (Cochrane) or Selection Bias (AHRQ)	Bias Due to Deviations From Intended Interventions (Cochrane) or Performance Bias (AHRQ)	Bias Due to Missing Outcome Data (Cochrane) or Attrition Bias (AHRQ)	Risk of Bias in Measurement of the Outcome (Cochrane) or Detection Bias (AHRQ)	Bias in Selection of Reported Result (Cochrane) or Reporting Bias (AHRQ)	Overall ROB
Abdallah 2022	Some Concerns	Low	Low	Low	Low	Some Concerns
Abraham 2021	Low	High	High	High	Low	High
Acierno 2021	Low	Low	Some Concerns	Some Concerns	Low	Some Concerns
Alon 2022	Low	Low	Low	Low	Low	Low
Baig 2022	Some Concerns	Low	High	Low	Low	High
Brady 2021	Some Concerns	High	Low	Low	Low	High
Bremner 2021	Low	Low	Low	Low	Low	Low
Dell 2022	Low	Low	Some Concerns	Low	Low	Low
Devilly 1999	Some Concerns	High	High	Low	Low	High
Doenyas-Barak 2022	Low	High	Low	Low	Low	High
Echiverri-Cohen 2021	High	Low	Some Concerns	High	Low	High
Fruchtman-Steinbok 2021	Some Concerns	Low	Some Concerns	High	Low	High
Gibert 2022	Some Concerns	Low	Low	High	Low	High
Isserles 2021	Low	Low	High	Low	Low	High
Jahanpour 2019	Some Concerns	Low	Low	High	Low	High
Jamshidi 2021	Some Concerns	Low	High	High	Low	High
Khan 2021	Low	Low	Low	High	Low	High
Kobayashi 2021	Low	Low	Low	Low	Low	Low
Koebach 2021	Low	Low	High	Low	Low	High
Leem 2021	Some Concerns	Low	Low	High	Low	High
Lehrner 2021	Low	Low	Low	Low	Low	Low
Meredith 2022	Some Concerns	Low	High	High	Low	High
Morland 2022	Low	Low	High	Low	Low	High
Norman 2022	Low	Low	Low	Low	Low	Low
Pigeon 2022	High	Low	High	Low	Low	High
Ramakrishnan 2021	High	Low	Low	Low	Low	High
Rudstam 2022	Low	Low	Low	High	Low	High
Shnurr 2022	Low	Low	Some Concerns	Low	Low	Some Concerns

Category of Bias	Bias Due to Randomization (Cochrane) or Selection Bias (AHRQ)	Bias Due to Deviations From Intended Interventions (Cochrane) or Performance Bias (AHRQ)	Bias Due to Missing Outcome Data (Cochrane) or Attrition Bias (AHRQ)	Risk of Bias in Measurement of the Outcome (Cochrane) or Detection Bias (AHRQ)	Bias in Selection of Reported Result (Cochrane) or Reporting Bias (AHRQ)	Overall ROB
Sloan 2022	Some Concerns	Low	Some Concerns	Low	Low	Some Concerns
Somohano 2022	Low	Low	High	High	Low	High
Stein 2021	Low	Low	Low	Low	Low	Low
Steuwe 2021	Some Concerns	Low	High	Low	Low	High
Susanty 2022	Low	Low	Low	High	Low	High
Thierree 2021	Low	Low	Some Concerns	Low	Low	Some Concerns
Van Vliet 2021	Low	Low	High	Some Concerns	Low	High
Vera 2021	Low	Low	Some Concerns	Low	Low	Some Concerns
Wallace 2022	High	Low	Low	High	Low	High
Yi 2022	Some Concerns	High	Low	High	Low	High
Zemestani 2022	Some Concerns	Low	Low	High	Low	High

Abbreviations: AHRQ = Agency for Healthcare Research and Quality; RoB = risk of bias

A total of 244 studies have been updated to RoB 2 assessments: 205 studies that were previously included and initially assessed using AHRQ methods, plus the 39 newly included studies (Appendix G-3). Of these studies, risk of bias was rated as high for 57 percent, some concerns for 26 percent, and low for 17 percent (Figure 21).

