Systematic Review Disposition of Comments Report

Research Review Title: *Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: 2022 Update of the PTSD-Repository Evidence Base*

Draft report available for public comment from February 2, 2022, to March 1, 2022.

Citation: O'Neil ME, Cheney TP, Yu Y, Hart EL, Holmes RS, Blazina I, Veazie SP, Griffin JC, Fu R, Carlson KF, Chou R. Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: 2022 Update of the PTSD-Repository Evidence Base. Systematic Review. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) AHRQ Publication No. 22(23)-EHC040. Rockville, MD: Agency for Healthcare Research and Quality; October 2022.
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Comments to Draft Report

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Comments on draft reports and the authors' responses to the comments are posted for public viewing on the website approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Peer Reviewer, Technical Expert, and Public Comments and Author Response

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1 (TEP)	Introduction	Adequate	No response needed.
Peer Reviewer #1 (TEP)	Methods	The section that describes the estimation of effect size doesn't explicitly state that a meta-analysis was not done. I can see readers thinking that a meta-analysis was done when you present Cohen and Hedges estimation. I would add make this explicit in the methods section. I also think table 7 may give the impression of a meta-analysis (the text preceding table 7 is vague about this issue).	The Standardized Effect Size Calculation section states: While data synthesis (e.g., quantitative synthesis in the form of a meta-analysis) was not included in the scope of this update, Appendix G provides a detailed example of how to find and compare effect size data across the studies using the Excel evidence tables in Appendix F.
Peer Reviewer #1 (TEP)	Methods	In the statistical section, there is a statement about followup scores being preferred over change scores. I would add the rationale for this preference.	Followup scores were preferred because they have been shown to be more conservative when combining RCTs compared to placebo, when baseline scores show some evidence of imbalance. When baseline scores are balanced, followup score and change score provide similar results. We included a reference to Fu, 2016.
Peer Reviewer #1 (TEP)	Results	In figure 15 and elsewhere in the test, consider changing "functioning" to "function".	We updated this.
Peer Reviewer #1 (TEP)	Discussion and Conclusions	Adequate	No response needed.
Peer Reviewer #1 (TEP)	General	I wouldn't use colloquial language "in-between" to describe the risk of bias. Please use standard language used by Cochrane to describe the medium risk of bias category. This is needed in 3 places, including the abstract.	We updated this.
Peer Reviewer #2 (TEP)	Introduction	The introduction is well done.	No response needed.
Peer Reviewer #2 (TEP)	Methods	Methods are appropriate. Perhaps the authors could note in the abstract that the strength of the evidence was not assessed for this review.	Due to space constraints, we do not discuss Strength of Evidence in the abstract. We state that Strength of Evidence was not assessed for this review in the Methods section of the text.
Peer Reviewer #2 (TEP)	Results	The results are appropriate and clear. The figures are very clear.	No response needed.
Peer Reviewer #2 (TEP)	Discussion and Conclusions	The summary and conclusions could be made more clinically useful with the strength of the evidence for every intervention, but that may be beyond the scope of this review.	This report did not synthesize results, and therefore cannot assess strength of evidence across studies for any interventions.

Source: https://effectivehealthcare.ahrq.gov/products/ptsd-pharm-non-pharm-treatment/research
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Peer Reviewer #2 (TEP)	General	The report is very well done, comprehensive yet concise, and clearly written. It is a very valuable resource for clinicians, researchers, and students. The authors should be commended for updating to the new Cochrane Risk of Bias 2 tool for randomized trials. The authors are especially commended for adding standardized effect sizes not only for the 38 new studies added, but also the total 427 studies in the database. This is a tremendously valuable resource for the community for which we are all grateful.	No response needed.
Peer Reviewer #2 (TEP)	General	Of the 38 new studies added, if only two are SUD, perhaps that doesn't need to be emphasized as including PTSD and SUD, or perhaps the authors could mention at that point that added two SUD studies.	Including PTSD-SUD studies was a scoping decision from the second report, published in 2020. We have updated the text to note that the decision to include PTSD-SUD studies was on the recommendation of the TEP and NCPTSD.
