Draft Systematic Review

Number XX

Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: 2024 Update of the Evidence Base for the PTSD Trials Standardized Data Repository

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Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

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Prepared by:
[To be included in the final report.]

Investigators:
[To be included in the final report.]

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This report is based on research conducted by the <EPC> 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.

AHRQ appreciates appropriate acknowledgment and citation of its work. This work was based on an evidence report, Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: 2024 Update of the Evidence Base for the PTSD Trials Standardized Data Repository, by the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ).

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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: Pacific Northwest Evidence-based Practice Center (Contract Number: <#>).

The reports and assessments provide organizations with comprehensive, evidence-based information on common 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 the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as 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.

Robert Otto Valdez, Ph.D., M.H.S.A.
Director
Agency for Healthcare Research and Quality

Therese Miller, Dr.P.H.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Christine Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Kim Wittenberg, M.A.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Jessica L. Hamblen, Ph.D.
Deputy Director of Education
National Center for Posttraumatic Stress Disorder
Department of Veterans Affairs

Sonya B. Norman, Ph.D.
Director
PTSD Consultation Program
National Center for Posttraumatic Stress Disorder
Department of Veterans Affairs

Acknowledgments

[To be included in the final report.]

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:

[To be included in the final report.]

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. AHRQ may also seek comments from other Federal agencies when appropriate.

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 follows:

[To be included in the final report.]

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

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 included trials.

Data sources. We searched PTSDpubs, Ovid® MEDLINE®, Cochrane CENTRAL, PsycINFO®, Embase®, CINAHL®, and Scopus® for eligible RCTs published from March 1, 2023, to September 11, 2023.

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 studies that met updated inclusion criteria for the database (e.g., interventions that do not require a provider). Evidence tables were also updated with calculated standardized effect sizes for continuous PTSD outcomes for all included studies. We assessed risk of bias (RoB) for all included studies using the Revised Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials.

Results. We added 32 RCTs examining treatments for PTSD, for a total of 528 included studies published from 1988 to September 11, 2023. Among all 528 included RCTs, studies of psychotherapy interventions were the most common (44%), followed by pharmacologic interventions (19%). 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 (i.e., not specifically military) participants (54%), and most were conducted in outpatient settings (77%). Studies typically enrolled participants with a mix of trauma types (51%). Among all 528 included RCTs, RoB was rated as low for 14 percent of studies, 27 percent were rated as having some concerns, and the remaining 59 percent were rated as high RoB.

Among the 32 newly added RCTs, psychotherapy interventions were the most commonly employed (31%), followed by nonpharmacologic cognitive interventions (19%). Approximately half of the studies were conducted in the United States (53%), and enrolled community participants (56%) and participants with a mix of trauma types (53%). Studies typically had sample sizes ranging from 25 to 99 participants (59%). Of the newly added RCTs, RoB was rated as low for 28 percent of studies, 25 percent were rated as having some concerns, and the remaining 47 percent were rated as high RoB.

Conclusions. This report updates the previous AHRQ report to add 32 RCTs, for a total of 528 studies. This update adds comprehensive data and RoB assessment for the newly included RCTs,

and standardized effect sizes for continuous PTSD outcomes for all included studies. 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 32 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 528.
- Across all 528 RCTs:
  - The most commonly studied intervention was psychotherapy (44%), followed by pharmacologic interventions (19%), and complementary and integrative health (6%); 7 percent of studies used both pharmacologic and psychotherapeutic interventions.
  - Overall, most studies were conducted in the United States (59%) and 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%).
  - Just under a third of studies (31%) provided data on race and ethnicity, and another 26 percent provided data on race only; data were not provided for race or ethnicity in 42 percent of studies.
  - Almost a third of studies (31%) 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 (2%); 51 percent allowed a mix of trauma types, and 18 percent did not provide information on participant trauma types.
  - Risk of bias (RoB) was rated as low for 14 percent, some concerns for 27 percent, and high for the remaining studies (59%).

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Main Points, continued

- Across the 32 newly added RCTs:
  - The most commonly studied intervention was psychotherapy (31%), followed by nonpharmacologic cognitive (19%) and pharmacologic interventions (16%); 6 percent of studies used both pharmacologic and psychotherapeutic interventions.
  - Just over half of the newly added RCTs were conducted in the United States (53%), and enrolled community (not specifically military) participants (56%); sample sizes were in the range of 25 to 99 participants in most studies (66%).
  - About half of studies allowed a mix of trauma types (53%); 38 percent did not provide information on participant trauma types.
  - RoB was rated as low for 28 percent, some concerns for 25 percent, and high for the remaining studies (47%).

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.[1,3,4,5,6] These data will inform the subsequent update and expansion of the PTSD-Repository, a publicly accessible clinical trials database maintained by the NCPTSD (accessible at https://www.ptsd.va.gov/ptsdrepository/index.asp).[2] 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.[7] For this update, we searched PTSDpubs (formerly PILOTS), Ovid® MEDLINE®, Cochrane CENTRAL, PsycINFO®, Embase®, CINAHL®, and Scopus® for eligible RCTs published from March 1, 2023, to September 11, 2023. We also reviewed previously excluded studies for interventions that meet the updated eligibility criteria, to include self-help or internet-based interventions (those that do not require a provider). We dually reviewed citations from the literature search and

potentially includable full-text articles for eligibility. One team member assessed RoB using Cochrane's RoB 2: A Revised Tool for Assessing Risk of Bias in Randomized Trials,[8] and a second reviewer checked for accuracy. Disagreements on eligibility or RoB were resolved through consensus. We developed evidence tables for the prior updates[1,3,4] 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. Standardized effect sizes for continuous PTSD outcomes were calculated by study biostatisticians.

Results

In this update, we added 32 RCTs examining treatments for PTSD for a total of 528 included RCTs overall. The updated report now includes 144 pharmacologic studies (trials with at least one medication arm) and 384 nonpharmacologic studies (trials with no medication arms). The 528 trials were published from 1988 to 2023. Across all 528 RCTs, the most commonly studied intervention was psychotherapy (44%), followed by pharmacologic interventions (19%), and complementary and integrative health (6%); 7 percent of studies used both pharmacologic and psychotherapeutic interventions. Interventions targeting comorbid PTSD/SUD or SUD were studied in 6% of included RCTs. Overall, most studies were conducted in the United States (59%), and enrolled community (i.e., not specifically military) populations (54%). A total of 45,738 participants are represented; sample sizes ranged from 8 to 1,001 with most studies (59%) enrolling 25 to 99 participants. The Clinician-Administered PTSD Scale (CAPS) and the PTSD CheckList (PCL) were measures most frequently used to assess continuous PTSD outcomes, used in 54 percent and 39 percent of studies, respectively. PTSD diagnostic change or clinically meaningful response were assessed in 54 percent of studies. Among non-PTSD outcomes, depression was the most commonly assessed (70%), followed by anxiety (33%). Across all 528 RCTs, RoB was rated as low RoB for 14 percent, some concerns for 27 percent, and high for the remaining studies (59%).

Among the 32 newly added RCTs, psychotherapy interventions were the most commonly employed (31%), followed by nonpharmacologic cognitive interventions (19%). Interventions targeting comorbid PTSD/SUD were studied in 6% of included RCTs. Just over half of studies were conducted in the United States (53%), enrolled community participants (56%), and enrolled participants with a mix of trauma types (51%). The newly added studies had sample sizes ranging from 22 to 1,001, with most studies (66%) having a sample size between 25 and 99 participants. The Clinician-Administered PTSD Scale (CAPS) and the PTSD CheckList (PCL) were measures most frequently used to assess continuous PTSD outcomes, used in 50 percent and 69 percent of studies, respectively. PTSD diagnostic change or clinically meaningful response were assessed in 53 percent of studies. Among non-PTSD outcomes, depression was the most commonly assessed (66% of the newly added studies). Of the 32 newly added RCTs, 47 percent were rated as high RoB, 25 percent were rated as some concerns, and 28 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 duration of PTSD diagnosis or symptoms, number of treatment-naïve participants, mean number of trauma types per participant, number of participants with a history of traumatic brain injuries, SUD, and other psychiatric comorbidities, and suicidal ideation/behavior.

Implications and Conclusions

This report updates the previous AHRQ report on this topic[1] with comprehensive data, calculated standardized effect sizes for continuous PTSD outcomes, and RoB assessment from 32 newly included trials. This update also includes calculated standardized effect sizes for continuous PTSD outcomes for all 528 included studies. As with the previous AHRQ reports on this topic,[1,3,4,5] 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. Inclusion of RoB assessment using the same scale for all studies and standardized effect sizes allows for more efficient and accurate comparisons across PTSD trials.

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1. Introduction

1.1 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 more likely to experience other mental health comorbidities compared to those without, particularly substance use and mood disorders such as depression.[3,6,7]

Since PTSD was first included by the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) in 1980, there have been over 500 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.

1.2 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.[13-17] The purpose of this update review, and the four 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.[18] 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. Previous updates[15-17] have included: 1) addition of 178 RCTs through extension of the search dates to include newly published studies and expansion of the inclusion criteria to include studies focused on treating comorbid PTSD/SUD; 2) revised evidence tables to include more detailed and discrete data elements and facilitate integration with the online PTSD-Repository; 3) abstraction of additional data elements (for example, information on comorbidities and suicide and self-harm related outcomes); 4) expanded abstraction of results data for PTSD outcomes; 5) calculation of standardized effect sizes for continuous PTSD outcomes; 6) RoB assessment using the Cochrane RoB 2 tool. This current update builds on the prior AHRQ reports by adding 32 RCTs (for a total of 528 trials in the database) with complete evidence tables and risk of bias assessment, updating inclusion criteria to include self-help or internet-based interventions (those that do not require a provider, on the recommendation of the Technical Expert Panel and NCPTSD), and providing calculated standardized effect sizes for all included studies.

1.3 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 Comparative Effectiveness Review No. 235.[15] The PICOTS (populations, interventions, comparators, outcomes, timing, settings, study design) criteria are:

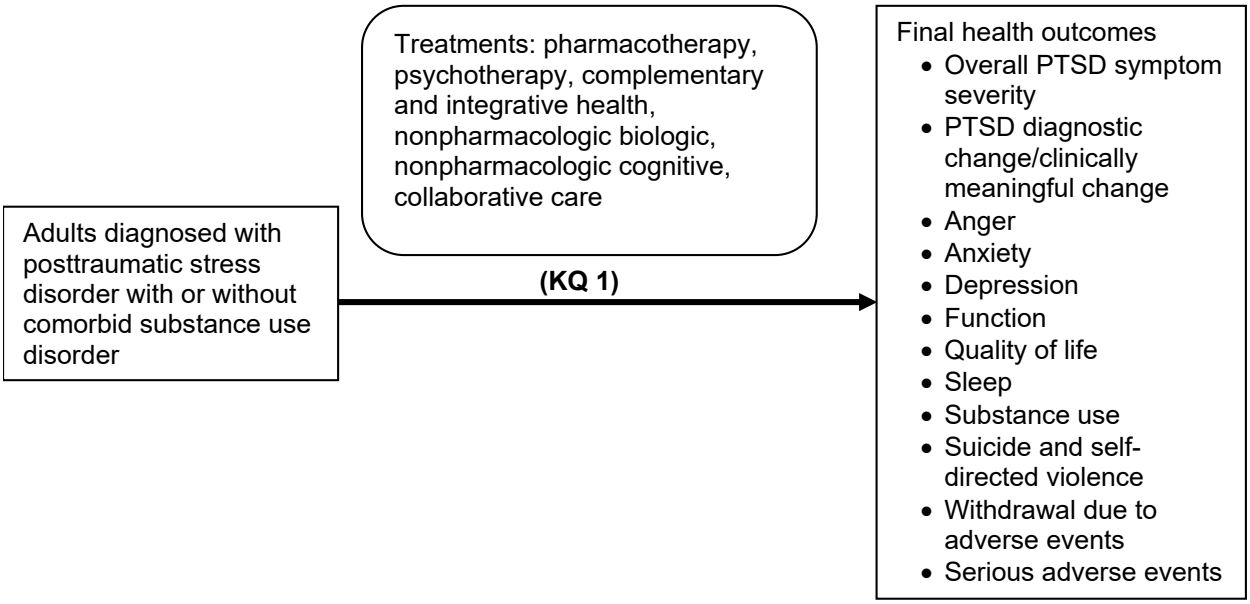
- **Population(s):**
  - Adults (≥18 years old) diagnosed with PTSD by a clinician or through a patient-reported assessment tool
- **Interventions:**
  - Pharmacologic and nonpharmacologic interventions, including complementary and integrative approaches, for treatment of PTSD or comorbid PTSD/SUD
- **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

1.4 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

2. Methods

This report follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews[19] 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-non-pharm-treatment-update/protocol).

2.1 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). We included treatments for posttraumatic stress disorder (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. These inclusion and exclusion criteria were updated from the previous update report[17] to include interventions that do not require a provider (e.g. mobile apps, attention bias modification).

2. Methods

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 targeting core symptoms of PTSD (e.g. insomnia and nightmares related to PTSD) are included • No limitation on delivery format or provider type; provider involvement not required (e.g. self-help or internet-based interventions are included)	• 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 are 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 • Studies that did not perform formal statistical test for between-group comparison of a 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)

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

2.2 Literature Search

Electronic databases were searched for evidence from March 1, 2023, to September 11, 2023. 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. We also reviewed previously excluded studies for interventions that meet the updated inclusion criterion. 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.

2.3 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 subsequent update reports[15-17] to include additional data elements such as detailed study inclusion/exclusion criteria and specific data elements for inclusion 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. These data elements were abstracted for all included studies and were provided in the evidence tables of the prior reports.

For the 2022 update,[16] 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 data integration processes could be automated using replicable syntax. The 2022 update also added calculation of standardized effect sizes for continuous PTSD outcomes for newly included studies, provided the study reported the necessary data. Both between and within group effect sizes were calculated, allowing users to examine and compare effectiveness of interventions. These updated processes were maintained in subsequent updates. This 2024 update adds calculated standardized effect size data for continuous PTSD outcomes for all 528 included studies (496 previously included studies and the 32 newly included studies). 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 risk of bias (RoB) assessments, described below. All studies were incorporated in the summarized results presented below, regardless of overall RoB rating.

2.4 Evidence Synthesis

The evidence tables are designed to enable a variety of syntheses that would be of interest to different stakeholders. 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.

2.5 Standardized Effect Size Calculation

Meta-analysis was not performed. To facilitate quantitative syntheses by users of the evidence tables, standardized effect sizes were calculated for continuous PTSD outcomes, provided the necessary data was reported in the study. This update includes calculated standardized effect sizes for continuous PTSD outcomes for all 528 included RCTs.

To facilitate comparison across studies and across outcomes, a within-arm effect size was calculated using the formula in 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 randomized controlled trials (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.[20] For studies not reporting standard deviation, it was calculated from 95 percent confidence interval whenever reported. All analyses were performed using R (version 4.2.3).

Figure 2. Within-arm effect size formula

$$d = \frac{Mean_{followup} - Mean_{baseline}}{s}$$

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

$$\text{Assuming correlation = 0.5 and } N_{baseline} = N_{followup}$$

2.6 Assessment of Methodological Risk of Bias of Individual Studies

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,[21] we updated RoB assessments for all included RCTs using Cochrane's RoB 2 system. The updated RoB assessments were completed for all included studies in the previous update report,[17] ensuring that all studies in the database

now use the same, gold standard RoB 2 assessment. To clarify aspects of the RoB assessments, and to ensure transparency and ease of future updating, we included detailed definitions related to how RoB was assessed and clearly described cutoff values (e.g., for attrition) applied when implementing the Cochrane RoB 2 system. 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). For newly included studies, RoB was assessed using the same assessment tool for RoB 2. Appendix G contains RoB assessments: 32 newly included studies (Appendix Table G-1); and 496 previously included studies (Appendix Table G-2).