Figure 22 shows the risk of bias ratings as a percentage of the total studies within each study class. In most study classes, the highest proportion of studies were rated as high risk of bias. Complementary and integrative health had the highest proportion of studies rated as high risk of bias (71%). About half of studies were rated as high risk of bias in pharmacotherapy (46%), nonpharmacologic biologic (50%), and other (53%) study classes. Most study classes had between 10 and 30 percent of studies assessed as some concerns (range 13% to 33%). Half of studies (50%) in the psychotherapy and pharmacotherapy study class were rated as low risk of bias, with nonpharmacologic biologic having the next highest proportion of studies with this rating (29%). About 10 to 20 percent of studies in all other study classes were rated as low risk of bias (range 11% to 21%). It is important to note that this may not be representative of all included studies in the database, as updating risk of bias assessments to RoB 2 is still in progress.

Figure 21. Risk of bias rating for all studies assessed using RoB 2 methods

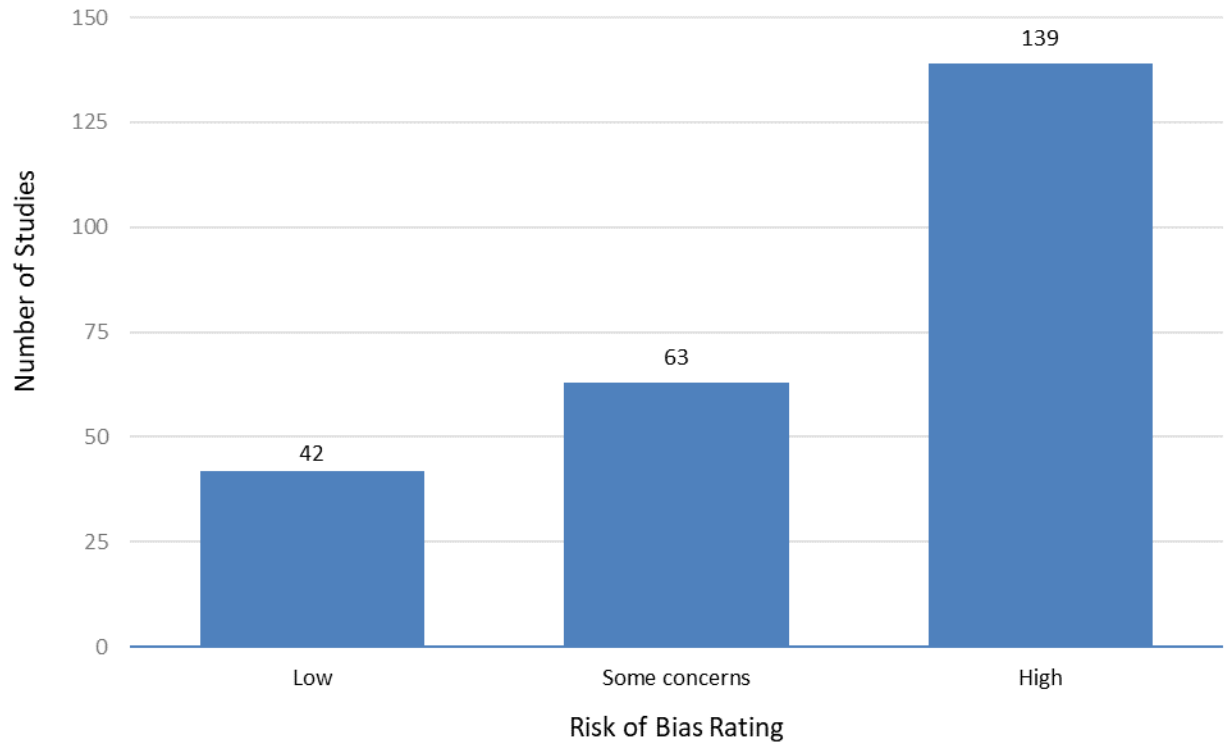
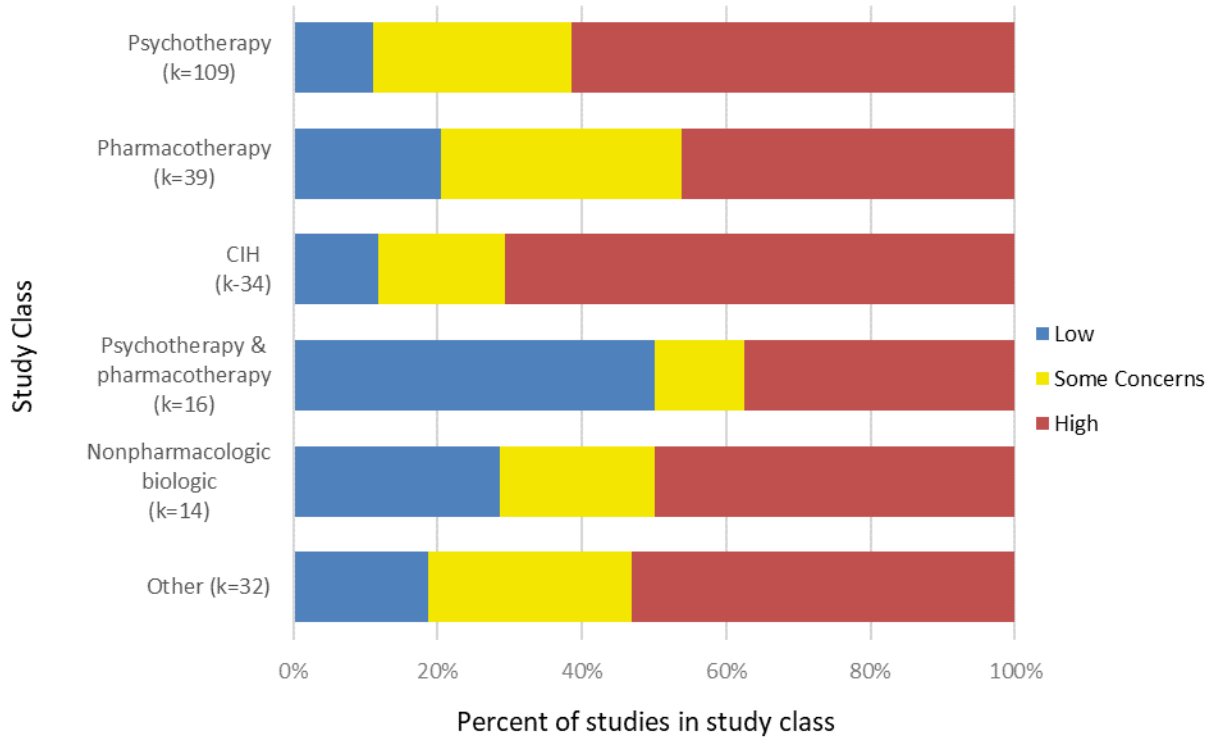