Peer Reviewer #2 (TEP)	General	The authors comment that "reporting was incomplete for many data elements…such as duration of PTSD diagnosis or symptoms (64 percent), number of trauma types (93 percent), or number of traumatic events (83 percent)." (p. ES-1). It is obvious from the high percentages of missing data that these are not commonly gathered in clinical trials. Perhaps the authors want to suggest new standards for the field? The data repository and this update are tremendously valuable resources.	While suggesting new standards is outside the scope of this report, the Summary and Implications section describes how the report may highlight research reporting gaps in the field.
Peer Reviewer #3 (TEP)	Introduction	P. 12, line 27 - How were the "subset of the previously included studies" chosen for assessment with Cochrane RoB 2? Will subsets of previously included studies be updated in regard to RoB until they are all completed, or will the focus be on newly included studies only moving forward?	The first subset of the previously included studies were selected in alphabetical order. Additional studies from the prior reports will be assessed for ROB2 in future annual updates.
Peer Reviewer #3 (TEP)	Methods	P. 16, line 16 – "Disagreements were resolved by consensus of the team of investigators" at all stages, from title/abstract through full text review? The authors mention in the discussion that RoB was assessed by one person and then checked, rather than by independent review and consensus – this information is not provided in the methods (p. 17). Will this continue to be the case moving forward? If so, the authors should provide a rationale for doing so, given the noted limitations of this approach.	This has been updated to reflect that one reviewer did initial assessment and another reviewer checked for accuracy.

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Peer Reviewer #3 (TEP)	Results	Can the authors clarify how "overall PTSD outcome" is represented in Table 5, given that this lists measures and then focuses on diagnostic change? This would help to align with all elements of the PICOTS outcomes of "overall PTSD outcome, PTSD diagnostic change, PTSD clinically meaningful change"	While studies must report an "overall" PTSD outcome for inclusion, these outcomes can be continuous (e.g., symptom severity scores), dichotomous (e.g., diagnostic change, etc.), or both. They are presented separately in Table 5, but all represent "overall" PTSD outcomes (i.e., overall symptoms or diagnosis, not individual components like individual symptom scores).
Peer Reviewer #3 (TEP)	Discussion and Conclusions	P. 52 – the authors describe several gaps and inconsistencies in reporting across studies. It might be helpful if they also provided clear recommendations for reporting standards as a guide for researchers	While suggesting new standards is outside the scope of this report, the Summary and Implications section describes how the report may highlight research reporting gaps in the field.
Peer Reviewer #3 (TEP)	General	The report is clear and provides specific information to distinguish this update from previous versions (i.e., inclusion of 38 new studies, use of Cochrane RoB 2). The key question is clearly stated and results are presented in line with this question and guiding framework. The audience is identified as "current clinical, research, and policy stakeholders."	No response needed.
Peer Reviewer #4 (TEP)	Introduction	The introduction is an appropriate length and clearly lays out the history of this report and the importance to the field. My only specific comment is about the outcome "clinically meaningful change" in the analytic framework 'final health outcomes' box. Is that really a separate outcome? It seems like it could be relevant to any of the outcomes listed in that box.	We have updated the analytic framework to reflect the outcome of interest is PTSD diagnostic change/clinically meaningful change.
Peer Reviewer #4 (TEP)	Methods	As with any update to a review, there are many legacy issues and decisions that were made that predate the current update. With that in mind, I think the criteria are justifiable and do not appear to have changed since the last update. Here are a few things I had questions about: 1. I am not a mental health clinician, so I would defer to others as to whether a patient-reported assessment tool is sufficient for diagnosis. I assume that while the tool may be patient-reported, a clinician verifies/validates the diagnosis through a clinical interview/assessment.	We established criteria for inclusion with the TEP and NCPTSD during earlier reports. The decision to include studies that include participants with PTSD based on patient-reported tools was made to ensure that important research wasn't left out. We did, however, abstract and classify the assessment procedures used in studies, and these data elements are available in the evidence tables. Users of the data can filter these studies if needed.

