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Project Harmony 2.0: Advancing patient-centered research using meta-analysis of individual patient data to identify clinically significant trajectories of PTSD/SUD and recovery outcomes

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REVIEW TITLE AND BASIC DETAILS

Review title

Project Harmony 2.0: Advancing patient-centered research using meta-analysis of individual patient data to identify clinically significant trajectories of PTSD/SUD and recovery outcomes

Condition or domain being studied

Individuals with Comorbid Posttraumatic Stress (PTSD) and and Substance Use (SUD) Disorders

Rationale for the review

Co-occurring posttraumatic stress disorder (PTSD) and substance use disorders (SUD) are common, costly, and associated with poor clinical and functional outcomes. Although numerous trials of pharmacologic, behavioral, and combined PTSD/SUD treatments exist, prior evidence syntheses have been limited by methodological constraints such as reliance on study-level summary data, inconsistent measurement across trials, inadequate handling of bias and confounding, and a narrow focus on symptom reduction rather than recovery. Existing reviews also

struggle to estimate comparative effectiveness across diverse treatment approaches and often cannot identify which interventions meaningfully improve patient outcomes.

This updated review addresses these gaps by aggregating data across a substantially expanded treatment literature, comparing multiple active interventions and controls, and examining both clinical severity and recovery-oriented outcomes that matter to patients. By applying contemporary analytic strategies to harmonized data, the review will provide more precise comparative effectiveness estimates, clarify which treatments offer the greatest likelihood of clinically meaningful improvement, and deliver actionable guidance for optimizing PTSD/SUD care in real-world settings.

Review objectives

1). Evaluate the comparative effectiveness of behavioral, pharmacologic, and combination treatments for co-occurring PTSD and SUD on both clinical severity and recovery-oriented outcomes, using an expanded dataset of newly available trials.

2). Apply advanced individual patient data meta-analytic methods, including Integrative Data Analysis (IDA) and propensity score weighting (PSW), to estimate the proportion of patients who demonstrate clinically significant improvement or deterioration across treatment classes.

3). Examine individual-level, treatment-level, and study-level moderators to identify which patients are most likely to benefit from each treatment approach, generating patient-centered guidance on optimal treatment matching for PTSD/SUD.

Keywords

Comorbidity; Ethanol; Humans; Stress Disorders; Post-traumatic stress disorder; Post-traumatic stress; Substance-Related Disorders; Alcohol-related disorders; Cannabis-Related Disorders; Clinical Trials as Topic; Cocaine related disorders; Cognitive behavioral therapy; Cognitive processing therapy; Combined Modality Therapy; Drug-Related Disorders; Dual diagnosis; Exposure Therapy; Humans, Meta-Analysis as Topic; Naltrexone; Network meta-analysis; Opioid-Related Disorders; Patient Dropouts; Pharmacotherapy; Prolonged exposure; Psychotherapy; Randomized controlled trials; Sertraline; Topiramate; Trauma and Stressor Related Disorders; Treatment Outcome; Individual participant data meta-analysis

Country

Australia; Canada; Egypt; France; Germany; Netherlands; United States of America

ELIGIBILITY CRITERIA

Population

Included

Adults (18-65 years) treated with a behavioral and/or pharmacological intervention with a diagnosis of comorbid (full or subthreshold) PSTD and SUD, targeting PTSD and /or SUD symptoms.

Intervention(s) or exposure(s)

Included

Studies must have evaluated any behavioral and/or pharmacological intervention targeting individuals living with comorbid (full or subthreshold) PTSD and SUD. Studies must have clinically determined diagnosis (or standardised level using a highly reliable diagnostic instrument or clinical determination as in a digital therapeutics study) for participant enrollment, collected psychometrically reliable baseline and post-treatment measures of PTSD and SUD and must have evidence of monitoring fidelity to treatment.

Comparator(s) or control(s)

Included
PICO tags selected: Placebo; Usual Care; Psychotherapy

Study design
Both randomized and nonrandomized study types will be included.

Context
Substance Use or Mental Health Inpatient Rehab/Intensive Outpatient/Outpatient/Community

TIMELINE OF THE REVIEW

Date of first submission to PROSPERO
17 December 2025

Review timeline
Start date: 1 June 2025. End date: 28 February 2029.

Date of registration in PROSPERO
23 December 2025

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol
A full protocol has been written and uploaded to PROSPERO. The protocol may be accessed through this link
https://www.crd.york.ac.uk/PROSPEROFILES/962bd7836d1c23a2954e0f41149ee102.pdf.

SEARCHING AND SCREENING

Search for unpublished studies
Both published and unpublished studies will be sought.

Main bibliographic databases that will be searched
The main databases to be searched are *CENTRAL - Cochrane Central Register of Controlled Trials*, *CLIB - The Cochrane Library*, *Embase - Embase via Ovid*, *Embase.com*, *MEDLINE*, *PsycInfo* and *PubMed*.