2.7 Grading the Strength of Evidence for Major Comparisons and Outcomes

Strength of evidence was not assessed for this review.

2.8 Assessing Applicability

Applicability was not assessed for this review.

2.9 Peer Review and Public Commentary

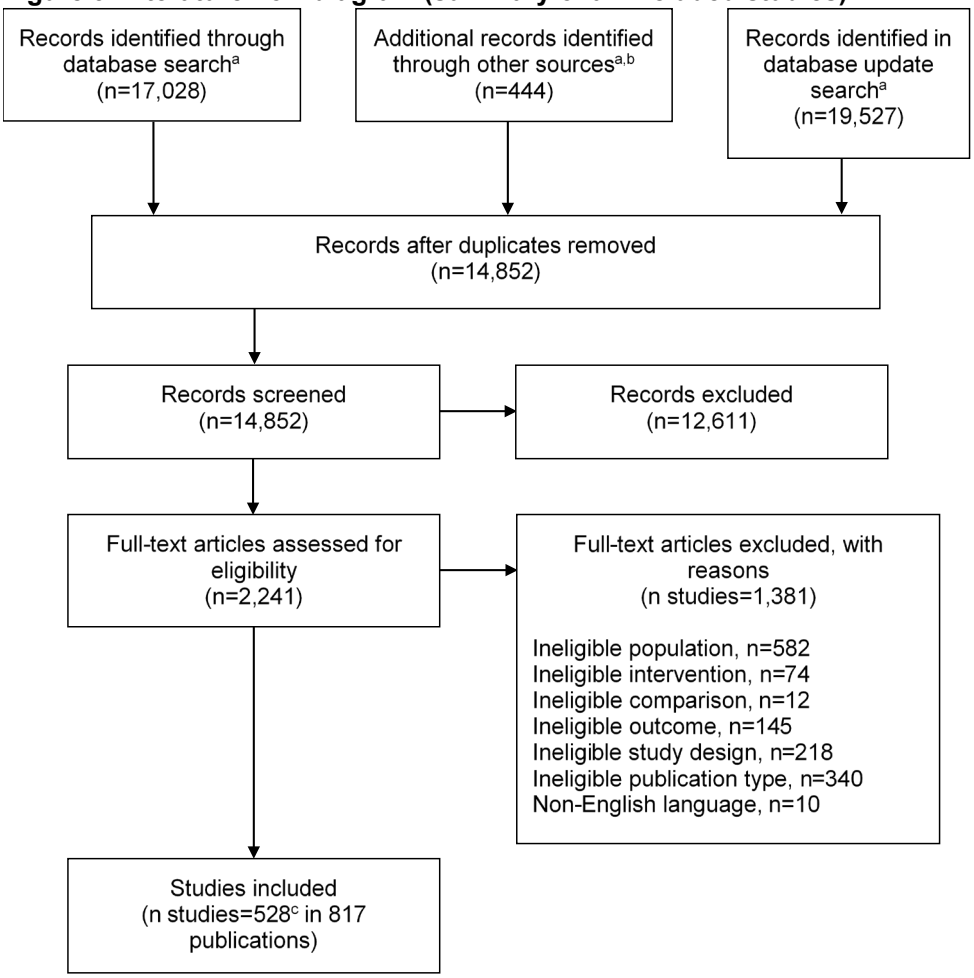
Experts in the field of PTSD will be invited to provide external peer review of this review and evidence tables. Comments and editorial review were also sought from the AHRQ Task Order Officer, an associate editor, and partners at NCPTSD. The draft report will be posted on the AHRQ website for 4 weeks 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.

3. Results

3.1 Results of Literature Search

In this update we included 32 new studies[22-53] published through September 11, 2023, bringing the total number of included studies in this report to 528 (in 817 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 14,852 unique records. After review of abstracts and titles, 2,241 articles were selected for full-text review, and 528 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)



[a]Multiple update searches were performed with overlapping search dates; number of records reflects the total sum of records from all searches including duplicate records.
[b]Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
[c]In this update report, there are 32 new trials.[22-53]

3.2 Characteristics of Included Studies

Interventions were first classified by treatment focus: posttraumatic stress disorder (PTSD), PTSD and substance use disorder (SUD), SUD, active control, or inactive control. In this classification, each arm was classified into a single category. Control arms were categorized based on the intervention and study design. Interventions without an active treatment component, such as waitlist or placebo, are coded as inactive control. Intervention arms being used to control for active components of another treatment are coded as active control if there is expected to be some active effect but less than the main treatment (e.g., superiority trials). For example, for a trial comparing prolonged exposure versus psychoeducation, with a superiority design hypothesizing larger effect with prolonged exposure, the psychoeducation arm would be coded as active control. In trials with a noninferiority design both intervention arms will have PTSD coded as the treatment focus.

Treatments were also classified by the intervention categories described in Table 2. These categories included pharmacologic treatments and five nonpharmacologic treatment categories (psychotherapy, nonpharmacologic biologic, nonpharmacologic cognitive, complementary and integrative health, and collaborative care), plus control. Study arms coded as active control for treatment focus above, are categorized as control and additionally categorized corresponding to the actual components of the treatment for intervention category. Using the same example as above, the prolonged exposure arm (coded as PTSD for treatment focus above) would be categorized as psychotherapy, and the psychoeducation arm (coded as active control for treatment focus) would be categorized as control and also as psychotherapy. 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 waitlist would have the first arm classified as both psychotherapy and pharmacotherapy, and the second arm as inactive control.

3.2 Results, Characteristics of Included Studies

Table 2. Intervention categories with examples[a]

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 Natural products 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
Inactive Control	Interventions which are essentially inactive or are not presumed to have an effect on mental health symptoms	Waitlist Placebo Assessment only

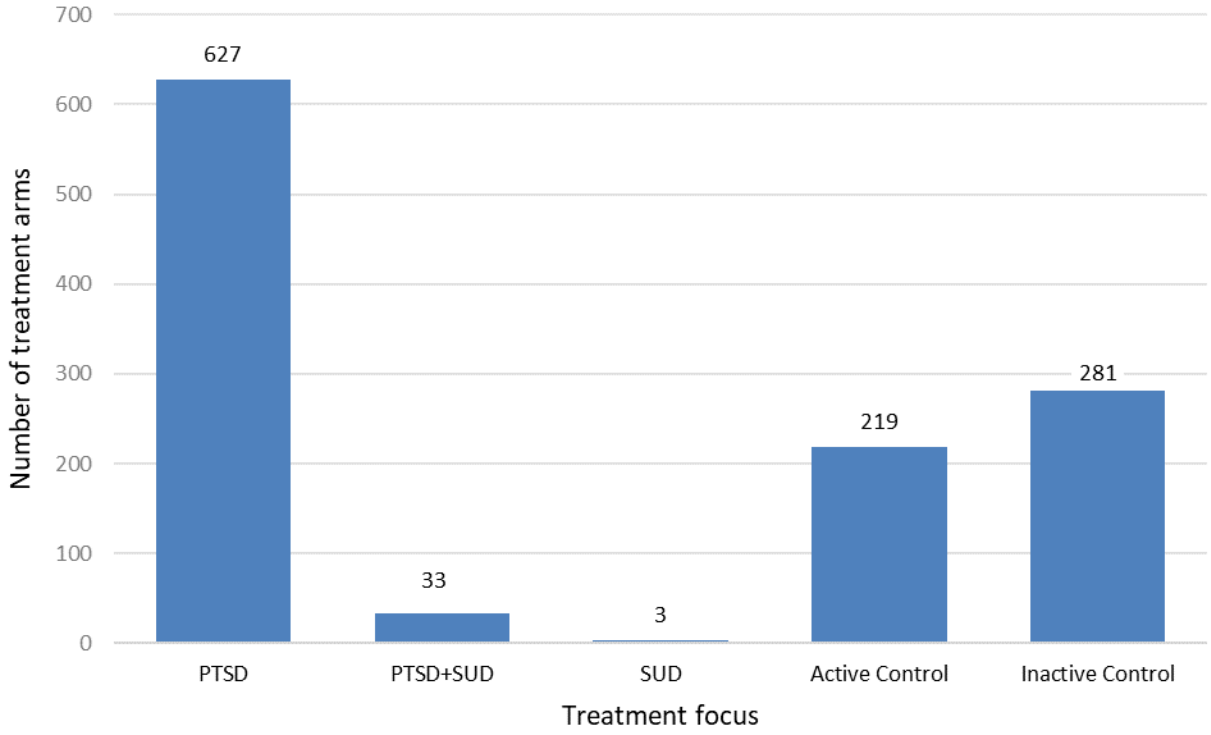
[a]Table 2 intervention lists and categories adapted from the 2017 Department of Veterans Affairs/Department of Defense clinical practice guideline.[54]

3.2.1 Overall Studies Included in the Evidence Tables

The data abstraction evidence tables (Appendix E and Appendix F) for this report present detailed information on study and population characteristics for the 528 total included studies.

Across included studies, comorbid PTSD/SUD was the focus for 3 percent of treatment arms and less than 1 percent focused on SUD (Figure 4). Fifty-four percent of treatment arms addressed PTSD, 19 percent were active controls, and 24 percent were inactive control arms.

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

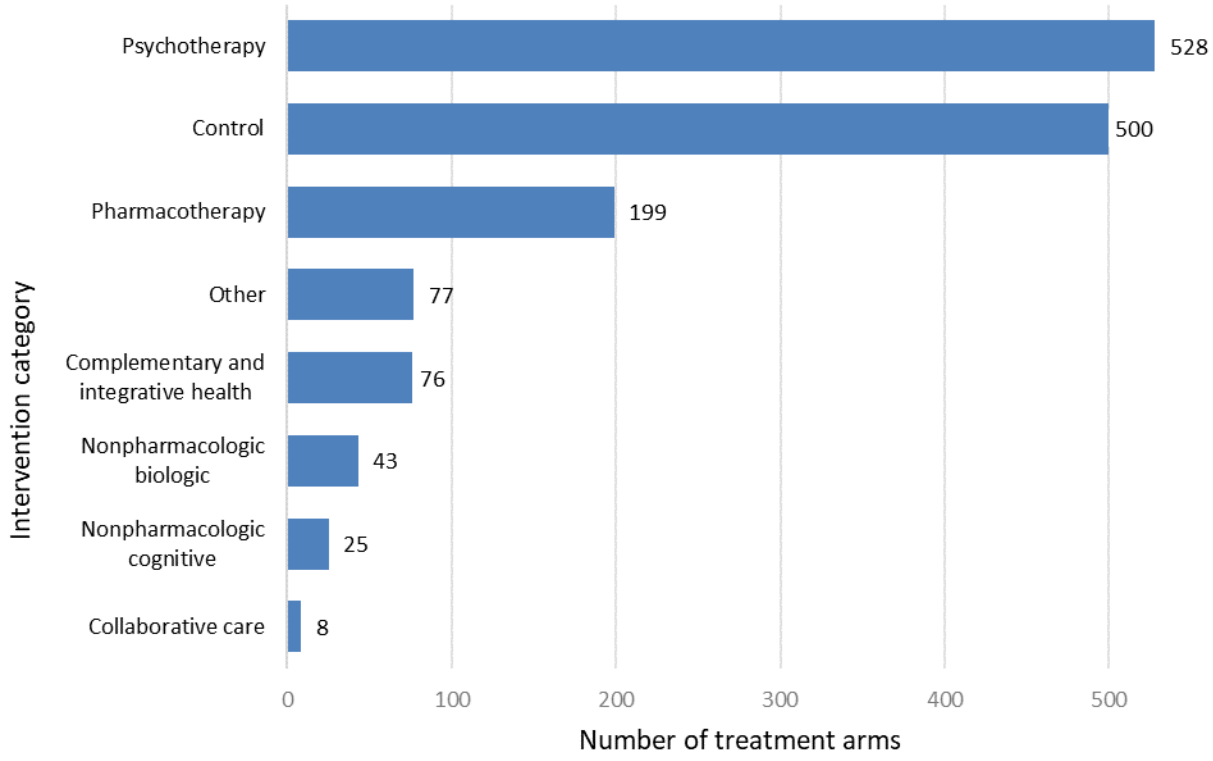


[a]Studies have more than one treatment arm.
Abbreviations: PTSD = posttraumatic stress disorder; SUD = substance use disorder

3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

The distribution of treatment arms by intervention category is shown in Figure 5. Psychotherapy was the most frequently studied treatment, employed in 45 percent of total treatment arms, followed by pharmacotherapy in 17 percent of treatment arms. Control arms comprised 43 percent of treatment arms (either inactive or active).

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



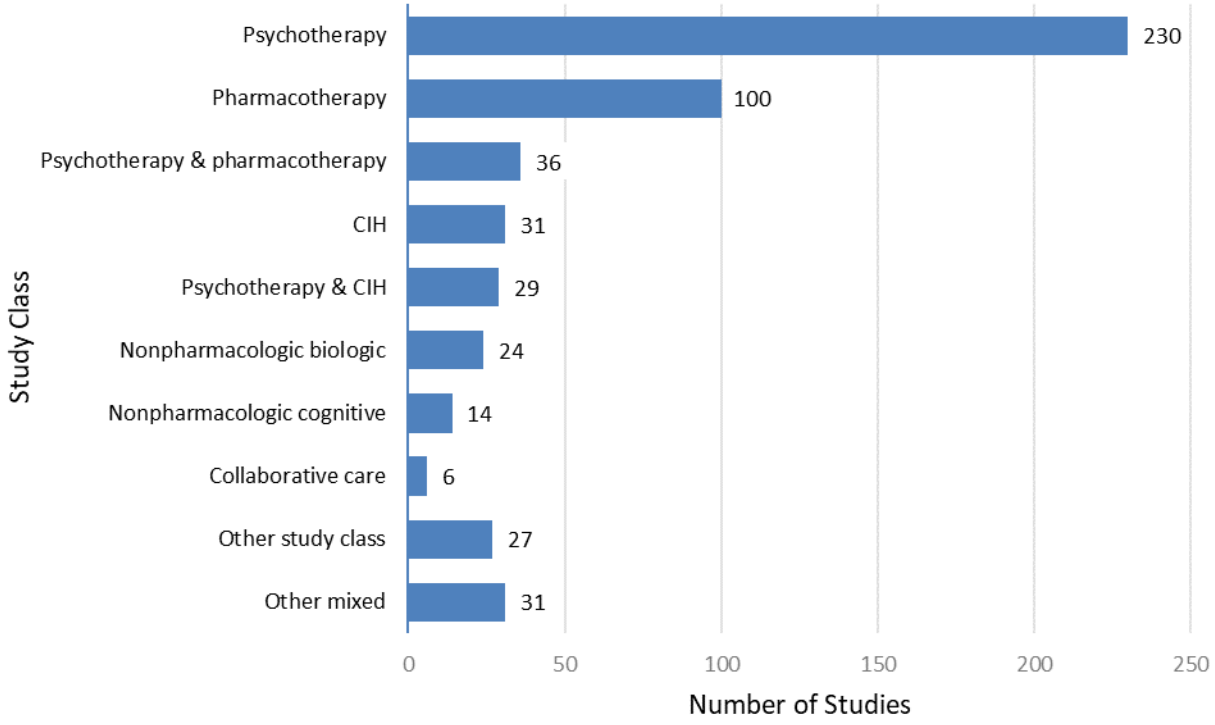
[a]Studies have more than one treatment arm. Counts for these categories sum to greater than the total of 1,163 treatment arms in the included studies since some treatment arms combine multiple interventions of different categories. For example, one treatment arm could combine a psychotherapy treatment with a pharmacotherapy treatment. Thus each category would count for one within this single arm.