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Peer Reviewer #4 (TEP)	Methods	2. Related to outcomes; the analytic framework lists many different outcomes, but the PICOTS tables only list PTSD outcomes. I interpret that to mean that only studies reporting a PTSD outcome were eligible to be included. Did you have any criteria around what measures were eligible to be abstracted for all of the other non-PTSD outcomes in the analytic framework? For example, did you require that only validated/reliable measures were eligible to be abstracted?	The PICOTS table only lists requirements, not other data abstracted; therefore, only "overall PTSD outcome" is listed under Outcomes in this table since this is the only outcome required to be present for inclusion in the update.
Peer Reviewer #4 (TEP)	Methods	3. I was particularly curious about what functioning outcomes were included. In the appendix I see ODI, is that Oswestry Disability Index? That seems like a curious measure to use in PTSD studies since it's designed to measure disability from chronic low back pain, but I guess I can see it being extrapolated to populations with chronic pain/disability resulting from accidents/combat trauma. Also, this is likely a legacy decision, but SF-36 is usually described as a QOL measure, but it is categorized as a functioning measure.	We have updated the report to categorize SF-36 as a QOL measure. We have included measures of function as reported in the studies, and the ODI was classified as a measure of function due to its focus even though it is more commonly used for pain rather than PTSD.
Peer Reviewer #4 (TEP)	Methods	The search strategy is very thorough and complete.	No response needed.
Peer Reviewer #4 (TEP)	Methods	In the data abstraction section of the methods, there is some language discussing restructuring of the Excel form used for abstraction and why that helped to automate the process. I don't really think any of that detail is necessary; that is all internal sausage-making and while I'm sure the EPC and VA team is super happy about the efficiencies gained, it's not critical to readers of this report to know about it. Similar text is in the discussion section (page 43, lines 33-41) and also seems unnecessary.	This report documents changes from prior reports, and while technical, it is important for transparency to explain why data tables have changed.
Peer Reviewer #4 (TEP)	Methods	In the assessment of ROB section, the methods mention that you updated ROB assessments for a subset of RCTs previously included. I was eagerly anticipating seeing the results from this exercise, but they don't appear to be included in this report. For that reason, perhaps you should consider dropping any mention that you updated a subset and just stick with the message that ROB assessments for previously included studies would be updated in a future version of the report. Also, you may want to add text mentioning that you evaluated ROB with respect to "assignment to an intervention" and not the alternative scenario in ROB 2 (adherence to an intervention).	Results from the first subset of RoB 2 assessments are included in Appendix Table H-3, and plan to complete the transition to the Cochrane RoB 2 system for the remaining studies in future updates.

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Peer Reviewer #4 (TEP)	Results	Overall the results section is clear and easy to follow. The tables and graphs are simple and easy to interpret. I am not super familiar with this content area so I would defer to the other peer reviewers as to whether any studies were missed. A few specific suggestions for this section follow to improve clarity: 1. Figure 3- it's always challenging to do the literature flow diagrams for updates and clearly portray the old and the new. Perhaps the box with n=21,877 could be labeled "Records identified through previous database searches" to distinguish it from the box with the update search. Since no gray literature search was done, I'm assuming the N=444 box are studies identified through reference checks from systematic reviews? The number of duplicates is quite large and suggests an overly sensitive search. If efficiency or resources are an issue in the next update, perhaps consider fewer data sources. To be honest the number of data sources used seems unnecessary since you are only interested in RCTs. For example, is the SCOPUS and EMBASE and CINAHL searches yielding anything unique not picked up by the other databases?	Search methods for this report are designed to be exhaustive, and therefore include capturing a large number of duplicates. These duplicates are removed prior to the research team reviewing references. We have added a footnote to explain "other sources."