Other important or specialist databases that will be searched

PTSDpubs, Web of Science

Search language restrictions
The review will only include studies published in English.

Search date restrictions
Databases will be searched for articles published from 1 April 2019, there are no search end date restrictions.

Other methods of identifying studies
Other studies will be identified by: *contacting authors or experts*, *looking through all the articles that cite the papers included in the review ("snowballing" or forward citation searching)*, *reference list checking (backward citation searching)*, *searching conference proceedings*, *searching dissertation and thesis databases* and *searching trial or study registers*.

Link to search strategy
A full search strategy has been uploaded to PROSPERO. The PDF may be accessed through this link https://www.crd.york.ac.uk/PROSPEROFILES/f7fa4becd6ea63b9ca0bdee2873a61ca.pdf.

Selection process
Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

Other relevant information about searching and screening
DATA COLLECTION PROCESS

One coder, together with two co-authors (DH and LR), conducted the initial abstract screening in Excel using the pre-defined inclusion and exclusion criteria established in Project Harmony 1.0 (PH 1.0). This was followed by full-text screening in Covidence by the research assistant team (SR, SC, TB, KM, and MM), with two research assistants independently reviewing each full text. Senior co-authors (DH and LR) also independently evaluated all full-text articles in Covidence to determine eligibility. The larger co-author team (AML, SB, SN, TLC, IP, LS, MS, and TK) subsequently reviewed excluded full-texts to confirm that exclusion decisions were appropriate. Any remaining full-text conflicts were resolved through group discussion led by the two senior reviewers (DH and LR).

Study criteria will be extracted for all studies and entered into a pre-formatted table in Covidence. Extracted information will include: the study setting and recruitment source; sample size, participant demographics; baseline PTSD and SUD characteristics; PTSD and SUD diagnostic/assessment methods; details of the intervention (components, duration, delivery format, fidelity, attendance) and comparator conditions; study design and methodological characteristics; randomization procedures (if applicable); recruitment, retention, and completion rates; outcome measures for PTSD, alcohol use, and drug use at all reported timepoints (baseline, end-of-treatment, and follow-up); indicators of acceptability or feasibility; any reported mechanisms of action; provider characteristics (training, credentials); and information required for assessing risk of bias. Two reviewers (SR, SC, TB, KM, and MM), will extract data independently in Covidence. Discrepancies will be identified within the platform and resolved through discussion.

DATA COLLECTION PROCESS

Data extraction from published articles and reports

Data will be extracted independently by at least two people (or person/machine combination) with a process to resolve differences.

Authors will be asked to provide any required data not available in published reports.

Study datasets/IPD will be obtained from study investigators or via a data repository

Study risk of bias or quality assessment

Risk of bias will be assessed using: *Cochrane RoB-1*

Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.

Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment

Risk of bias assessment is included in the Covidence software, using the standard Cochrane Risk of Bias domains, including: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and other potential threats to validity, incomplete outcome data or absence of intention-to-treat analysis, selective outcome reporting and 'other issues'. Specifically, two review authors will independently assess the risk of bias in included studies by considering the following characteristics:

1) Was the allocation sequence adequately generated?

2) Was the allocated treatment adequately concealed from study participants and clinicians and other healthcare or research staff at the enrollment stage?

3) Were the personnel assessing outcomes and analysing data sufficiently blinded to the intervention allocation throughout the trial? 4) Were participant exclusions, attrition and incomplete outcome data adequately addressed in the published report?

5) Is there evidence of selective outcome reporting and might this have affected the study results?

6) Was the trial apparently free of any other problems that could produce a high risk of bias?

7) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.

8) Was the study free of other sources of bias, including baseline imbalance, contamination between treatment conditions, treatment fidelity concerns, or deviations from intended interventions?

Certainty assessment

We will evaluate the certainty of the evidence for each prespecified outcome using the GRADE framework. Reviewers (ET and DH) will independently assess each of the GRADE domains: study limitations (risk of bias), inconsistency, imprecision, indirectness, and potential publication bias. After considering these factors, we will rate the certainty of the evidence for each outcome on a

four-level scale: high, moderate, low, or very low.. We will also consider GRADE criteria that may increase confidence in the evidence when appropriate. These criteria include the presence of a large magnitude of effect, a dose response pattern, or situations in which all plausible confounding would reduce the observed effect rather than strengthen it. Our approach will follow the guidance provided in Sections 8.5 and 8.7 and Chapters 11 and 12 of the Cochrane Handbook for Systematic Reviews of Interventions.

OUTCOMES TO BE ANALYSED

Main outcomes

PTSD and SUD diagnosis and symptom severity, and completion of treatment (# of patients at end of study). Efficacy and effectiveness will be defined as mean change scores (pre- to post-treatment and follow-up period) on measures of PTSD and SUD severity, and/or percentage of reduction to clinically significant levels.