3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

Studies were grouped into ten 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 inactive control, the study was categorized as the study class of the active treatment(s). For example, a study of prolonged exposure (psychotherapy) versus waitlist (inactive control) would be categorized as psychotherapy for the study class. The category Other study class includes studies in which all interventions are classified as Other for intervention category. 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 complementary and integrative health [CIH]). Other combinations were grouped in the Other mixed study class.

Psychotherapy was the most commonly studied intervention (44% of studies), followed by pharmacotherapy interventions (19%), and combined psychotherapy and pharmacotherapy (7%) (Figure 6).

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

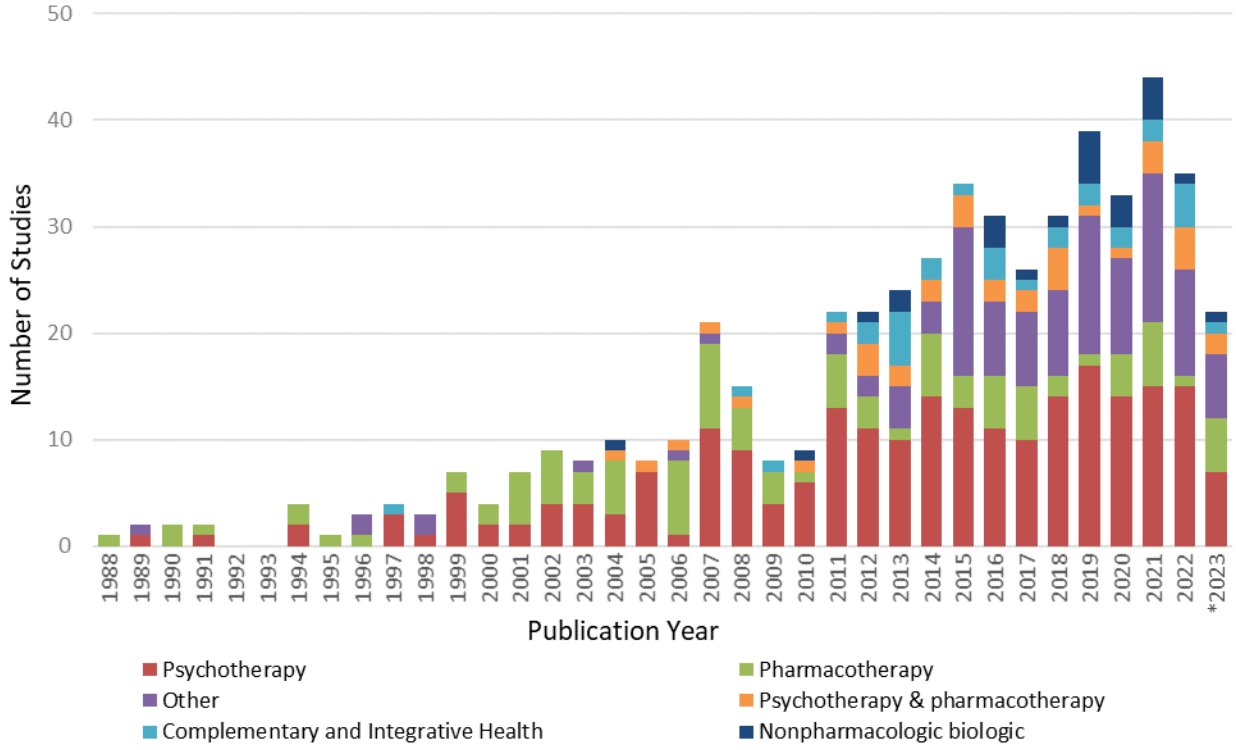


Other mixed includes studies in which the interventions studied were a combination other than psychotherapy & pharmacotherapy or psychotherapy & CIH (e.g. nonpharmacologic biologic & psychotherapy). Other study class includes studies of interventions classified as Other for intervention category.
Abbreviations: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

3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

The publication dates of the included studies ranged from 1988 to partway through 2023 (Figure 7). Forty-four studies were published in 2021, the highest amount of any year. The number of studies published per year increased in the 2000s then again in the 2010s. Most studies of CIH interventions were published in the last ten years, a trend also observed with studies of nonpharmacologic biologic treatments.

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

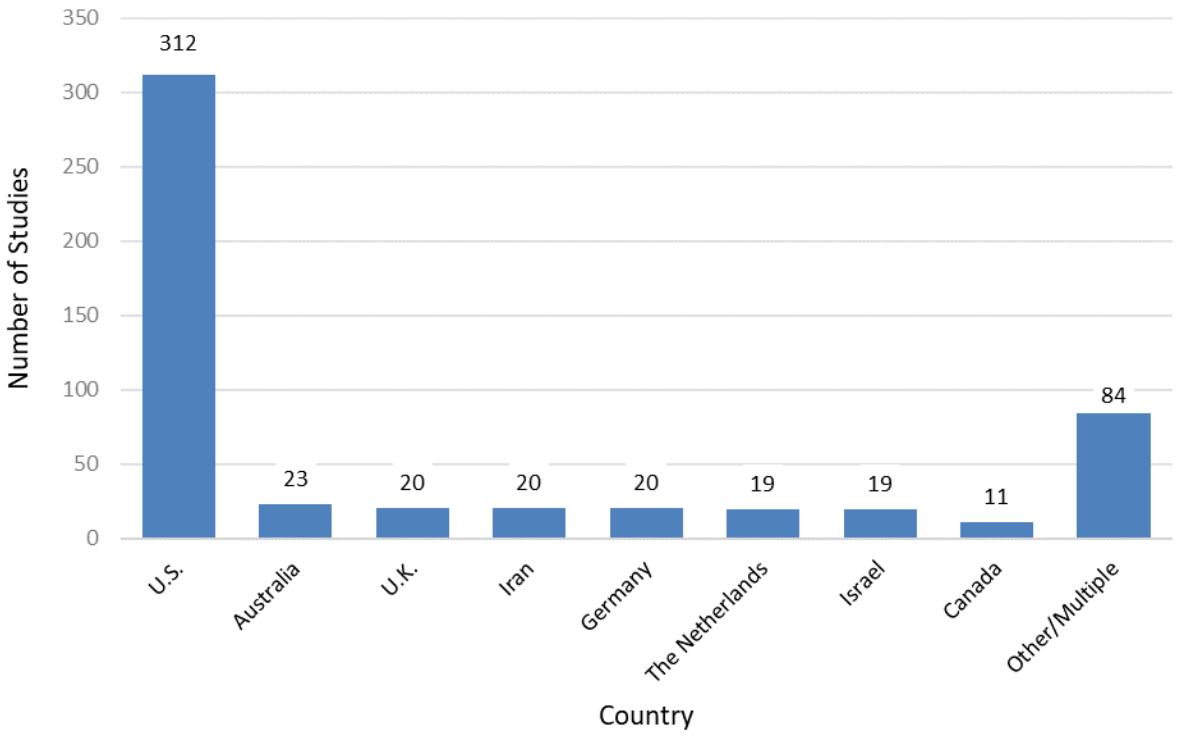


[a]2023 is a partial year (search date was through September 2023).

3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

The majority of studies (59%) were conducted in the United States (Figure 8), though it is important to note that inclusion eligibility required that the study was published in English.

Figure 8. Summary of all included studies: distribution of included studies by country

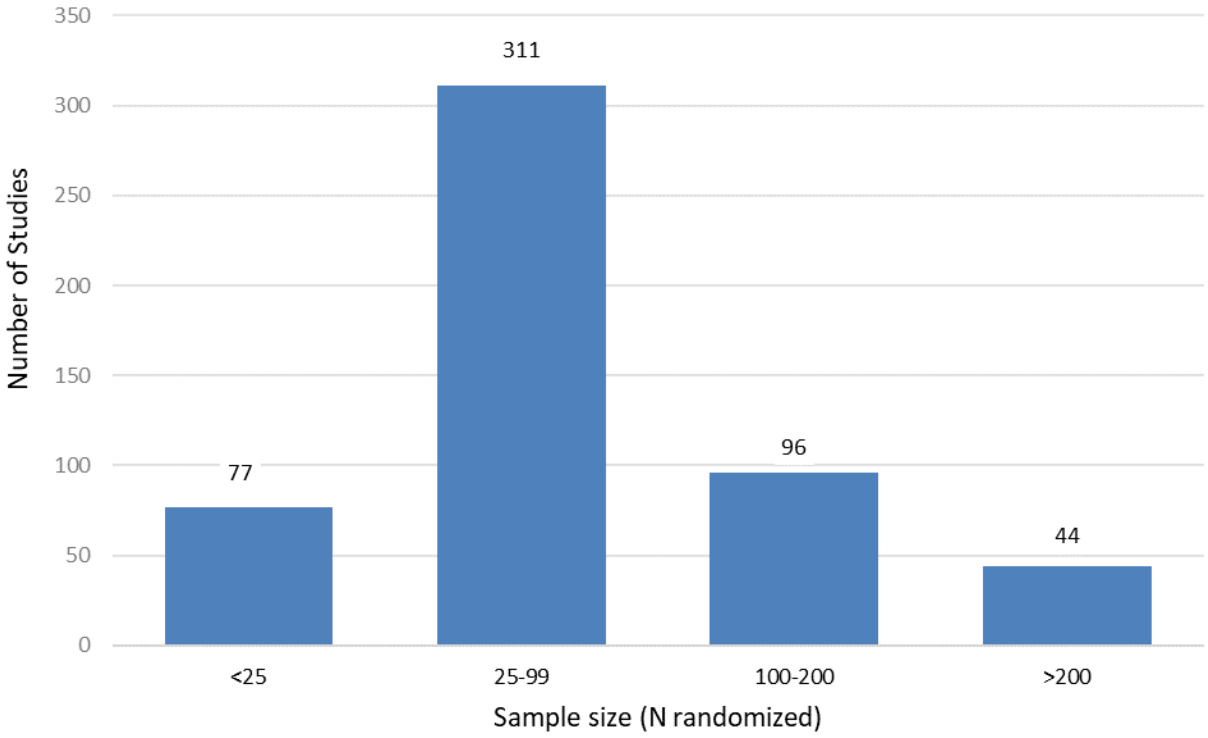


Multiple = study conducted in multiple countries. Only the eight countries with largest number of studies were included in this graph, studies conducted in the remaining countries are counted in "Other/Multiple".
Abbreviations: U.K. = United Kingdom; U.S. = United States

3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

There was no restriction on sample size for study inclusion. Sample sizes across included studies ranged from 8 to 1,001 participants, with a total of 45,738 participants included in the database. The median sample size was 58 (interquartile range [IQR] 31 to 102). 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 (15%) enrolled fewer than 25 participants (Figure 9).

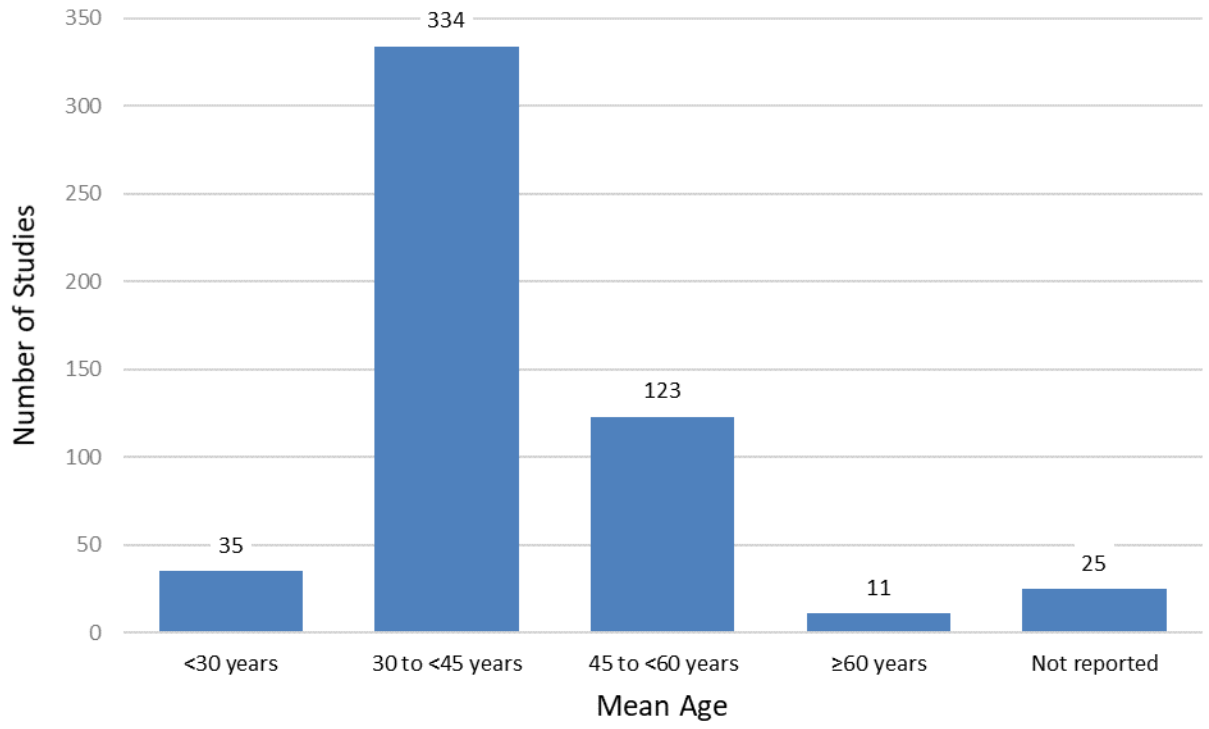
Figure 9. Summary of all included studies: studies by sample size



3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

The sample mean age ranged from 18 to 71 years (median 40 years). Most studies were conducted in younger populations (Figure 10). The sample mean age was 30 to <45 years for 63 percent of studies, while about a quarter of studies had sample mean age from 45 to <60 years (23%); five percent of studies did not provide mean age for the sample.

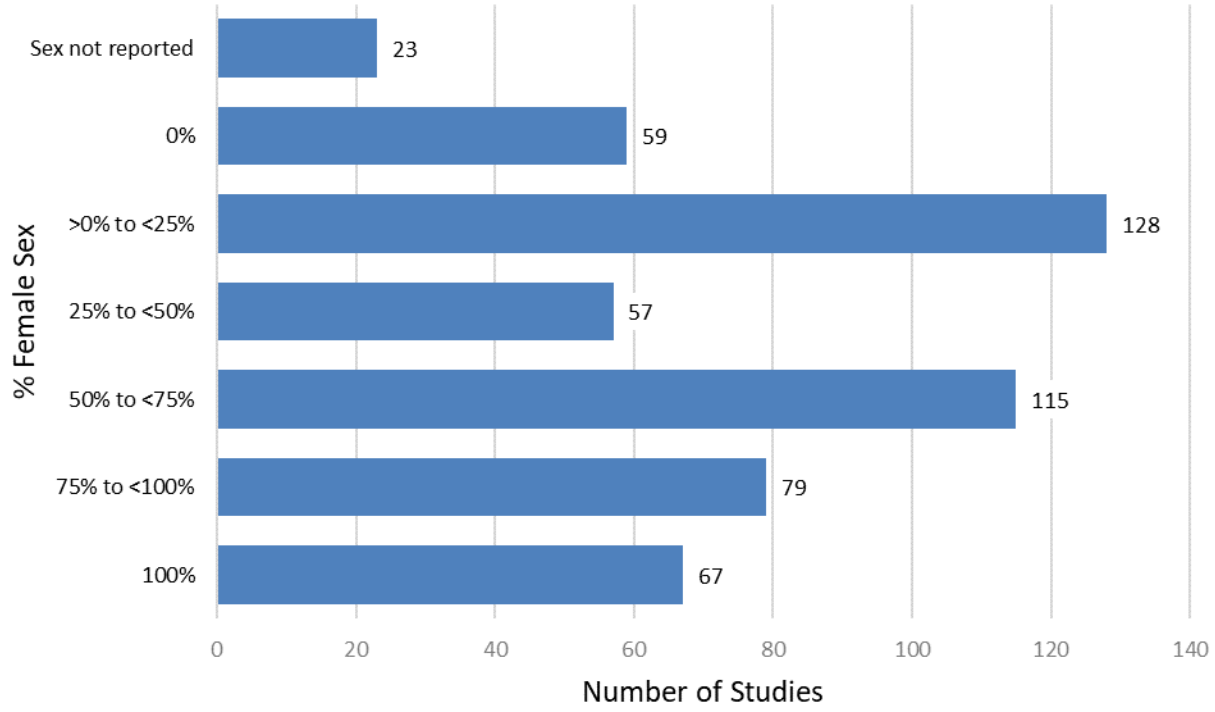
Figure 10. Summary of all included studies: studies by mean age



3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

Most studies enrolled both female and male participants, at varying proportions (Figure 11). About a quarter of studies included only one sex: 13 percent (67 studies) included only female participants and 11 percent (59 studies) included only male participants. A small number (23 studies, 4%) did not report sex of the participants. Thirteen studies (2%) reported data for gender identity and/or sexual orientation of the sample.