Peer Reviewer #4 (TEP)	Results	2. Table 2- I'm wondering whether an alternative term for "non-pharmacologic biologic" is more suitable here. FDA considers 'biologics' a subset class of drugs (e.g., infliximab) so that could be confusing for some readers. And I think most people would call the examples in that category "medical devices or procedures" and not biologic interventions. So perhaps call this category "device or procedure". One other suggestion would be to put the "control" category last in the table so that all of the active interventions are described first.	For consistency across project phases and with the PTSD-Repository, and based on recommendations by the TEP and NCPTSD, we are using this terminology adapted from the VA/DoD CPG as described in the table note. We moved control to the end of table.
Peer Reviewer #4 (TEP)	Results	3. Figure 7-consider footnoting the Year 2021 since the data for it are only for part of the year.	We added a footnote for dates included in the figure.
Peer Reviewer #4 (TEP)	Results	4. Figure 11-the figure note refers to a category "child other abuse" but I do not see this category represented on the graph.	We updated the figure note.

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Peer Reviewer #4 (TEP)	Results	5. Table 4 is of course formatted to be 508-compliant, but it is difficult to quickly skim. First, the title should probably indicate that the unit of description (i.e. row) here is treatment arms, not studies. There is a lot of redundant information since each study is captured by more than one row. Heavier lines in the table to demarcate between studies might also help. Given that the ultimate destination for all of this information is the online repository with more advanced data visualization capabilities than is possible on 2D paper, I don't think it's critical to reformat this table.	We updated the Table 4 title.
Peer Reviewer #4 (TEP)	Results	6. Table 5-although pretty obvious, you may want to indicate "Y" =yes and "N" =no in the table notes. The shading is helpful because it allows a quick assessment of what outcomes are present. Although I was looking for a legend to see what the shading meant until I figured out that all of the Ys were shaded. Maybe a note to that effect will help other readers.	We added "Y" and "N" to the abbreviations list. 508 compliance dictates that shading can add emphasis, but not meaning.
Peer Reviewer #4 (TEP)	Results	7. ROB assessment-as noted above, I was expecting to also see results of ROB 2 assessments from the subset of the older studies as was mentioned in the methods. I was also a little surprised to see so few of the new studies rated as 'some concerns' . Usually 'some concerns' ends up being the most common category, and fewer studies end up rated as high or low. I reviewed the ROB 2 tables in the appendix in detail. Given the number of studies that used wait list or attention control groups in this evidence base (and so are not blinded to the patient or interventionist), I was surprised that no studies ended up as 'some concerns' for the deviations from intended intervention domain. But this is actually the domain that the developers of ROB 2 thought would lead to a potential difference between ROB 1 and 2 for unblinded trials so I'm not that concerned about it, but it will be critical to ensure that as you go back to the older studies that you implement a consistent approach to this domain.	We completed 82 RoB 2 assessments of studies from the prior reports. We will continue to update the prior studies in future annual updates.

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Peer Reviewer #4 (TEP)	Results	I am not surprised to see that problems with missing data or measurement of the outcome were the most common reasons studies got rated as high ROB. It will be interesting to see what happens to the ROB ratings from the older studies. The statement in the discussion (page 42, line 18) "Newer studies are more likely to report and use more advanced and robust study designs and statistical methods." doesn't seem to jive with the fact that so many new studies were rated as high ROB.	We completed 82 RoB 2 assessments of studies from the prior reports. We will continue to update the prior studies in future annual updates.
Peer Reviewer #4 (TEP)	Discussion and Conclusions	The authors do a nice job of summarizing the findings and putting them into the present context of this ongoing project that has both a history and a future. The limitations are described adequately. 1. Pg 42, line 15: are there any other trends that the authors noticed among the new studies. For, example the proportion of studies reporting PCL seems a lot higher than among the older studies, and the opposite for the CAPS measure. Does this reflect a move towards more patient-reported outcomes?	While some trends for the newly included studies were able to be identified in the summary section, that is not the focus of this report. However, the online interactive PTSD-Repository is designed to allow users to explore the data and identify possible trends.