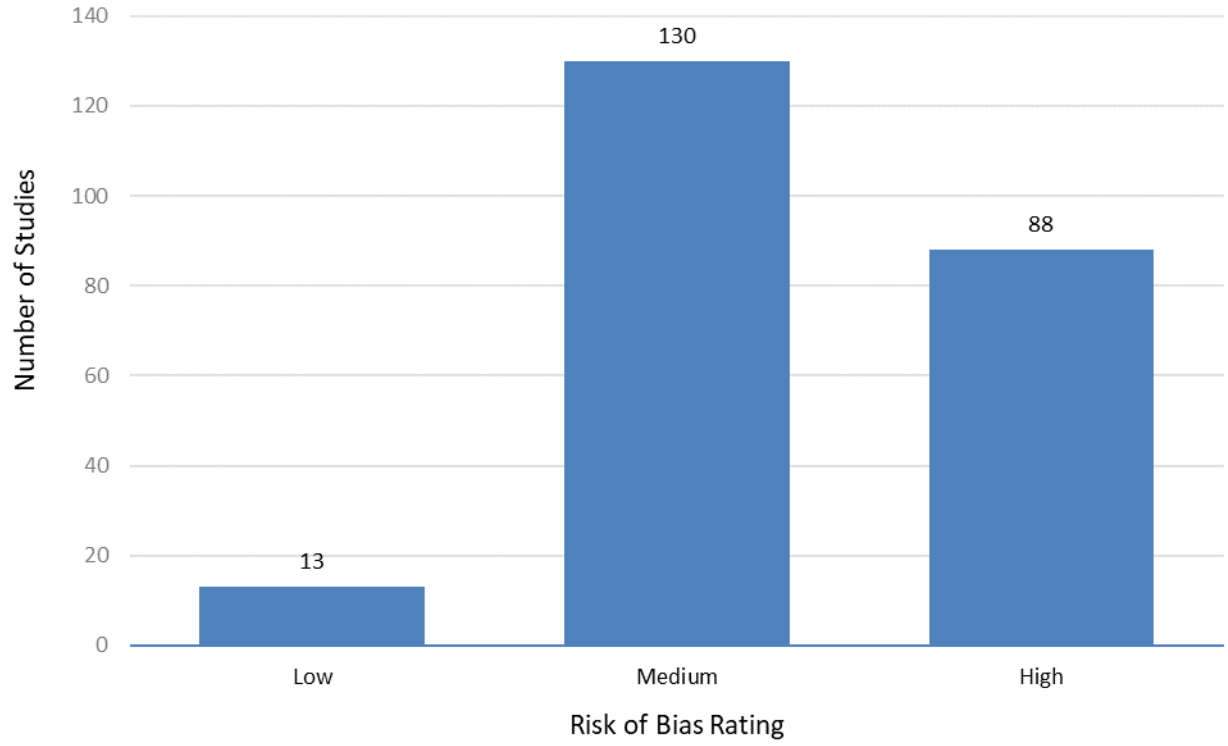
Figure 22. Risk of bias ratings using RoB 2 methods by study class



Abbreviations: CIH = complementary and integrative health; k = number of studies

There are a remaining 231 studies not yet updated with RoB 2 ratings. Risk of bias was assessed for these in prior reports using AHRQ methods, and these are presented in Appendix G-2. Risk of bias was rated as high for 38 percent of these studies, medium for 56 percent, and 6 percent were rated as low risk of bias (Figure 23).

Figure 23. Risk of bias rating for studies not yet updated to RoB 2 (assessed using AHRQ methods)



Because we used different tools to assess RoB for some of the previously included studies and updating all studies to the same RoB 2 assessment is still in process, readers should be wary of combining RoB results across these 2 groups of studies. While technically possible to compare assessments across the original RoB and RoB 2 tools, the systems do result in different ratings.

Discussion

Summary and Implications

This report is updated to include detailed data extraction and risk of bias assessments for 39 recently published randomized controlled trials (RCTs) of posttraumatic stress disorder (PTSD) treatments for those with PTSD and comorbid PTSD/substance use disorder (SUD). The updated evidence tables are being used by the National Center for PTSD (NCPTSD) to update the PTSD-Repository, a publicly available trials database accessible at https://ptsd-va.data.socrata.com/ and from the NCPTSD homepage (https://www.ptsd.va.gov/ptsdrepository/index.asp). A total of 475 RCTs are now included with detailed data abstraction and risk of bias (RoB) assessment. RoB assessments for the 39 new trials were conducted using Cochrane's RoB 2 tool for trials[62] and RoB for studies added in previous reports are in the process of being updated using this new RoB assessment tool.