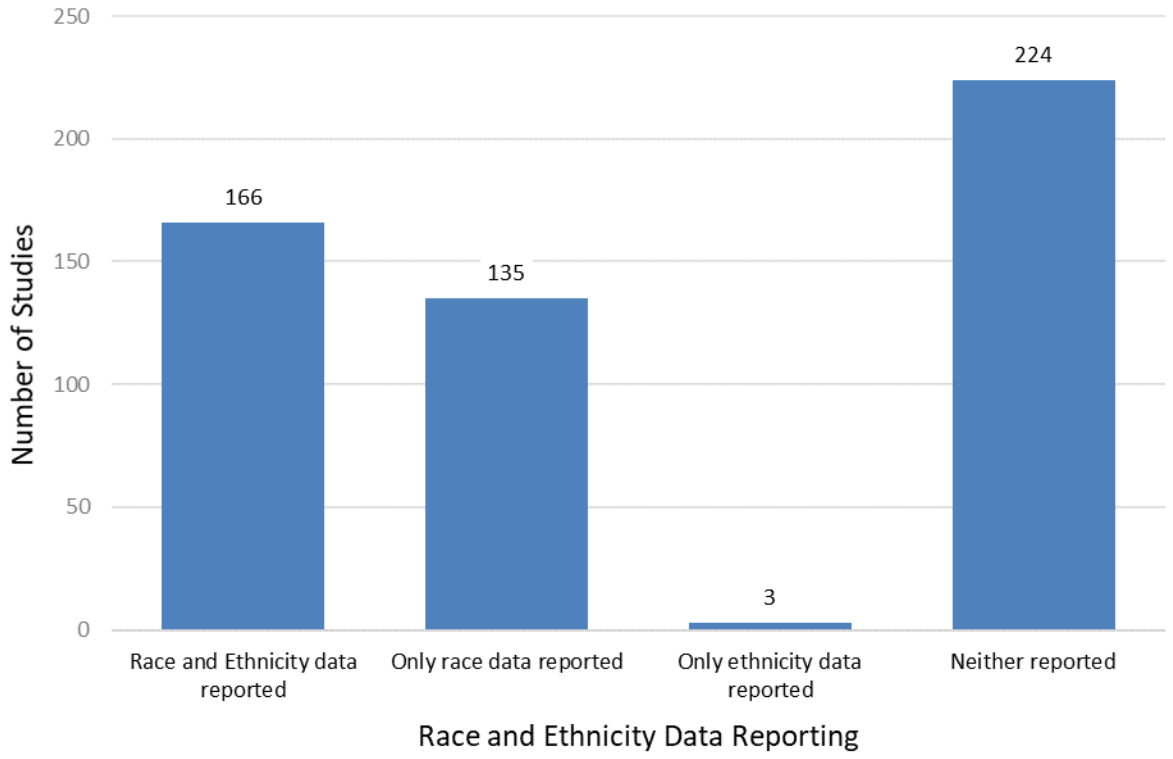
Figure 11. Summary of all included studies: studies by participant sex



3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

Race and ethnicity data were abstracted according to U.S. Census categories. Because race and ethnicity data were reported in different ways (i.e., grouped into different, non-U.S. Census categories) across many studies, some data were not able to be abstracted because they could not be accurately grouped into U.S. Census categories. Additionally, race and ethnicity data were sometimes reported inconsistently or not reported across some studies. Just under a third of studies (31%) provided data on both race and ethnicity that could be grouped into U.S. Census categories; another 26 percent provided data on race only and 3 studies (<1%) provided data on ethnicity only (Figure 12). Data were not provided for race or ethnicity corresponding to U.S. Census categories in 42 percent of studies

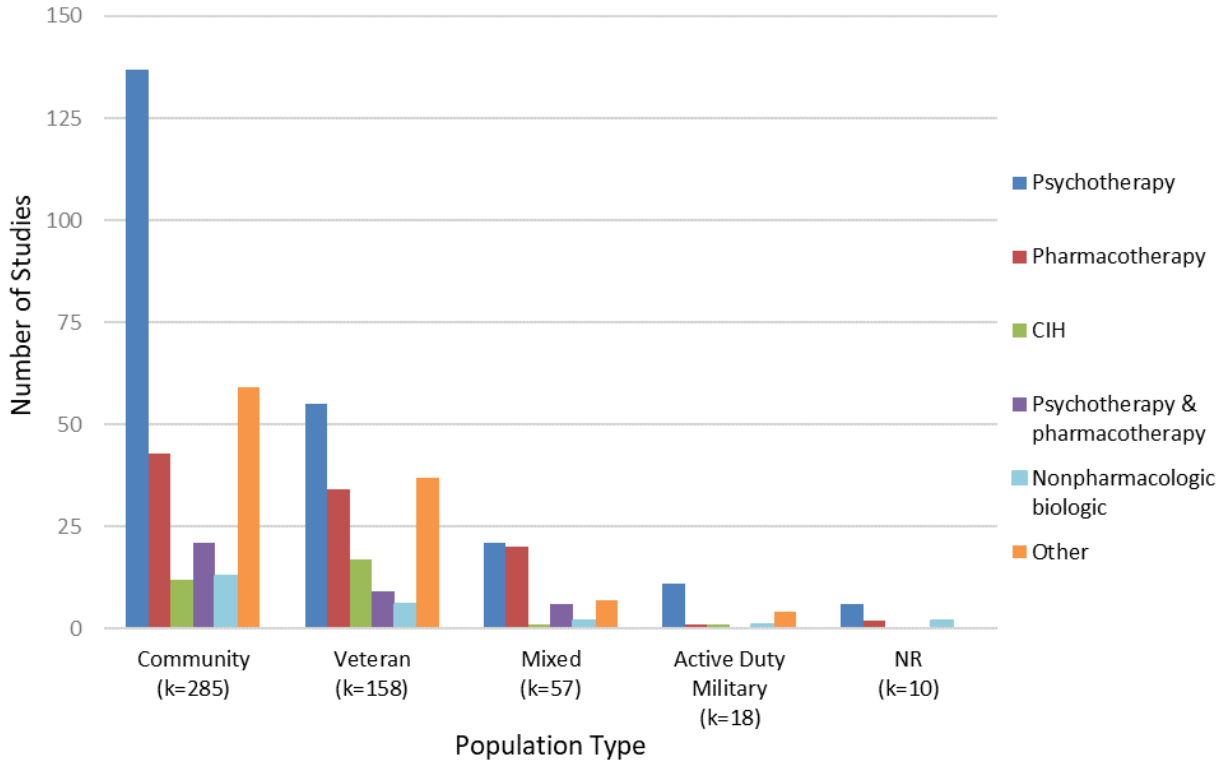
Figure 12. Summary of all included studies: studies reporting on race and ethnicity



3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

Slightly more studies enrolled participants from a community population (54% of studies) than from a military, veteran, or mixed population (Figure 13). 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 (55%; 17 of 31 studies) were among veterans.

Figure 13. Summary of all included studies: distribution of included studies by population type



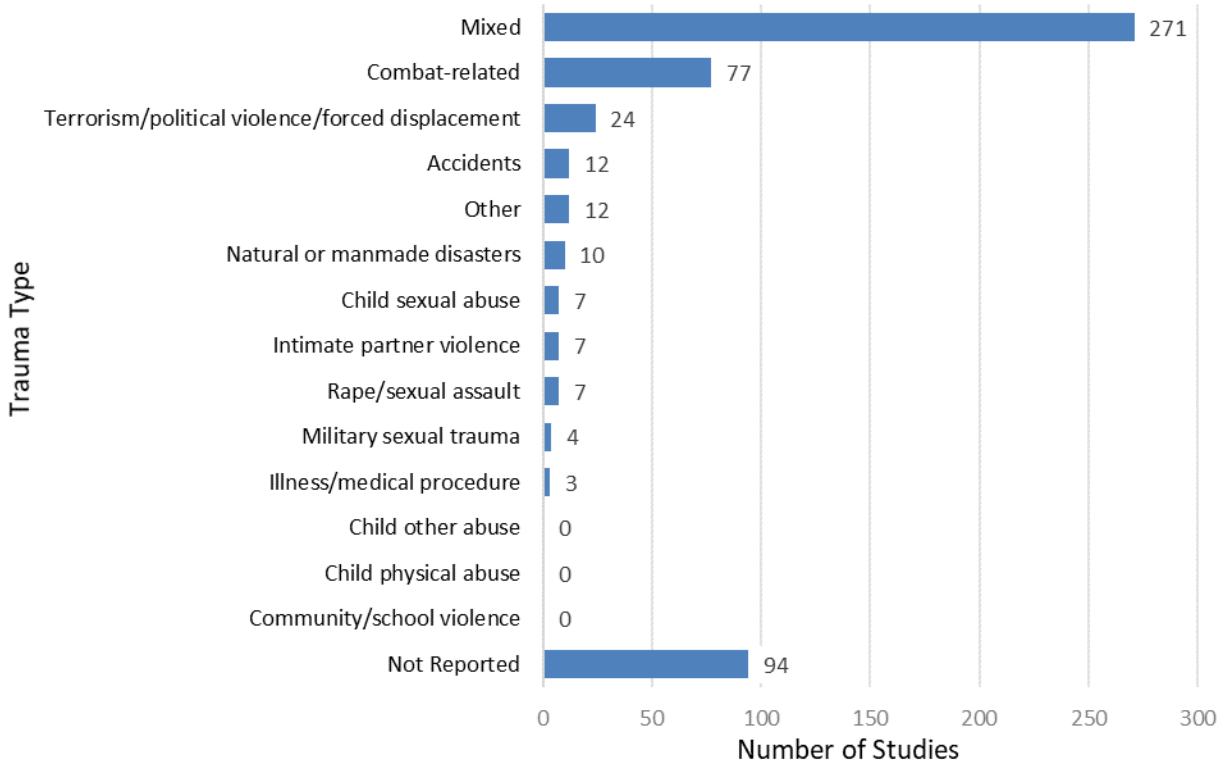
Mixed = Any combination of active duty military, veteran, and community-based samples.
Abbreviations: CIH = complementary and integrative health; k = number of studies; NR = not reported

Only a small proportion of studies (8%, 41 studies) 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 (77%) were conducted in the outpatient setting.

3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

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 14, with mixed trauma types being most prevalent among these study populations (51%), followed by combat-related trauma (15%).

Figure 14. Summary of all included studies: distribution of included studies by trauma type

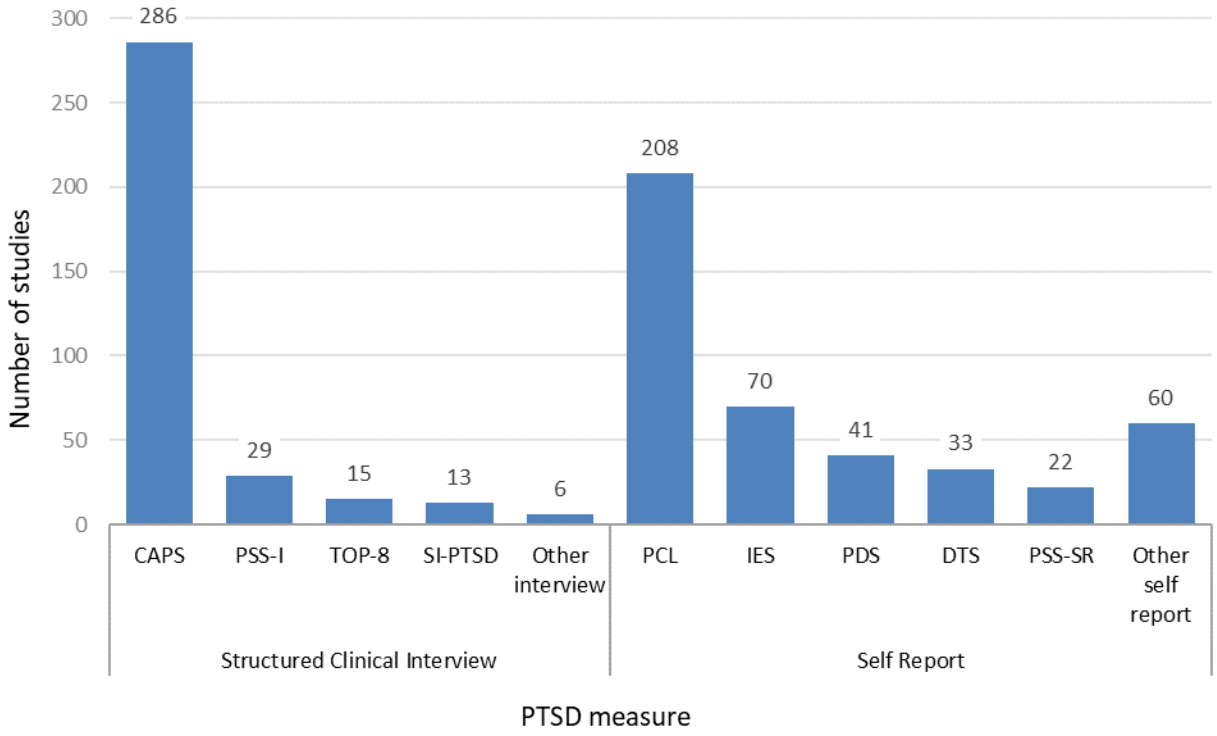


Notes: Active Duty member reporting sexual assault outside of military was categorized as rape/sexual assault. Intimate partner violence includes domestic violence. Accidents includes motor vehicle accidents, transportation-related accidents, and accidents due to construction. Natural or manmade disasters 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).

3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

The measure most frequently used to assess continuous PTSD outcomes was the Clinician-Administered PTSD Scale (CAPS), used in 54 percent of studies (Figure 15). Other structured clinical interview measures were used in another 12 percent of studies (some studies used both CAPS and another interview measure); 37 percent of studies did not use any interview measure. A larger number of studies used a self report measure (399 studies, 76%). The self report measures most frequently used were the PTSD Checklist (PCL) (39%), Impact of Event Scale (IES) (13%), and Posttraumatic Diagnostic Scale (PDS) (8%).