Peer Reviewer #4 (TEP)	Discussion and Conclusions	2. Next Steps Section. Expansions and changes in scope, data elements, and ROB methodology have to be considered really carefully. The future additions articulated in the "next steps" section are very ambitious considering the number of studies already in the database that might have to be revisited for relevant data, and the number of non-randomized studies that are potentially out there. Shoring up an old evidence base for changes in scope or methods is often more work than de novo synthesis. I would hope that careful consideration of the added value from these additions is done, and that should the additions move forward that the effort is adequately resourced.	Any changes to scope or inclusion will be made after extensive discussions with TEPs and NCPTSD.
Peer Reviewer #4 (TEP)	Discussion and Conclusions	3. In several places in the report (page 2, line 23; page 42, line 13) the Cochrane ROB 2 tool is described as being validated and I don't think that's a correct characterization. The tool was developed and piloted and revised based on feedback. The term validation implies a level of quantitative comparison against some reference standard and that's not the case here. I'm not aware of any studies reporting 'validation' of the tool, and the only reference I see cited is the Sterne 2019 BMJ article which is a descriptive paper describing its development and contents.	"Validated" has been changed to "pilot tested" throughout the document.

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Peer Reviewer #4 (TEP)	General	This AHRQ EPC report was commissioned for a very specific purpose, to support updates to an existing database repository of PTSD trials. As such, it's not a traditional/typical report; however, it clearly lays out the objectives of the report, provides detailed and transparent reporting of the methods used, and provides the right amount of data summary in the results section, including tables and figures. Overall, the report was easy to read and follow. There were several challenges in this update that the authors identified that are common in research involving mental health conditions and behavioral interventions but aren't usually discussed at length by review authors and I appreciated the transparency and detail with which the authors discussed them. Specifically I am referring to the issues relating to how they approached calculating standardized effect sizes and the lack of standards for reporting continuous data in primary trials and the issue of whether to treat lack of efficacy as a 'harm' and categorizing outcomes like suicidal ideation and attempts as efficacy or harm outcomes.	No response needed.
Peer Reviewer #4 (TEP)	General	Lastly, I am *dying* to know the outcome of the updated ROB 2.0 assessments, and I would encourage the team to consider writing a separate methods paper describing what they found. This is of real importance and value to the evidence synthesis community who need to decide how to use limited resources and make decisions about whether to update previous ROB ratings based on changes in ROB tools and guidance.	The process of updating the RoB assessment to Cochrane's RoB 2 tool for trials is still in progress, and therefore summary statistics across all included studies are not possible due to the different assessment methods. The RoB 2 assessments for the first subset of 82 papers is available in Appendix Table H-3.
Peer Reviewer #5	Methods	Criteria for article search and evaluation are appropriate.	No response needed.
Peer Reviewer #5	Results	The level of detail is probably useful for the goal of the manuscript. The included studies appear appropriate.	No response needed.
Peer Reviewer #5	Discussion and Conclusions	No major findings. Limitations described.	No response needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	The report is a description of PTSD studies added to the National Center for PTSD data repository and has no clinically relevant results in itself. Of note, the PTSD field commonly conflates "military" PTSD with PTSD due to combat exposure. PTSD from traumatic events during military service can be from accidents, military sexual trauma, etc. and does not equate to combat exposure (page 17). The authors are understandably at the mercy of how articles are described, but it would be useful to recognize this caveat.	No response needed.
Peer Reviewer #5	General	What is the definition of "subthreshold PTSD" (page 17, line 10)? If a person does not meet the diagnostic threshold for PTSD, it is not PTSD.	Noted. We edited the PICOTS table to indicate that subthreshold was as defined in each of the studies, when relevant, since definitions used in studies differed.
Peer Reviewer #6 (TEP)	Introduction	I do not have any comments about the Introduction. I do think the title should be changed to reflect that it applies to adults only.	No response needed.