The PTSD-Repository serves a variety of clinical, research, and policy purposes, and its recent expansion and release as a Web-based, interactive database is designed to serve a broad range of stakeholders including patients, providers, researchers, and policymakers. As part of these dissemination efforts to a broad range of stakeholders, data visualizations and data stories are available as curated, accessible summaries of key findings from PTSD-Repository trials. These summaries explain how to use the PTSD-Repository data and focus on topics such as "Who Has Been Studied?"[63]

These resources provide an accurate, standardized, and up-to-date source for PTSD trial data that can be used in a variety of contexts such as serving as source data for systematic reviews to examine the efficacy of various treatments, quickly informing mental health or government organizations when they are asked to respond to media requests about the state of research on a particular intervention, providing a source of reliable information for researchers identifying research gaps or writing background/rationale sections of grants, and many other purposes. Other such databases in related fields of traumatic brain injury[64] and depression[65,66] have served these and other purposes and have been used as the basis for numerous publications and grant-funded studies.

Estimated standardized effect sizes for continuous PTSD outcomes across the studies were added for newly included studies in this update and in the previous 2022 update.[17] Future updates will include calculated standardized effect sizes for all previously included studies. This will facilitate comparison across trials. However, users of these data are cautioned to carefully consider which studies are appropriate to compare, as the PTSD-Repository includes a diverse group of trials in terms of populations, interventions, comparators, outcomes, timing, and settings studied.

This work developing and updating the evidence tables was undertaken with guidance from NCPTSD and Technical Expert Panels (TEPs). These discussions emphasized how to scope the project, which data elements and studies to abstract and include in future updates, how to maintain data accuracy and relevance in large evidence tables, how to update and conduct risk of bias assessments, and potential next steps for the PTSD-Repository. The TEPs and NCPTSD recommended regular updates in order to keep the PTSD-Repository updated with the most current trial data. Ongoing discussions with the TEPs and NCPTSD have also highlighted the importance of developing a process to refine variable definitions, add variables, adjust the scope (e.g., add studies targeting comorbidities or those including participants meeting a broader definition of PTSD or subthreshold PTSD), and revise data management processes to ensure fluid integration into the Web-based database. Examples of these revisions include recent updates to the ways that suicide-related variables were abstracted and coded, the addition of detailed inclusion/exclusion criteria for each study, and the current process of updating RoB assessments using the newly available, pilot-tested Cochrane RoB 2 tool for randomized trials.

The 39 new included studies identified for this update were published from August 1, 2021 through June 14, 2022. Combined with the first three reports, this overarching project includes studies dating back to 1988.[15]

The evidence tables (Appendix E and Appendix F) for this report are extensive and far more detailed than typical systematic review evidence tables, reflecting the objective of displaying detailed data elements in a data repository that is designed to be formatted for public availability. We devoted considerable time and attention to developing standard conventions for recording data (e.g., abbreviations, data formatting) and data abstraction instructions to ensure consistent and comprehensive reporting of the many elements of study data being abstracted for this

repository. This update includes detailed data from 39 newly published studies of treatments for PTSD or comorbid PTSD and SUDs as well as calculated standardized effect size estimates for PTSD outcomes reported in these trials. We also updated risk of bias assessment using Cochrane's RoB 2[62] tool for trials to assess the newly included studies and a subset of previously included studies. Future updates will expand these to all previously included studies, adding calculated standardized effect sizes and RoB2 study assessments for the entire body of evidence.

Variations in study designs and approaches to reporting presented many challenges to the data abstraction process. For example, some studies reported difference in change from baseline between groups, while others only reported within-group change from baseline or endpoint difference between groups. In some instances, the RCT may have analyzed a primary outcome other than PTSD, such as anxiety or sleep outcomes. However, provided that a study analyzed and reported an overall PTSD outcome, the study was included in the evidence tables. In some instances, distinguishing harms from negative outcomes (e.g., unintended adverse consequences of treatment vs. lack in efficacy of the intervention) was challenging because certain variables (e.g., increased suicidal ideation/behavior) were classified as an outcome in some studies, and as an adverse event in others. Many studies of both pharmacologic and nonpharmacologic interventions did not report details about adverse events.