Figure 15. Summary of all included studies: PTSD measures used to assess continuous PTSD outcomes[a]



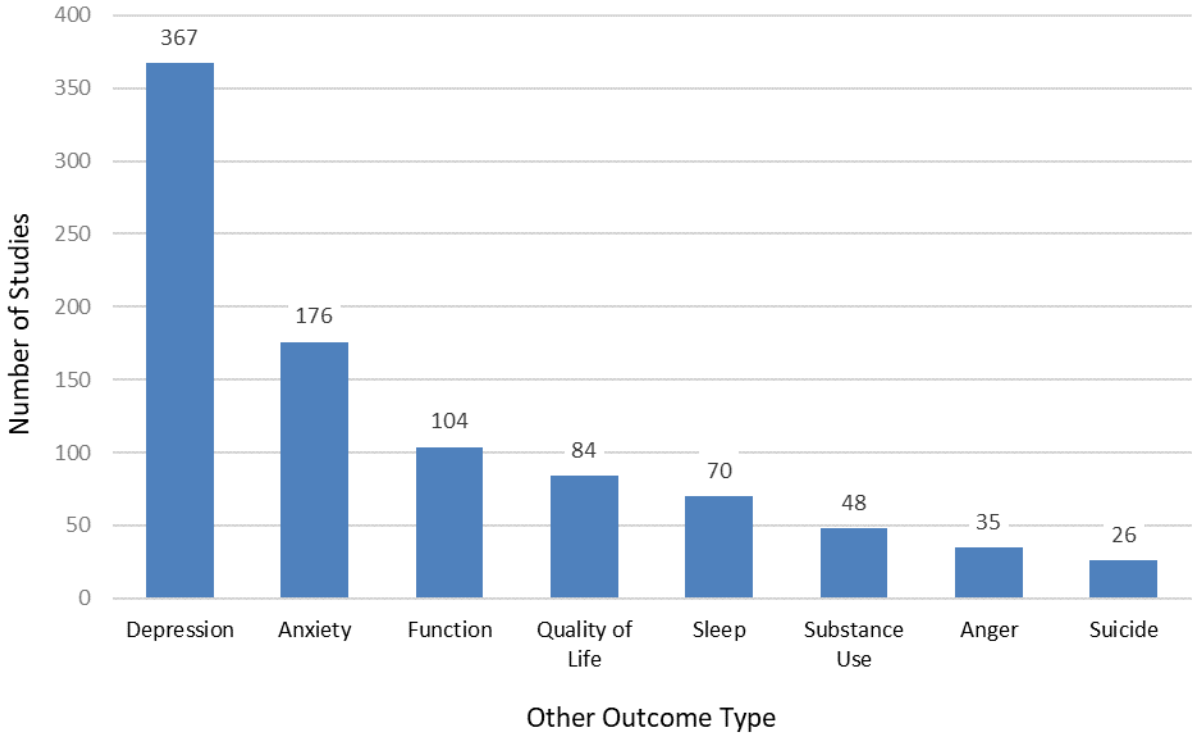
[a]Studies may have used more than one measure to assess PTSD outcomes. Measures used in 10 or fewer studies are grouped as categories within the measure type ("Other interview" and "Other self report").
Abbreviations: CAPS = Clinician-Administered PTSD Scale; IES = Impact of Event Scale; PCL = PTSD Checklist; PDS = Posttraumatic Diagnostic Scale; PSS-I = PTSD Symptom Scale - Interview; PSS-SR = PTSD Symptom Scale – Self-Report; PTSD = posttraumatic stress disorder; SI-PTSD = Structured Interview for PTSD; TOP-8 = Treatment-Outcome Posttraumatic Stress Disorder Scale.

PTSD diagnostic change and clinically meaningful response were included as dichotomous outcomes, with just over half of studies (54%) reporting at least one of these outcomes. Slightly more studies reported clinically meaningful response (39%) than diagnostic change (34%); 18 percent of studies reported both outcomes.

3.2.1 Results, Characteristics of Included Studies, Overall Studies Included in the Evidence Tables

Among other (non-PTSD) outcomes (Figure 16), depression was the most commonly assessed (70% of studies), followed by anxiety (33%), function (20%), and quality of life (16%).

Figure 16. Summary of all included studies: non-PTSD outcomes reported[a]



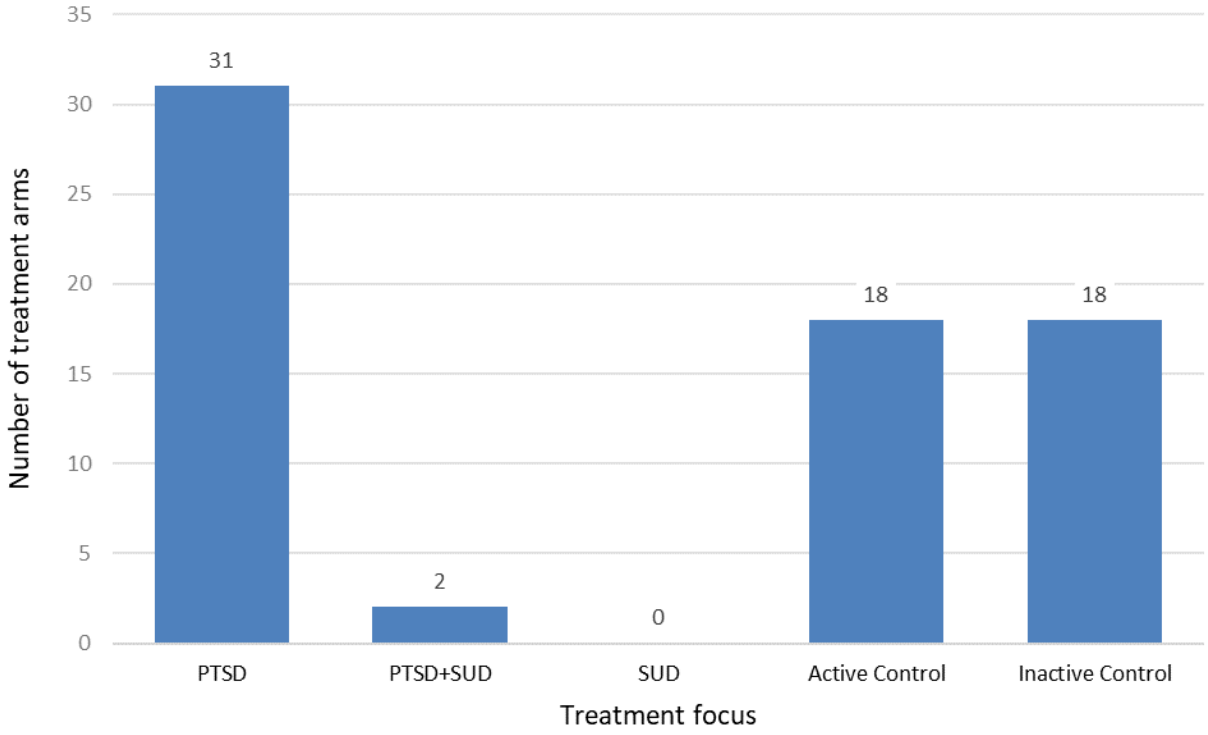
[a]Studies may have reported more than one other outcome type.
Abbreviations: PTSD = posttraumatic stress disorder

3.2.2 Studies Added in This Update

Key characteristics for the 32 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 is included in the detailed data abstraction evidence tables in Appendix E.

Among the 32 newly included studies, the treatment focus of the interventions was mostly PTSD (45% of treatment arms); 2 arms (3%) focused on comorbid PTSD/SUD, and none focused on SUD alone. The remaining arms were control arms, with equal numbers of active control and inactive control (26% each) (Figure 17).

Figure 17. Summary of newly 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.

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

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
Allen, 2022[36]	Psychotherapy	49	Australia	Telehealth	Community	Not Reported	Mixed
Back, 2023[37]	Pharmacotherapy	141	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	NR
Darvish, 2019[27]	Other study class	66	Iran	Outpatient clinic	Veteran	Not Reported	NR
de Kleine, 2019[29]	Nonpharmacologic cognitive	107	The Netherlands	Outpatient clinic	Community	Not Reported	Mixed
Duek, 2023[39]	Psychotherapy & pharmacotherapy	28	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	Mixed
Dunn, 2007[22]	Psychotherapy	101	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	Combat-related
Ehlers, 2023[45]	Psychotherapy	217	U.K.	Other	Community	Race data reported	Mixed
Feder, 2023[46]	Pharmacotherapy	30	U.S.	Outpatient clinic	Community	Race and Ethnicity data reported	Mixed
Fonzo, 2019[28]	Other mixed	84	U.S.	Outpatient clinic	Mixed	Race data reported	NR
Golier, 2023[40]	Pharmacotherapy	80	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	Mixed
Haller, 2023[41]	Psychotherapy & CIH	74	Germany	Outpatient clinic	Community	Not Reported	NR
Himmerich, 2016[26]	Psychotherapy	38	Germany	Mixed	Active Duty Military	Not Reported	Combat-related
Kanaan, 2023[47]	Pharmacotherapy	104	Australia	Other	Community	Not Reported	NR
Kearney, 2023[53]	Psychotherapy	59	Canada	Outpatient clinic	Community	Race and Ethnicity data reported	Mixed
Kuhn, 2017[23]	Other mixed	120	U.S.	Other	Community	Race and Ethnicity data reported	Mixed
Larsen, 2019b[31]	Nonpharmacologic cognitive	29	U.S.	Outpatient clinic	Veteran	Race and Ethnicity data reported	NR
Lazarov, 2019[30]	Nonpharmacologic cognitive	50	U.S.	Outpatient clinic	Community	Not Reported	NR
Litz, 2007[25]	Psychotherapy	45	U.S.	Outpatient clinic	Mixed	Not Reported	Mixed
Miller-Graff, 2021[35]	Other study class	105	Egypt	Other	Community	Not Reported	NR
Miner, 2016[24]	Other mixed	49	U.S.	Other	Community	Race and Ethnicity data reported	NR
Niles, 2020[34]	Nonpharmacologic cognitive	1001	U.S.	Other	Community	Race and Ethnicity data reported	Mixed
Peck, 2023[38]	Psychotherapy & pharmacotherapy	30	U.S.	Mixed	Community	Race data reported	Mixed
Prguda, 2023[49]	Psychotherapy	31	Australia	Outpatient clinic	Veteran	Race data reported	NR

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Author, Year	Study Class	Sample Size	Countries	Clinical Setting	Military Status	Race/Ethnicity Reported	Trauma Type
Rajabi, 2023[48]	Pharmacotherapy	26	Iran	Outpatient clinic	Active Duty Military	Not Reported	Combat-related
Segal, 2020[32]	Nonpharmacologic cognitive	60	Israel	Outpatient clinic	Community	Not Reported	Mixed
Taylor, 2023[42]	Psychotherapy	93	U.S.	Outpatient clinic	Mixed	Race and Ethnicity data reported	NR
Voorendonk, 2023[52]	Other mixed	119	The Netherlands	Outpatient clinic	Community	Not Reported	Mixed
Wakusawa, 2023[51]	Other mixed	22	Japan	Outpatient clinic	Community	Not Reported	Mixed
Walter, 2023[50]	Psychotherapy	94	U.S.	Outpatient clinic	Active Duty Military	Race and Ethnicity data reported	Mixed
Watkins, 2023[43]	Psychotherapy	112	U.S.	Outpatient clinic	Mixed	Race data reported	Mixed
Woud, 2021[33]	Nonpharmacologic cognitive	80	Germany	Residential inpatient	Community	Not Reported	Mixed
Zhao, 2023[44]	Nonpharmacologic biological	27	U.S.	Outpatient clinic	Community	Race and Ethnicity data reported	NR

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

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Table 4. Summary of newly included studies: intervention characteristics

Author, Year	Intervention Group[a]	Treatment Name	Treatment Focus	Intervention Categorization	Intervention Format	Intervention Delivery Method
Allen, 2022[36]	A	Internet-based CBT	PTSD	Psychotherapy	Individual	Technology Assisted
Allen, 2022[36]	B	Waitlist	Inactive Control	Inactive Control	NA	NA
Back, 2023[37]	A	Doxazosin	PTSD+SUD	Pharmacotherapy	Individual	In Person
Back, 2023[37]	B	Placebo	Inactive Control	Inactive Control	Individual	In Person
Darvish, 2019[27]	A	Text messaging-based psychiatric nursing program	PTSD	Other	Individual	Technology Alone
Darvish, 2019[27]	B	TAU	Inactive Control	Inactive Control	Individual	NA
de Kleine, 2019[29]	A	Cognitive bias modification	PTSD	Nonpharmacologic Cognitive	Individual	Technology Alone
de Kleine, 2019[29]	B	Control training	Inactive Control	Inactive Control	Individual	Technology Alone
Duek, 2023[39]	A	Ketamine + PE	PTSD	Psychotherapy & Pharmacotherapy	Individual	In Person
Duek, 2023[39]	B	Midazolam + PE	Active Control	Psychotherapy & Pharmacotherapy	Individual	In Person
Dunn, 2007[22]	A	Self-management group therapy	PTSD	Psychotherapy	Group	In Person
Dunn, 2007[22]	B	Psychoeducational group therapy	Active Control	Psychotherapy	Group	In Person
Ehlers, 2023[45]	A	Internet-delivered cognitive therapy for PTSD	PTSD	Psychotherapy	Individual	Technology Assisted
Ehlers, 2023[45]	B	Internet-delivered stress management therapy for PTSD	Active Control	Psychotherapy	Individual	Technology Assisted
Ehlers, 2023[45]	C	Waitlist with TAU	Inactive Control	Inactive Control	NA	NA
Feder, 2023[46]	A	Ketamine	PTSD	Pharmacotherapy	Individual	In Person
Feder, 2023[46]	B	Midazolam	Active Control	Pharmacotherapy	Individual	In Person
Fonzo, 2019[28]	A	Cognitive/affective remediation training	PTSD	Other	Individual	Technology Alone
Fonzo, 2019[28]	B	Attention control	Inactive Control	Inactive Control	Individual	Technology Alone
Golier, 2023[40]	A	Mifepristone	PTSD	Pharmacotherapy	Individual	In Person
Golier, 2023[40]	B	Placebo	Inactive Control	Inactive Control	Individual	In Person
Haller, 2023[41]	A	Pranayama-assisted trauma-focused CBT	PTSD	Psychotherapy & CIH	Individual	In Person
Haller, 2023[41]	B	Trauma-focused CBT	Active Control	Psychotherapy	Individual	In Person

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Author, Year	Intervention Group[a]	Treatment Name	Treatment Focus	Intervention Categorization	Intervention Format	Intervention Delivery Method
Himmerich, 2016[26]	A	Inpatient psychotherapy	PTSD	Psychotherapy & Other	Mixed	In Person
Himmerich, 2016[26]	B	Outpatient clinical management	Active Control	Psychotherapy	Mixed	In Person
Kanaan, 2023[47]	A	N-acetylcysteine + TAU	PTSD	Pharmacotherapy	Individual	Mixed
Kanaan, 2023[47]	B	Placebo + TAU	Inactive Control	Inactive Control	Individual	Mixed
Kearney, 2023[53]	A	Deep-brain reorienting	PTSD	Psychotherapy	Individual	Video
Kearney, 2023[53]	B	Waitlist	Inactive Control	Inactive Control	NA	NA
Kuhn, 2017[23]	A	PTSD Coach smartphone application	PTSD	Other	Individual	Technology Alone
Kuhn, 2017[23]	B	Waitlist	Inactive Control	Inactive Control	NA	NA
Larsen, 2019b[31]	A	Adaptive computerized working memory training	PTSD	Nonpharmacologic Cognitive	Individual	Technology Alone
Larsen, 2019b[31]	B	Non-adaptive computerized working memory training	Active Control	Nonpharmacologic Cognitive	Individual	Technology Alone
Lazarov, 2019[30]	A	Bias-contingent attention bias modification	PTSD	Nonpharmacologic Cognitive	Individual	Technology Alone
Lazarov, 2019[30]	B	Attention control training	PTSD	Nonpharmacologic Cognitive	Individual	Technology Alone
Litz, 2007[25]	A	Internet-delivered self-management CBT	PTSD	Psychotherapy	Individual	Mixed
Litz, 2007[25]	B	Internet-delivered supportive counseling	Active Control	Psychotherapy	Individual	Mixed
Miller-Graff, 2021[35]	A	PTSD Coach Online-Arabic	PTSD	Other	Individual	Technology Alone
Miller-Graff, 2021[35]	B	Waitlist	Inactive Control	Inactive Control	NA	NA
Miner, 2016[24]	A	PTSD Coach smartphone application	PTSD	Other	Individual	Technology Alone
Miner, 2016[24]	B	Waitlist	Inactive Control	Inactive Control	NA	NA
Niles, 2020[34]	A	Personalized attention bias modification	PTSD	Nonpharmacologic Cognitive	Individual	Technology Alone
Niles, 2020[34]	B	Non-personalized attention bias modification	Active Control	Nonpharmacologic Cognitive	Individual	Technology Alone
Niles, 2020[34]	C	Placebo	Inactive Control	Inactive Control	Individual	Technology Alone
Peck, 2023[38]	A	PE + financial incentives + TAU for opioid use disorder	PTSD+SUD	Psychotherapy & Pharmacotherapy	Individual	Mixed