Peer Reviewer #6 (TEP)	Methods	The inclusion and exclusion criteria are appropriate and justifiable. The search strategies are stated explicitly and logical. Definitions and diagnostic criteria are appropriate for the outcome measures. I am not a statistician, but what is presented seems appropriate to me.	No response needed.
Peer Reviewer #6 (TEP)	Results	The amount of detail was appropriate. I did find myself wanting to know the findings from the new trials and how they mesh with an approach to treatment. I know of no omissions in the search. The tables, figures, and appendices were easily understandable. I do recommend positioning the abbreviations/acronyms key at the beginning of the document to make it easier to access. I found myself consulting it frequently.	The acronym table is placed at the end in accordance with AHRQ publications guidelines.
Peer Reviewer #6 (TEP)	Discussion and Conclusions	I found the Discussion and Conclusion very helpful in putting the findings into perspective about how to use the information and what needs to come next.	No response needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6 (TEP)	General	Overall, I think this is a marvelous update to valuable document. I can't state that the report is directly clinically meaningful as it does not attempt to provide clinical guidance on which therapies are better or which is appropriate for a given patient. It does provide an excellent beginning for those who wish to answer a specific question or draft some form of clinical guidance. This use, the target population, and audience are explicitly defined in the Discussion. The key questions are appropriate and explicitly stated.	No response needed.
Peer Reviewer #7: Number not used			
Peer Reviewer #8	Introduction	The introduction is concise and clearly articulated. The Key Questions are well identified and well thought out. The report uses standard PICOTS framework-and spells it out well. the need for an update and the inclusion of risk of bias is well defended. The only issue is the relevance for some of the identified stakeholders. It would have been nice if there is any information/data on whether previous versions have been helpful and to which audience. Is this being tracked? Even information on how many times it has been cited or downloaded would have helped.	The report authors are not involved in tracking reports on the AHRQ website. For questions about the AHRQ program, visit: https://effectivehealthcare.ahrq.gov/contact.
Peer Reviewer #8	Methods	The methods are very well detailed-following a standard protocol. The INCLUSION/EXCLUSION criteria are also well defined and seem reasonable for this type of report. The data abstraction, effect size calculation and risk of bias seem reasonable. There were no major concerns. A minor concern: Did the authors also review Clinical Trials to see if there are other studies that are currently being conducted? Since there are only 38 new studies (from a total of 427) the question is -are there studies that are close to completion where waiting a year or 2 might have yielded more meaningful results?	We conduct an annual update in order to continuously capture newly published studies, but we do not search clinicaltrials.gov for this report.
Peer Reviewer #8	Results	The results, with 38 new studies of 427, suggest that this report is not that different from the previous version. The new studies are detailed and seem reasonable for inclusion. Similarly the categories (pharmacology/nonpharm/complementary/psychotherapy/control collaborative care) are reasonable and cover most (all?) of the categories. It is unclear why non-pharmacologic/cognitive gets is own category).	The categories have been set by the NCPTSD and are designed to reflect not only interventions that already exist, but others that may be tested in trials soon. In this case, "cognitive" doesn't refer to psychotherapy interventions with cognitive components (classified as psychotherapy); rather, it refers to cognitive rehabilitation types of interventions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	Results	The inclusion of PTSD/SUD as its own category is a strength; although it should be noted that other comorbidities are also relevant.	No response needed.
Peer Reviewer #8	Results	There are no studies that were overlooked that come to mind.	No response needed.
Peer Reviewer #8	Discussion and Conclusions	Results are well organized, with tables and figures to highlight findings. The literature flow diagram is clear; the intervention Table (Table 2) is also easy to understand: it is unclear why "Control" has its own category.	Control is listed as a separate category since all study arms, even comparator arms that are not standalone interventions, are included in the evidence tables.
Peer Reviewer #8	Discussion and Conclusions	the figures in which studies could be listed more than once are a little confusing for the reader. Figure 5 similarly has a SUD category ; is that different than PTSD/SUD. Figure 6: how were studies that used more than 1 category handled?	The text has been updated to more clearly describe the difference between PTSD/SUD and SUD categories. Classification for Figure 6 is described in the text in more detail: “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 & pharmacotherapy, and psychotherapy & CIH). Other combinations were grouped in the other mixed study class.”