For some data elements, standardization was not possible, and our data abstraction was guided by what the study reported and how the study reported the data (e.g., labeling of control interventions as placebo, usual care, minimal intervention, active placebo, etc.; gender categories and/or sexual orientation; race/ethnicity; current or historical substance use disorder or depression; clinically meaningful response; loss of diagnosis as an outcome); we report qualitative details related to study descriptions of such elements in the evidence tables in columns with the 'details' label (Appendix E and Appendix F). Akin to other data elements reported differently across studies, results and effect sizes were inconsistently reported and reported using different statistics in the included studies; therefore, we had to use a variety of methods to calculate comparable, standardized effect sizes depending on data availability across the diverse group of studies, as described in the methods. Lastly, gaps in reporting of certain data elements resulted in many evidence table cells listing 'not reported' (NR). Similar gaps in reporting of RoB-related elements also were apparent, particularly in earlier studies. Recognition of these gaps may help future researchers to report study methods and results more comprehensively.

Finally, there are also some limitations to the RoB assessment in this report. First, RoB was assessed by one person and checked for accuracy by another person rather than by a dual independent review and consensus process. This leads to the possibility that systematic differences between raters or by research groups might be reflected in the ratings. Most importantly, the process of updating the RoB assessment to Cochrane's RoB 2 tool for trials is still in progress, and therefore summary statistics across all included studies are not possible due to the different assessment methods. These will be updated and assessed on the same scale in future update reports, allowing for a more robust examination of RoB domains across the studies.

Next Steps

The completion of this project signifies the end of the fourth phase of work and expansion of the PTSD-Repository evidence tables. In this phase, we added newly published RCTs, added qualitative reporting on inclusion and exclusion criteria for all studies, continued the process of updating all studies to the Cochrane RoB 2 system, and continued calculating standard effect

sizes for the included studies. The NCPTSD created the web-based, searchable, interactive PTSD-Repository database, and the current project updates and expands the evidence tables that serve as the foundation for that work.[63,67,68]

In addition to updates to include newly published RCTs, future additions to the evidence tables have been explored and recommended by the TEP. These future additions could include reporting outcomes for PTSD symptom clusters, item-level data, individual participant-level data, subgroup analyses (e.g., to provide data on what works for whom), participant populations with >20 percent subthreshold PTSD, broader PTSD diagnostic criteria applied for inclusion, interventions designed to prevent PTSD or treat comorbid PTSD and other disorders such as depression, nonrandomized trials that control for important confounders, and qualitative and quantitative synthesis of key outcome data. We base these suggestions on our interaction with the evidence base, the TEP, and NCPTSD.

The PTSD-Repository can (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] The TEP highlighted how adding variables, outcomes, subpopulations, updated RoB 2 assessment, and other studies in the future could be useful to researchers, policymakers, clinicians, and patients and help achieve the aforementioned goals of developing this database. This report and future updates aim to aid in the dissemination of the PTSD-Repository. We plan to continue to provide data for all types of potential PTSD-Repository users, so that content can be developed to support ease and accuracy of use, such as updated data dictionaries and data stories that provide both information on how to use the PTSD-Repository as well as summaries of key findings from PTSD-Repository data. The TEP comments compiled during the initial and continuation stages of this project provide a guide for future work in updating the evidence tables of the PTSD-Repository.