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Author, Year	Intervention Group[a]	Treatment Name	Treatment Focus	Intervention Categorization	Intervention Format	Intervention Delivery Method
Peck, 2023[38]	B	PE + TAU for opioid use disorder	Active Control	Psychotherapy & Pharmacotherapy	Individual	Mixed
Peck, 2023[38]	C	TAU for opioid use disorder	Active Control	Pharmacotherapy	Individual	Mixed
Prguda, 2023[49]	A	CBT for insomnia + imagery rehearsal therapy for nightmares	PTSD	Psychotherapy	Group	In Person
Prguda, 2023[49]	B	CBT for insomnia	Active Control	Psychotherapy	Group	In Person
Rajabi, 2023[48]	A	Memantine	PTSD	Pharmacotherapy	Individual	In Person
Rajabi, 2023[48]	B	Placebo	Inactive Control	Inactive Control	Individual	In Person
Segal, 2020[32]	A	Personalized attention control therapy	PTSD	Nonpharmacologic Cognitive	Individual	In Person
Segal, 2020[32]	B	Non-personalized attention control therapy	Active Control	Nonpharmacologic Cognitive	Individual	In Person
Segal, 2020[32]	C	Control	Inactive Control	Inactive Control	Individual	In Person
Taylor, 2023[42]	A	CBT for insomnia and nightmares followed by CPT	PTSD	Psychotherapy	Individual	In Person
Taylor, 2023[42]	B	CPT followed by CBT for insomnia and nightmares	Active Control	Psychotherapy	Individual	In Person
Taylor, 2023[42]	C	CPT	Active Control	Psychotherapy	Individual	In Person
Voorendonk, 2023[52]	A	Intensive trauma-focused treatment for PTSD + Physical activity	PTSD	Psychotherapy & Other	Mixed	Mixed
Voorendonk, 2023[52]	B	Intensive trauma-focused treatment for PTSD + Non-physical activity	Active Control	Psychotherapy & CIH	Mixed	Mixed
Wakusawa, 2023[51]	A	Traumatic stress protocol	PTSD	Psychotherapy & Pharmacotherapy & CIH	Individual	In Person
Wakusawa, 2023[51]	B	Waitlist	Inactive Control	Inactive Control	NA	NA
Walter, 2023[50]	A	Behavioral activation + CPT	PTSD	Psychotherapy	Individual	In Person
Walter, 2023[50]	B	CPT	Active Control	Psychotherapy	Individual	In Person
Watkins, 2023[43]	A	CPT	PTSD	Psychotherapy	Individual	In Person
Watkins, 2023[43]	B	Waitlist	Inactive Control	Inactive Control	Individual	Phone
Woud, 2021[33]	A	Cognitive Bias Modification - Appraisal + TAU	PTSD	Psychotherapy & CIH & Nonpharmacologic Cognitive & Other	Mixed	Mixed
Woud, 2021[33]	B	Peripheral Vision Task + TAU	Active Control	Psychotherapy & CIH & Other	Mixed	Mixed

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Author, Year	Intervention Group[a]	Treatment Name	Treatment Focus	Intervention Categorization	Intervention Format	Intervention Delivery Method
Zhao, 2023[44]	A	Personalized neurofeedback	PTSD	Nonpharmacologic Biologic	Individual	In Person
Zhao, 2023[44]	B	Sham neurofeedback	Inactive Control	Inactive Control	Individual	In Person

[a]Each intervention group (study arm) is labeled with a letter (A, B, C) and listed in a separate row, therefore studies are listed in multiple rows.
Abbreviations: CBT = cognitive behavioral therapy; CIH = complementary and integrative health; CPT = cognitive processing therapy; NA = not applicable; PE = prolonged exposure; PTSD = posttraumatic stress disorder; SUD = substance use disorder; TAU = treatment as usual

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

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
Allen, 2022[36]	PCL	Y	Y	N	Y	Y	N	N	N	N	N
Back, 2023[37]	CAPS, PCL	N	N	N	N	N	N	N	N	Y	N
Darvish, 2019[27]	Self-rating scale for PTSD	Y	N	N	N	N	N	N	N	N	N
de Kleine, 2019[29]	PSS-SR	N	N	N	N	Y	N	N	N	N	N
Duek, 2023[39]	PCL	N	N	N	N	Y	N	N	N	N	N
Dunn, 2007[22]	CAPS, DTS	N	N	N	N	Y	N	N	N	N	N
Ehlers, 2023[45]	CAPS, IES, PCL	Y	Y	N	Y	Y	Y	Y	Y	N	N
Feder, 2023[46]	CAPS	N	Y	N	N	Y	N	N	N	N	Y
Fonzo, 2019[28]	CAPS	N	N	N	N	N	N	N	N	N	N
Golier, 2023[40]	CAPS, PCL	N	Y	Y	N	Y	N	N	Y	N	N
Haller, 2023[41]	PCL	N	N	N	Y	Y	N	Y	N	N	N
Himmerich, 2016[26]	PDS	N	N	N	N	N	N	N	N	N	N
Kanaan, 2023[47]	CAPS, PCL	Y	N	N	Y	Y	N	Y	N	Y	N
Kearney, 2023[53]	CAPS	Y	N	N	N	N	N	N	N	N	N
Kuhn, 2017[23]	PCL	N	Y	N	N	Y	Y	N	N	N	N
Larsen, 2019b[31]	PCL	N	Y	N	Y	Y	N	N	N	N	N
Lazarov, 2019[30]	CAPS, PCL	N	Y	N	N	Y	N	N	N	N	N
Litz, 2007[25]	PSS-I	Y	Y	N	Y	Y	N	N	N	N	N
Miller-Graff, 2021[35]	PCL	N	N	N	Y	Y	N	N	N	N	N
Miner, 2016[24]	PCL	N	Y	N	N	N	N	N	N	N	N
Niles, 2020[34]	PCL	N	N	N	Y	Y	N	N	N	N	N
Peck, 2023[38]	CAPS, PCL	Y	N	N	Y	Y	N	N	N	N	N
Prguda, 2023[49]	PCL	N	N	N	Y	Y	N	N	Y	N	N
Rajabi, 2023[48]	CAPS	N	N	N	N	N	N	N	N	N	N

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

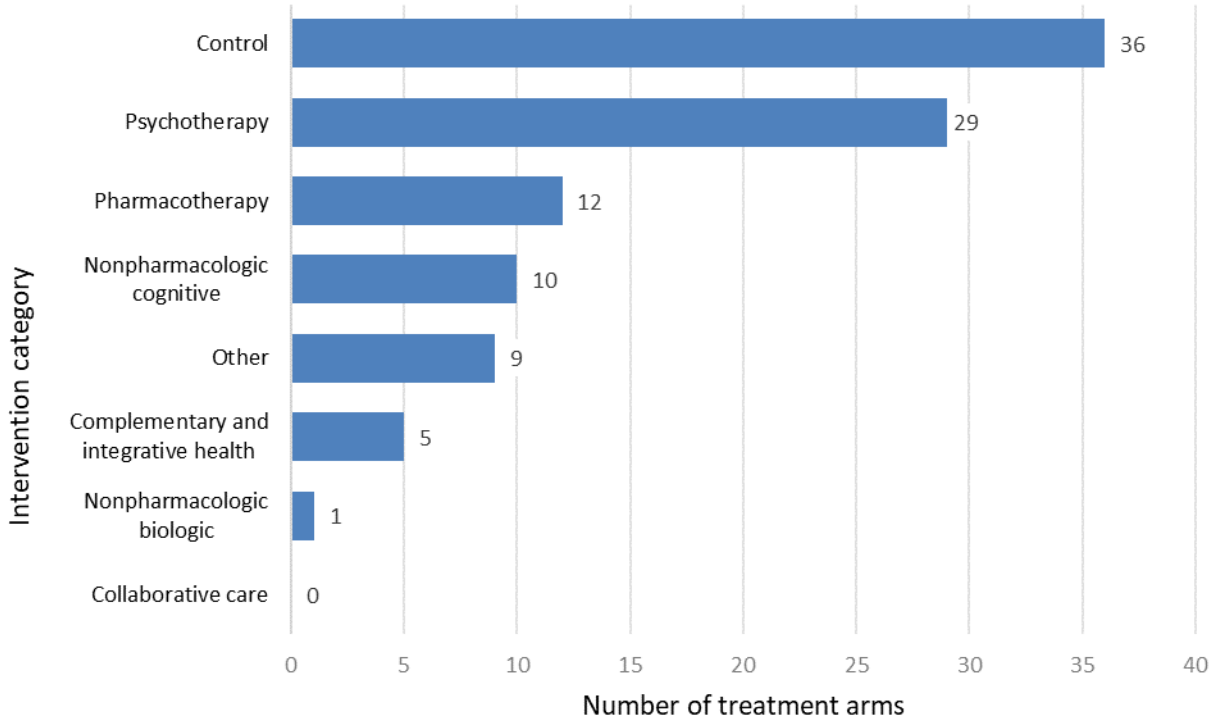
Author, Year	PTSD Continuous Outcome Measure(s)	PTSD Diagnostic Change	PTSD Clinically Meaningful Response	Anger	Anxiety	Depression	Function	Quality of Life	Sleep	Substance Use	Suicide
Segal, 2020[32]	CAPS, PCL	Y	N	N	N	Y	N	N	N	N	N
Taylor, 2023[42]	PCL	Y	Y	N	N	N	N	N	Y	N	N
Voorendonk, 2023[52]	CAPS, PCL	Y	N	N	Y	Y	N	Y	Y	N	N
Wakusawa, 2023[51]	IES	N	N	N	N	N	N	N	N	N	N
Walter, 2023[50]	CAPS, PCL	Y	Y	N	N	Y	N	N	N	N	N
Watkins, 2023[43]	CAPS, PCL	N	N	N	Y	Y	N	N	Y	N	N
Woud, 2021[33]	PCL	N	N	N	N	N	N	N	N	N	Y
Zhao, 2023[44]	CAPS, PCL	N	N	N	N	N	N	N	N	N	N

Abbreviations: CAPS = Clinician-Administered PTSD Scale; DTS = Davidson Trauma Scale; IES = Impact of Event 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.
Note: cells containing "Y" are shaded green

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

The distribution of treatment arms by intervention category is shown in Figure 18. Psychotherapy was the most frequently employed (42% of treatment arms); other treatments employed included pharmacotherapy (17%), nonpharmacologic cognitive interventions (14%), and CIH (7%). Because inclusion criteria were expanded during this update to include interventions that do not require a provider, there are relatively higher numbers of studies employing nonpharmacologic cognitive and other intervention category treatments compared to the rates of these intervention categories in previously included studies.

Figure 18. Summary of newly included studies: distribution of treatment arms by intervention category[a]

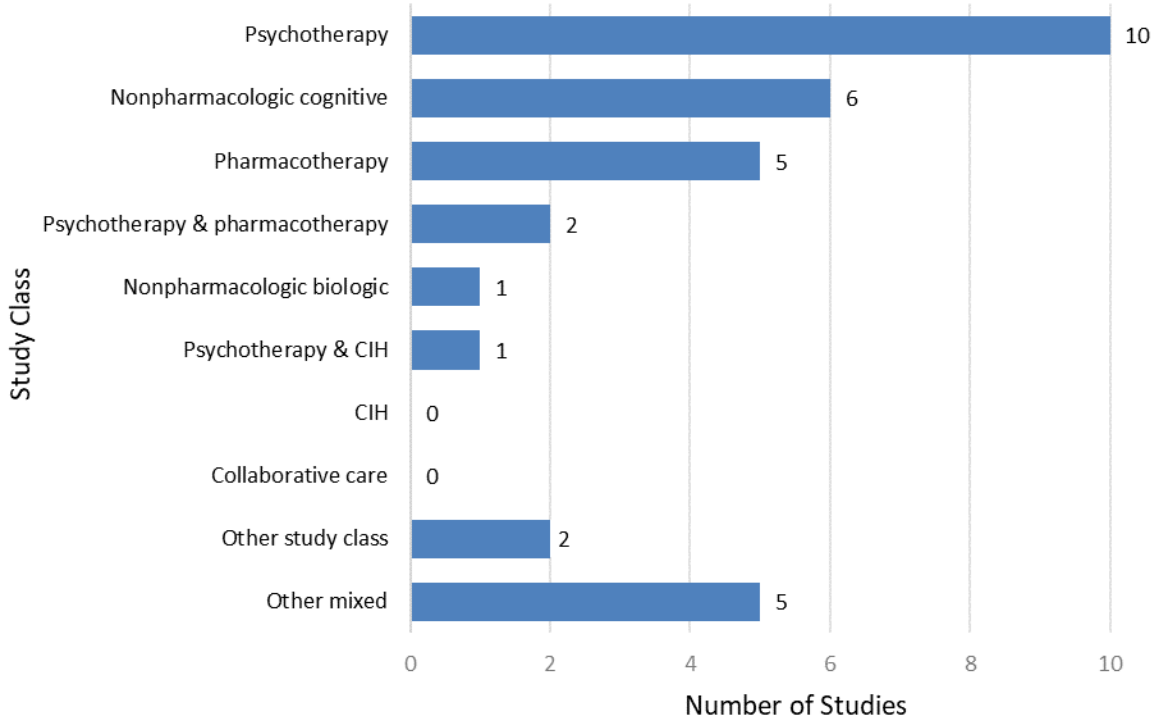


[a]Studies have more than one treatment arm. Counts for these categories sum to greater than the total number of treatment arms in the included studies since some treatment arms combine multiple interventions of different categories. For example, one treatment arm could combine a psychotherapy treatment with a pharmacotherapy treatment. Thus each category would count for one within this single arm.

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Almost all the studies (24/32, 75%) examined interventions within a single category versus a control. The predominant intervention studied was psychotherapy treatments (31%), with the remainder of studies classified as nonpharmacologic cognitive (19%), pharmacotherapy (16%), psychotherapy & pharmacotherapy (6%), nonpharmacologic biologic (3%), psychotherapy & CIH (3%), other study class (6%) and other mixed (16%) (Figure 19).