Peer Reviewer #8	Discussion and Conclusions	It is not clear what a RCT with <25 subjects adds to the literature.	The PTSD-Repository is meant to capture all RCTs, regardless of sample size.
Peer Reviewer #8	General	This is a well written and comprehensive report; an update from a previously written document. The addition of the newer studies are well researched. The inclusion of the risk of bias is also a welcome addition. The use for future systemic reviews has been accomplished. It should be noted that this document is probably best for other researchers and academics. Its utility for clinicians is questionable, since most clinicians want some synthesis of the results-while this discussion focuses on methodology and availability of resources. This is even more relevant for patients/families. The format and density make it a daunting document. Nevertheless, this has accomplished the goal of coordinating the available literature.	No response needed.
Peer Reviewer #9	Methods	I appreciate that the key questions include individuals with comorbid SUD.	No response needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Methods	In the PICOTS table, I am unclear when it says “Any overall PTSD outcome,”- what about the other outcomes discussed?	The PICOTS table only lists requirements, not other data abstracted; therefore, only “overall PTSD outcome” is listed under “Outcomes” in this table since this is the only outcome required to be present for inclusion in the update.
Peer Reviewer #9	Methods	I appreciate that an extra updated literature search will be conducted concurrently with the peer review and public comment process and commend you on your thoroughness.	No response needed.
Peer Reviewer #9	Methods	Was psychodynamic included in the psychotherapy search? If so, it might be worth mentioning this or including in the examples in Table 2, and/or noting if no research was available as this specific treatment was of particular interest to a large subset of our members.	We updated Table 2 to with psychodynamic therapy as an example of psychotherapy.
Peer Reviewer #9	Results	Similar to the request for evidence profiles, can forest plots be developed to help facilitate interpretation of the data?	The PTSD-Repository provides featured visualizations, data stories, and access to data sets at: https://ptsd-va.data.socrata.com//
Peer Reviewer #9	Results	PDF page 19, I appreciate that characteristics are reported. Please consider adding more details about race/ethnicity when they are reported in a study.	While we hoped to be able to provide more detailed race/ethnicity data, because of the many different ways studies reported these categories, combining and summarizing these data was often not possible. We extracted data related to census categories and were able to report when studies provided data that fit into those categories, but could not describe race and ethnicity summary data across studies in greater detail.
Peer Reviewer #9	Results	Can a network meta-analysis be conducted on the data comparing the interventions? This could help to inform clinical practice guideline development.	The scope of this report was limited to identifying the included studies, and did not include meta-analysis. One of the purposes of this report is to provide researchers with the data to perform analyses. A detailed explanation of how to find and use effect size data is available in Appendix G.
Peer Reviewer #9	Results	Can usual care be defined/detailed whenever possible?	We report qualitative details related to study descriptions of such elements in the evidence tables in columns with the “details” label (Appendix F).
Peer Reviewer #9	Results	Page 10- some awkward wording in this sentence on this page, “… first for overall 427 studies, then separately for the 38 new studies…”	Revised for clarity.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Results	Is my understanding correct that interventions included in the Nonpharmacologic Cognitive category do not involve psychotherapy? If so, I recommend clarifying this point.	That is correct. Psychotherapy was given its own category.
Peer Reviewer #9	Results	I am confused about the use of the term "*Integrated* Cognitive Behavioral Therapy." Is the "integrated" intended to emphasize that it is the various components together? Can this point be clarified, or can terminology be switched to simply state cognitive behavioral therapy (remove the word integrated)?	For consistency across project phases and with the PTSD-Repository, and based on recommendations by the TEP and NCPTSD, we are using this terminology adapted from the VA/DoD CPG as described in the table note. We have updated this to Cognitive Behavioral Therapy.