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Abbreviations and Acronyms

Acronym or Abbreviation	Definition
AHRQ	Agency for Healthcare Research and Quality
AMR	applied muscle relaxation
CA-CBT	culturally adapted cognitive behavioral therapy
CAPS	Clinician-Administered PTSD Scale
CBCT	cognitive-behavioral conjoint therapy
CBD	cannabidiol
CBSRT	Cognitive Behavioral Social Rhythm Group Therapy
CBT	cognitive behavioral therapy
CBTi	cognitive behavioral therapy for insomnia
CD	compact disc
CER	comparative effectiveness review
CIDI	Composite International Diagnostic Interview
CIH	complementary and integrative health
CMS	Civilian Mississippi Scale for PTSD
COPE	Concurrent Treatment for PTSD and Substance Use Disorder Using Prolonged Exposure
CPG	clinical practice guideline
CPT	Cognitive Processing Therapy
DBT-PTSD	dialectical behavior therapy for PTSD
DoD	Department of Defense
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTS	Davidson Trauma Scale
DVD	digital video disc
ECT	electroconvulsive therapy
EMDR	Eye Movement Desensitization and Reprocessing
EPC	evidence-based practice center
FORNET	Forensic Offender Rehabilitation narrative exposure therapy
HOPE	Helping to Overcome PTSD through Empowerment
HTQ	Harvard Trauma Questionnaire
ICBT	Integrated Cognitive Behavioral Therapy
ICD	International Statistical Classification of Diseases and Related Health Problems
IES	Impact of Event Scale
IPT	Interpersonal Psychotherapy
IQR	Interquartile range
IRT	Imagery Rehearsal Training
ITT	intent-to-treat
k	number of studies
KQ	Key Question
MAOI	monoamine oxidase inhibitor
MBSR	Mindfulness-based Stress Reduction
MDMA	3,4-methylenedioxy-methamphetamine

Acronym or Abbreviation	Definition
MINI	Mini-International Neuropsychiatric Interview
MPSS	Modified PTSD Symptom Scale
MST	military sexual trauma
N	No, data element was not reported for the study
NA	not applicable
NCPTSD	National Center for Posttraumatic Stress Disorder
NET	Narrative Exposure Therapy
NR	not reported
NSESSS	National Stressful Events Survey PTSD Short Scale
PC-PTSD	Primary Care PTSD Screen
PCL	PTSD Checklist
PCT	Present-Centered Therapy
PCT+	Present-Centered Therapy
PDS	Posttraumatic Diagnostic Scale
PE	Prolonged Exposure
PICOTS	populations, interventions, comparators, outcomes, timing, settings, study design
PSS-I	PTSD Symptom Scale-Interview
PSS-SR	PTSD Symptom Scale-Self-Report
PTSD	posttraumatic stress disorder
PTSD-Repository	PTSD Trials Standardized Data Repository
RCT	randomized controlled trial
RoB	risk of bias
RTM	Reconsolidation of Traumatic Memories
rTMS	repetitive transcranial magnetic stimulation
SCID	structured clinical interview for the DSM
SEADS	Supplemental Evidence And Data for Systematic Review
SI-PTSD	Structured Interview for PTSD
SNRI	serotonin and norepinephrine reuptake inhibit
SSRI	selective serotonin reuptake inhibitor
STAIR	Skills Training in Affective and Interpersonal Regulation
STAIR-PC	Skills Training in Affective and Interpersonal Regulation for PTSD treatment in primary care
SUD	substance use disorder
TAU	treatment as usual
TBCT	trial-based cognitive therapy
TBI	traumatic brain injury
TCA	tricyclic antidepressant
tDSC	transcranial direct current stimulation
TEP	Technical Expert Panel
TF-CBT	trauma-focused cognitive behavioral therapy
THC	tetrahydrocannabinol
TMS	transcranial magnetic stimulation
TNX-102	cyclobenzaprine hydrochloride

Acronym or Abbreviation	Definition
VA	U.S. Department of Veterans Affairs
VA/DoD CPG	Department of Veterans Affairs/Department of Defense clinical practice guideline
WET	Written Exposure Therapy
Y	Yes, outcome was reported for study