Figure 19. Summary of newly included studies: distribution by study class[a]

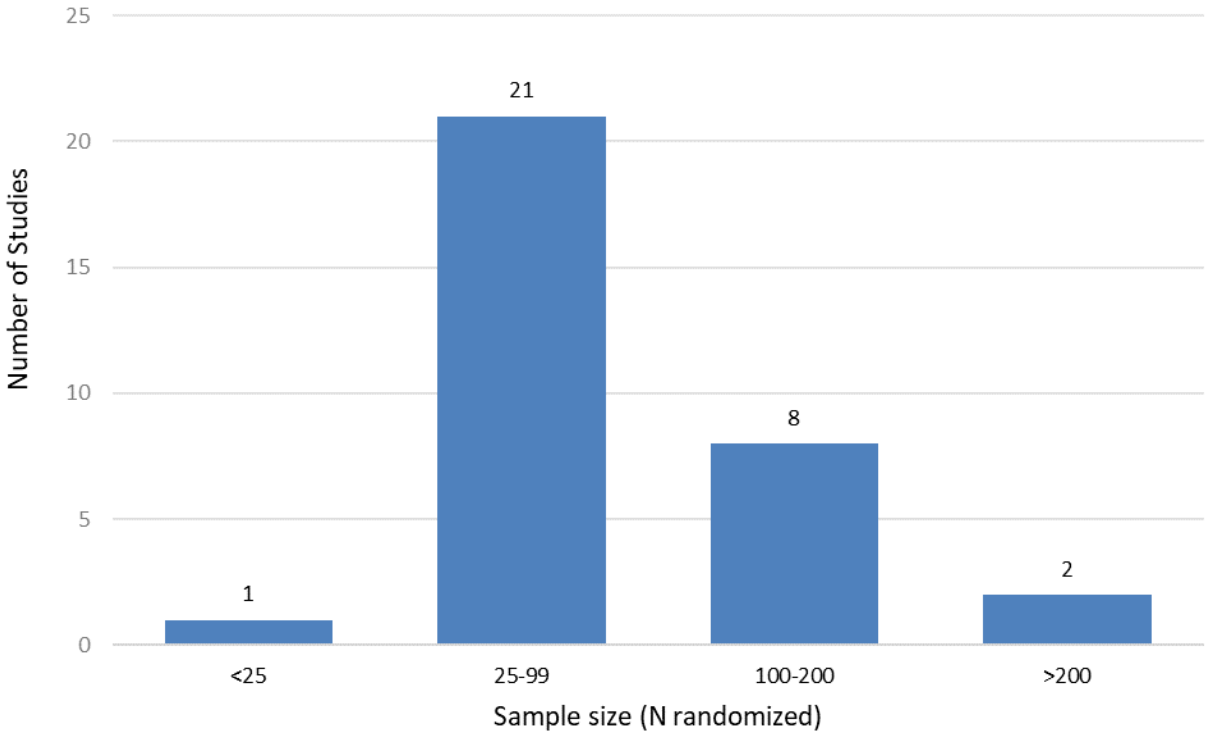


[a]Other mixed includes studies in which the interventions studied were a combination other than psychotherapy & pharmacotherapy or psychotherapy & CIH (e.g. nonpharmacologic biologic & psychotherapy). Other study class includes studies of interventions classified as Other for intervention category.
Abbreviations: CIH = complementary and integrative health.

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

A total of 3,271 participants were enrolled in the newly included studies, with sample sizes ranging from 22 to 1,001. Most studies (66%) had sample sizes between 25 and 99 participants (Figure 20). There were two studies with over 200 participants.

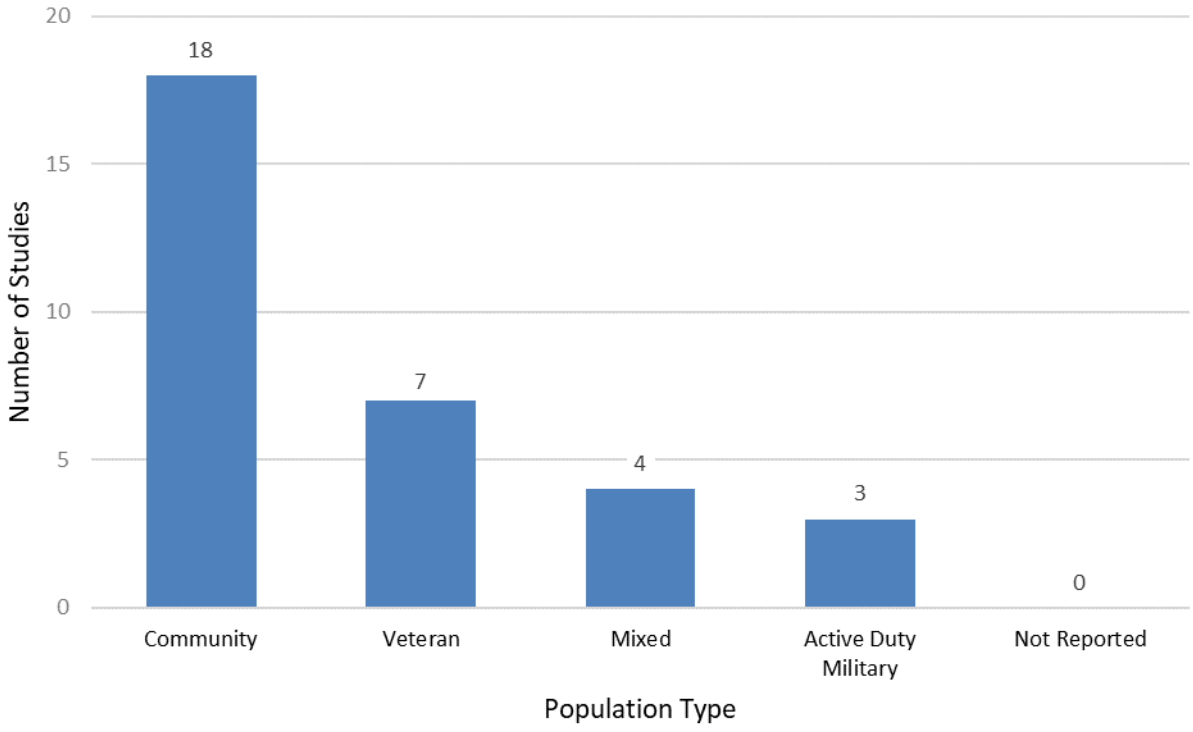
Figure 20. Summary of newly included studies: distribution of studies by sample size



3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Participants were drawn from the community population in 56 percent of studies, veterans in 22 percent of studies, and Active Duty Military in 9 percent of studies; 4 studies (13%) were in a mixed population (Figure 21).

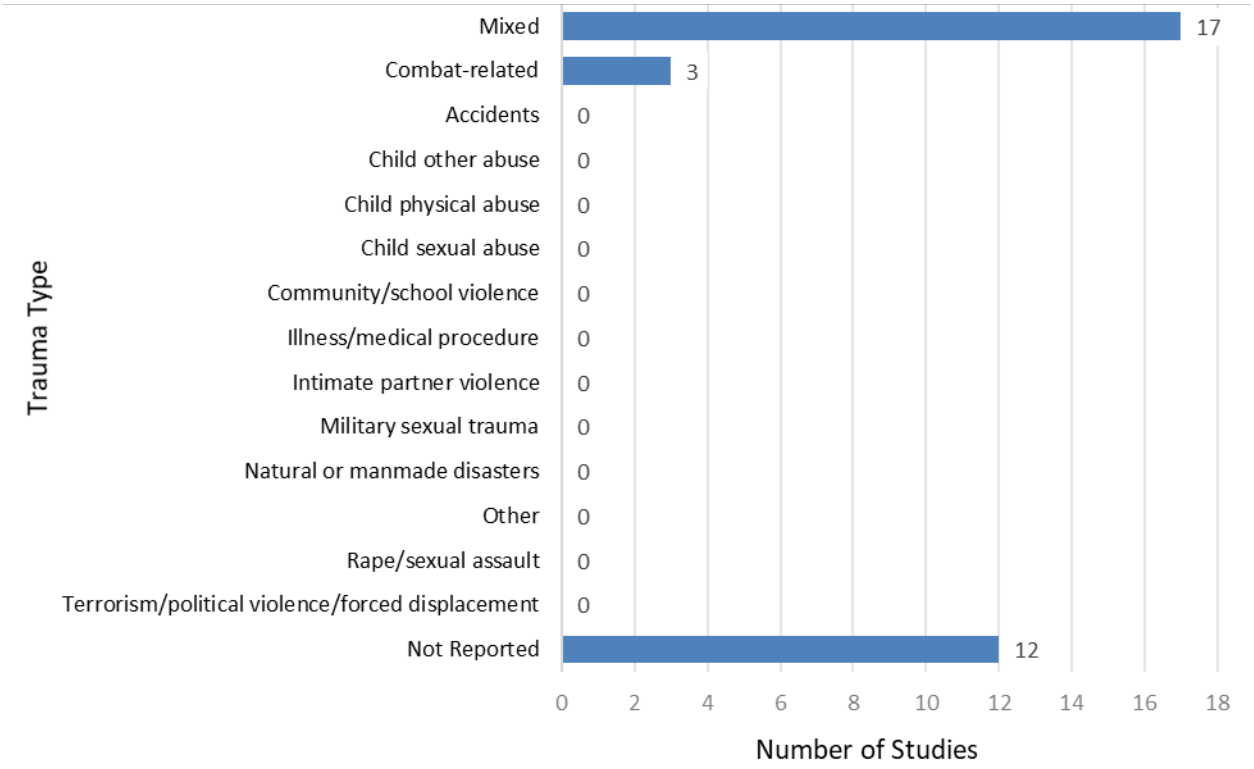
Figure 21. Summary of newly included studies: distribution of studies by population type



3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Three studies limited inclusion to participants who had experienced specific trauma types, and 12 studies (38%) did not provide information on trauma types (Figure 22). The largest number of studies allowed a mix of trauma types (17 studies, 53%).

Figure 22. 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).

Additional study and sample characteristics for studies added in this update are summarized in Table 6. Most studies were conducted in younger populations: the sample mean age was 30 to <45 years for 69 percent of studies, and no studies had a sample mean age 60 years or higher. Most studies enrolled both female and male participants, at varying proportions. No studies included only female participants, and 9 percent of studies included only male participants. Three studies (9%) reported data for gender identity, and none reported data for sexual orientation of the sample. Over half of studies reported data on race that could be grouped into U.S. Census categories (57%), and 41 percent provided both race and ethnicity data. Data were not provided for race or ethnicity corresponding to U.S. Census categories in 44 percent of the studies.

Just over half of the studies (53%) were conducted in the U.S. Other countries in which at least two studies were conducted are Australia, Germany and Iran. The majority of studies were conducted in the outpatient setting (69%).

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

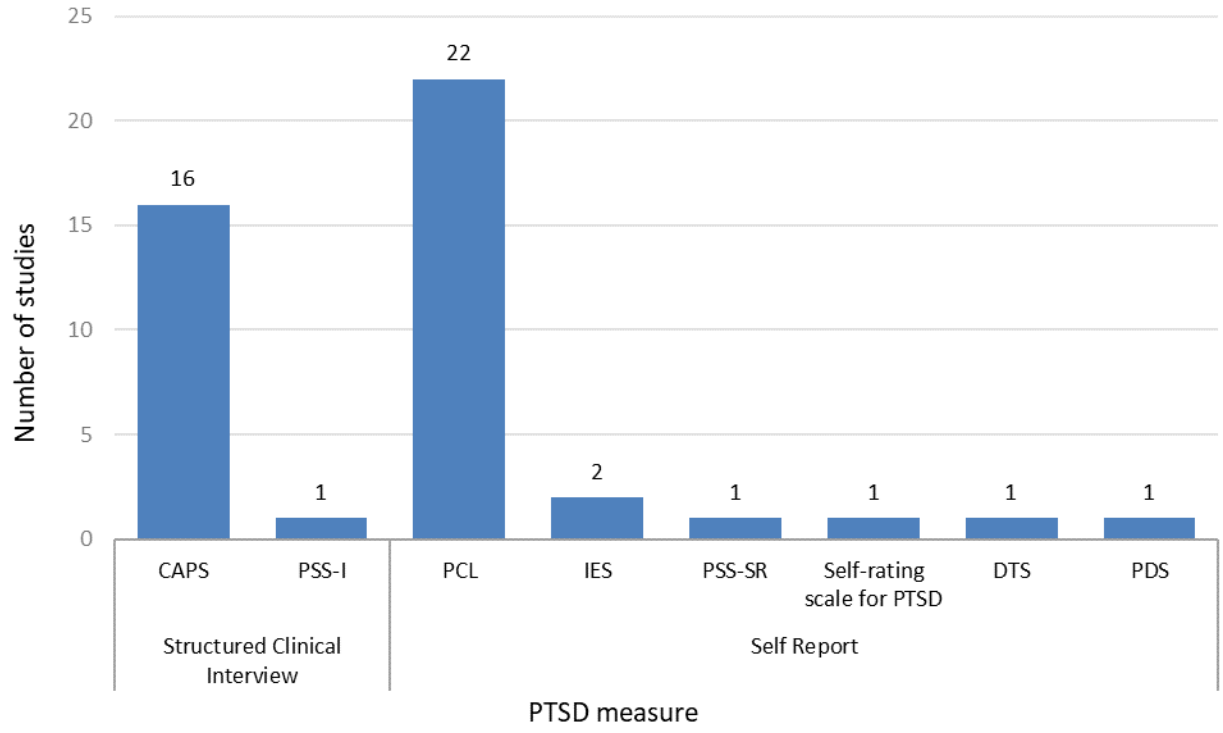
Table 6. Summary of sample and study characteristics for newly included studies

Characteristics	Categories	N studies	% of total studies
Age, sample mean	<30 years	3	9%
	30 to <45 years	22	69%
	45 to <60 years	7	22%
	≥60 years	0	0%
	Not reported	0	0%
Sex, % Female	100%	0	0%
	75% to <100%	11	34%
	50% to <75%	10	31%
	25% to <50%	2	6%
	>0% to <25%	5	16%
	0%	3	9%
	Sex not reported	1	3%
Gender and sexual orientation	Gender data reported	3	9%
	Sexual orientation data reported	0	0%
	Neither reported	29	91%
Race and ethnicity	Both race and ethnicity data reported	13	41%
	Only race data reported	5	16%
	Only ethnicity data reported	0	0%
	Neither reported	14	44%
Country	United States	17	53%
	Australia	3	9%
	Germany	3	9%
	Iran	2	6%
	Other	7	22%
Setting	Outpatient clinic	22	69%
	Primary care clinic	1	3%
	Other	9	28%

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Most studies (84%) used a self-report measure to assess continuous PTSD outcomes; the PCL was used in 69 percent of studies (Figure 23). An interview measure was used in just over half of studies (53%, 17 studies); 16 studies (50%) used the CAPS, and the PTSD Symptom Scale-Interview (PSS-I) was used in one study.

Figure 23. Summary of newly included studies: PTSD measures used to assess continuous PTSD outcomes[a]



[a]Studies may have used more than one measure to assess PTSD outcomes.
Abbreviations: CAPS = Clinician-Administered PTSD Scale; DTS = Davidson Trauma Scale; IES = Impact of Event 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.

3.2.2 Results, Characteristics of Included Studies, Studies Added in This Update

Just over half of studies (53%) reported either at least one dichotomous PTSD outcome. PTSD diagnostic change and clinically meaningful response were reported in 11 studies each (34%), and both outcomes were reported in 5 studies (16%) (Table 7). Among other (non-PTSD) outcomes, depression was the most commonly assessed (66% of studies), followed by anxiety (38%), sleep (19%) and quality of life (13%).