Peer Reviewer #9	Results	Table 5- please clarify columns in table- I assume they are indicating if an outcome was measured or not but would be helpful to clearly specify this in the title of table or description.	We revised Table 5 title.
Peer Reviewer #9	Results	I appreciate the clear statements and data about which elements were not reported in studies.	No response needed.
Peer Reviewer #9	Discussion and Conclusions	Please consider including as assessment and discussion of applicability in your report. This information would be very useful for guideline developers seeking to use this data and report as part of clinical practice guideline development. For example, in the American Psychological Association's clinical practice guideline development process, Applicability is one of four main factors used when making decisions about treatment recommendations.	We did not synthesize results, and cannot provide an assessment of applicability for the body of evidence.
Peer Reviewer #9	General	I appreciate where you have noted additional information about the characteristics of the study and participants as available, such as the location of the study, trauma type, etc. I also appreciate that you specifically note when certain desired information is not available in the research studies.	No response needed.
Peer Reviewer #9	General	Would it be possible to create evidence profiles of the data for this and future updates going forward? These profiles would be very helpful to guideline developers and facilitate their use of this report and data when creating clinical practice guidelines.	The PTSD-Repository provides data stories to help users learn about the included studies and draw insights from the data about PTSD treatments. The PTSD-Repository Stories can be accessed at: https://ptsd-va.data.socrata.com/stories/s/jyb7-yupa.
Peer Reviewer #9	General	I especially appreciate the comments about the way in which race/ethnicity was reported or not and the associated challenges with grouping and categorizing when considering analyzing for subgroup effects.	No response needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	General	For the Appendices: Can a cover page be added to the first appendix file with a table of contents for the appendix so readers can easily see the title and page number of file location (for excel files) for each appendix?	We have added a table of contents to the appendix.
Peer Reviewer #10	Introduction	The reason for including the PTSD/SUD group (as opposed to PTSD with any other important comorbidities) is not described.	Including PTSD-SUD studies was a scoping decision from the second report, published in 2020. We have updated the text to note that the decision to include PTSD-SUD studies was on the recommendation of the TEP and NCPTSD.
Peer Reviewer #10	Methods	Appropriately describes the inclusion/exclusion criteria using the PICOTS format. The search strategy is well-described and clear. It may be useful to define a "grey literature search" for those not familiar with the term. The data extraction and effect size calculation processes are clear and appropriate.	No response needed.
Peer Reviewer #10	General	Basically, I thought it was great. I did suggest defining "grey literature." It's also not clear why PTSD + SUD was the focus as opposed to other major comorbidities; I thought that could be explained a bit better.	No response needed.
Public Reviewer #1: Sunny Etheridge	General	The conclusion summarized the data well and explained some of the limitations and, for lack of a better word, deficiencies, in the study. The amount of high bias seen was alarming and could cause some to question the efficacy and legitimacy of the study all together. However, the gaps were identified and honestly welcomed, per the comment "Recognition of these gaps may help future researchers to report study methods and results more comprehensively." It was evident that the team exhausted all efforts to gather and report the data in a way that was uniformed and focused. They brought to light the Grand Canyon sized gaps in information received in regards to PTSD and the call to action desperately needed to close those gaps. I believe the report started with high expectations for one result, but ended up with another. This was a very positive outcome, in my opinion.	No response needed.
Public Reviewer #1: Sunny Etheridge	General	Although I am just a Bachelor Degree Nurse, I was able to understand the information better than usually can with reports such as these. The language used at times was plain and some may not appreciate the reasoning behind this. As a layman, I applaud the team for presenting the data and information in plainer terms. It encourages more response and is less intimidating.	No response needed.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2: Ignacio Jarero	General	We believe that the study "Jarero, I., Schnaider, S., Givaudan, M. (2019). EMDR Protocol for Recent Critical Incidents and Ongoing Traumatic Stress with First Responders: A Randomized Controlled Trial. Journal of EMDR Practice and Research,13(2),100-110" fulfill your inclusion criteria and could be included on this updated document. You can find the published paper in the Supporting Documentation.	Included