Table 7. Summary of PTSD and other outcomes for newly included studies

Outcome	N studies	% of studies
PTSD clinically meaningful response	11	34%
PTSD diagnostic change	11	34%
Anger	1	3%
Anxiety	12	38%
Depression	21	66%
Function	2	6%
Quality of Life	4	13%
Sleep	6	19%
Substance Use	2	6%
Suicide	2	6%

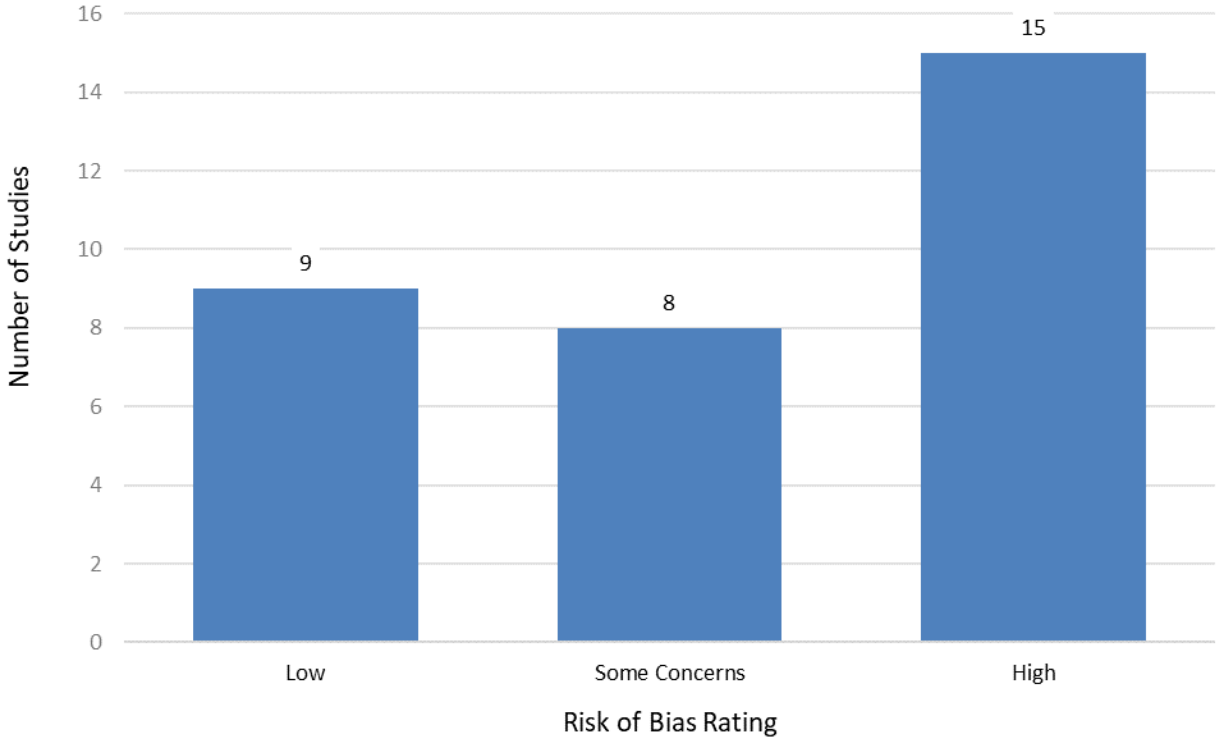
Abbreviations: PTSD = posttraumatic stress disorder.

3.3 Risk of Bias Assessment

Risk of bias (RoB) was assessed using Cochrane's RoB 2 tool, as described in the Methods section. Detailed RoB ratings are presented in Appendix G.

In this update, 32 newly included studies were assessed using Cochrane's RoB 2 tool for trials (Table 8). The overall risk of bias was assessed as high for 47 percent of studies, some concerns for 25 percent of studies, and low for 28 percent (Figure 24). Studies were rated as high risk of bias mainly due to missing outcome data or measurement of the outcome.

Figure 24. Risk of bias rating for newly included studies (RoB 2 methods)



3.3 Results, Risk of Bias Assessment

Table 8. Newly included studies: risk of bias ratings using Cochrane RoB 2 methods (k=32)

Author, Year	Bias Due to Randomization	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Outcome Data	Risk of Bias in Measurement of the Outcome	Bias in Selection of Reported Result	Overall RoB Assessment
Allen, 2022[36]	Low	High	High	High	Low	High
Back, 2023[37]	Low	Low	Some Concerns	Low	Low	Some Concerns
Darvish, 2019[27]	Low	High	Low	High	Low	High
de Kleine, 2019[29]	Low	Low	Low	Low	Low	Low
Duek, 2023[39]	Low	Low	Low	Low	Low	Low
Dunn, 2007[22]	Low	High	High	Some Concerns	Low	High
Ehlers, 2023[45]	Low	Low	Low	High	Low	High
Feder, 2023[46]	Low	Low	Low	Low	Low	Low
Fonzo, 2019[28]	Low	Low	High	Low	Low	High
Golier, 2023[40]	Low	Low	Low	Low	Low	Low
Haller, 2023[41]	Low	Low	Low	Some Concerns	Low	Some Concerns
Himmerich, 2016[26]	Some Concerns	High	High	High	Low	High
Kanaan, 2023[47]	Low	Low	Low	Low	Low	Low
Kearney, 2023[53]	Some Concerns	High	Low	Low	Low	High
Kuhn, 2017[23]	Low	Low	Low	High	Low	High
Larsen, 2019b[31]	Some Concerns	Low	Some Concerns	Some Concerns	Low	Some Concerns
Lazarov, 2019[30]	Low	Low	Low	Low	Low	Low
Litz, 2007[25]	Some Concerns	Low	Some Concerns	Low	Low	Some Concerns
Miller-Graff, 2021[35]	Low	High	Some Concerns	High	Low	High
Miner, 2016[24]	Some Concerns	Low	Low	High	Low	High
Niles, 2020[34]	Low	Low	Some Concerns	Low	Low	Some Concerns
Peck, 2023[38]	Some Concerns	Low	Low	High	Low	High
Prguda, 2023[49]	Some Concerns	Low	Low	Some Concerns	Low	Some Concerns
Rajabi, 2023[48]	Low	Low	Low	Low	Low	Low
Segal, 2020[32]	Low	Low	Low	Low	Low	Low
Taylor, 2023[42]	Some Concerns	Low	High	Some Concerns	Low	High
Voorendonk, 2023[52]	Low	Low	Low	Some Concerns	Low	Some Concerns
Wakusawa, 2023[51]	Some Concerns	Low	Low	High	Low	High
Walter, 2023[50]	Low	Low	Low	Some Concerns	Low	Some Concerns
Watkins, 2023[43]	Low	Low	Low	High	Low	High
Woud, 2021[33]	Low	Low	Low	Low	Low	Low
Zhao, 2023[44]	Some Concerns	High	Low	Some Concerns	Low	High

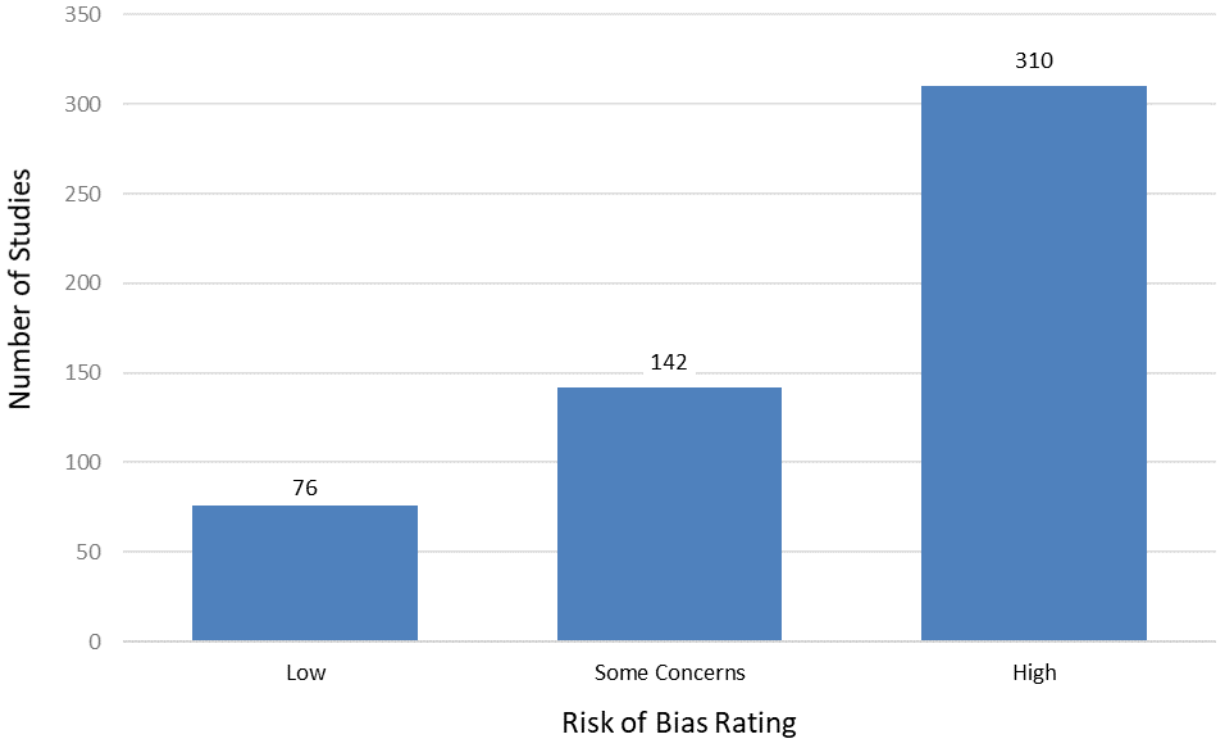
Abbreviations: AHRQ = Agency for Healthcare Research and Quality; ROB = risk of bias

Note: cells are shaded corresponding to the value: “High” shaded in red, “Some Concerns” in yellow, and “Low” in green.

3.3 Results, Risk of Bias Assessment

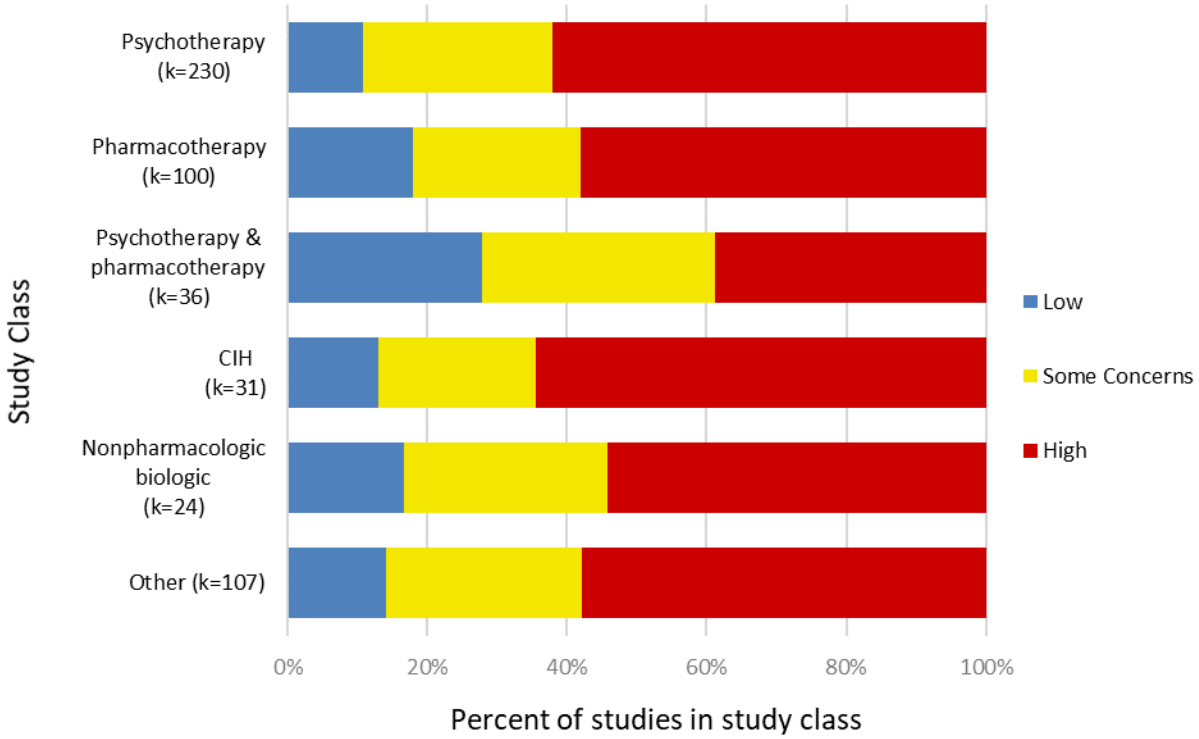
Across all 528 included studies, RoB was rated as high for 59 percent, some concerns for 27 percent, and low for 14 percent (Figure 26). Figure 27 shows the risk of bias ratings as a percentage of the total studies within each study class. In all study classes, the majority of studies were rated as high risk of bias. Complementary and integrative health had the highest proportion of studies rated as high risk of bias (65%). Slightly lower proportions of studies were rated as high risk of bias in psychotherapy (62%), pharmacotherapy (58%), and other (58%) study classes. Most study classes had between 20 and 30 percent of studies rated as some concerns (range 23% to 33%). About a quarter of studies (28%) in the psychotherapy and pharmacotherapy study class were rated as low risk of bias, followed by pharmacotherapy (18%) and nonpharmacologic biologic (17%). For studies in all other study classes, 11 to 14 percent were rated as low risk of bias.

Figure 26. Risk of bias rating for all included studies assessed using Cochrane RoB 2 methods



3.3 Results, Risk of Bias Assessment

Figure 27. Risk of bias ratings for all included studies using Cochrane RoB 2 methods by study class



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

4. Discussion

4.1 Summary and Implications

This report is updated to include detailed data extraction and risk of bias (RoB) assessments for 32 newly included 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 528 RCTs are now included with detailed data abstraction, calculated standardized effect sizes for continuous PTSD outcomes, and RoB assessment using Cochrane's RoB 2 tool for trials.[55]

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?"[56] Additionally, data from the PTSD-Repository evidence tables were recently incorporated into the Metapsy project,[57] a meta-analysis web resource focused on mental health trial data (https://www.metapsy.org/database/ptsd).

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 and meta-analyses 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[58] and depression[59,60] 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 were added in this update for newly included studies and studies included prior to the 2022 update.[16] These data are now provided for all 528 included trials, facilitating 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). In earlier phases of this project, 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 RoB 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. In the current update, the TEP guidance emphasized the importance of including interventions that do not require a provider interaction, such as computer-based nonpharmacologic cognitive interventions, online support tools or apps, etc. These recommendations informed expansion of the inclusion criteria during this update.

This update added RCTs published through September 11, 2023. Combined with the first four reports, this overarching project includes evidence from over a 35-year span, with the earliest studies dating back to 1988.[13,15-17]

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 32 newly included studies of treatments for PTSD or comorbid PTSD and SUDs as well as RoB assessment using Cochrane's RoB 2[55] tool for trials and calculated standardized effect size estimates for continuous PTSD outcomes for all 528 included studies.

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. To standardize our approach for data entry, suicide attempts and completion were always abstracted as harms; where appropriate data was provided, additional information on other suicide-related data and self-harm was abstracted as outcomes. 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: 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 might be reflected in the ratings. However, we implemented detailed guidance for raters, including definitions related to how RoB was assessed and thresholds (e.g., for attrition), to reduce interrater variability and provide transparency in methodology. We also implemented an automated data validation process to check that RoB ratings were congruent with the Cochrane RoB 2.0 algorithm as an additional check for errors or inconsistencies, and two reviewers checked any discrepancies identified during this process.

4.2 Next Steps

The completion of this project signifies the end of the fifth phase of work and expansion of the PTSD-Repository evidence tables. In this phase, we added newly included RCTs, with detailed data abstraction into evidence tables, RoB assessment, and provide calculated standard effect sizes for all 528 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.[17,56,61,62]

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 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
CAPS	Clinician-Administered PTSD Scale
CBT	cognitive behavioral therapy
CIH	complementary and integrative health
CPT	Cognitive Processing Therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPC	evidence-based practice center
IES	Impact of Event Scale
IQR	Interquartile range
k	number of studies
KQ	Key Question
N	No, data element was not reported for the study
NA	not applicable
NCPTSD	National Center for Posttraumatic Stress Disorder
NR	not reported
PCL	PTSD Checklist
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
SEADS	Supplemental Evidence And Data for Systematic Review
SI-PTSD	Structured Interview for PTSD
SUD	substance use disorder
TAU	treatment as usual
TEP	Technical Expert Panel
TOP-8	Treatment-Outcome Posttraumatic Stress Disorder Scale
U.K.	United Kingdom
U.S.	United States
Y	Yes, outcome was reported for study