Measures of effect

Studies will be included with a baseline measurement of the outcome and at least one post-intervention follow-up.

Outcomes will be examined using meta-analysis of individual patient data (MIPD), integrative data analysis (IDA), and propensity score weighting (PSW). Treatment effects will be evaluated using pre- to post-treatment and follow-up changes in PTSD and SUD severity; clinically significant change metrics estimating the proportion of participants who demonstrate meaningful improvement or deterioration; and IDA-derived, bias-corrected latent scores for PTSD, SUD, and recovery-related constructs to ensure comparability across trials with different measurement instruments.

Additional outcomes

Subgroup analyses include individual versus group modality, trauma-focused versus non-trauma focused, psych intervention versus treatment as usual, or psych intervention versus active comparator

Recovery-oriented outcomes (e.g., functioning, quality of life, psychosocial recovery) will first be assessed for dimensionality using moderated nonlinear factor analysis (MNLFA) and weighted least squares estimation (WLSMV), after which MNLFA-adjusted scale scores will be used to characterize change over time once measurement bias is removed across studies and populations.

Additional Moderators – age, race/ethnicity, sex/gender, SES, education, income

Measures of effect

Subgroup studies will be included with a baseline measurement of the moderator.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

Following GRADE guidelines, we will provide tabular and descriptive analyses of all studies categorized by type (i.e., trauma focused, non-trauma focused; medications (y/n)). We will provide

a narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, type of outcome and intervention content. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous outcomes). Where sufficient data are available, we will also conduct traditional pairwise meta-analyses and explore the feasibility of a network meta-analysis (NMA) to compare multiple intervention types simultaneously across psychotherapies and pharmacologic treatments. The data analytic frameworks we will include are meta-analysis of individual patient data (MIPD), integrative data analysis (IDA), and propensity score weighting (PSW) specific to moderation and mediation analysis. MIPD estimates the distribution of treatment effects across multiple studies using raw individual-level data in a manner that directly addresses known limitations of conventional meta-analysis. In concert with MIPD, we propose the use of (1) IDA, a special case of Item Response Theory models, to create comparable scale scores across studies that may have different measures of the same construct, and (2) PSW to address selection bias among key moderators and mediators that were not part of within-study randomization.

Analysis of subgroups or subsets

Descriptive analyses of subgroups will be conducted. If the necessary data are available, subgroup analyses for treatment duration, by age, by study quality, by control groups, by civilian versus military status. Tables and summaries will be generated.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work	✓	✓
Formal searching/study identification	✓	✓
Screening search results against inclusion criteria	✓	✓
Data extraction or receipt of IPD		
Risk of bias/quality assessment		
Data synthesis		

Review status
The review is currently planned or ongoing.

Publication of review results
Results of the review will be published in English.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

Dr Denise Hien (review guarantor and contact) Rutgers Center of Alcohol & Substance Use Studies. United States of America.

No conflict of interest declared.

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No conflict of interest declared.

Dr Sudie Back. Medical University of South Carolina. United States of America.

No conflict of interest declared.

Dr Shannon Blakey. RTI International. United States of America.

No conflict of interest declared.

Dr Angelo M. DiBello. Rutgers Center of Alcohol & Substance Use Studies. United States of America.

No conflict of interest declared.

Dr Therese Killeen. Medical University of South Carolina. United States of America.

No conflict of interest declared.

Dr Teresa Lopez-Castro. City College of NY. United States of America.

No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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Review affiliation

Rutgers Center of Alcohol & Substance Use Studies

RTI International

Funding source

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1R01DA061338

Additional non-commercial funding information
National Institute on Drug Abuse (NIDA)

Peer review

This review forms part of a project funded through a peer-reviewed grant from the National Institute on Drug Abuse (NIDA). The proposal underwent NIH's standard scientific peer-review process, in which an independent study section evaluated the significance, methodology, investigative team, and overall scientific merit. Funding was awarded following this competitive review, indicating that the study design and proposed methods met established NIH standards for rigor and feasibility.

ADDITIONAL INFORMATION

Additional information

Project Harmony 2.0 builds directly on the infrastructure and findings of Project Harmony 1.0 (PH 1.0), an integrated individual participant data (IPD) dataset and Virtual Clinical Trial synthesizing psychological and pharmacologic treatments for comorbid PTSD and alcohol or other drug use disorders. PH 2.0 expands this existing harmonized dataset by adding newly available trials and updated datasets.

PH 1.0 addressed four primary aims:

Aim 1: Develop commensurate PTSD and AOD severity scores in the presence of study-level measurement non-invariance.

Aim 2: Compare the effectiveness of evidence-based treatment models for comorbid PTSD and AOD.

Aim 3: Test potential mediators of treatment effects on AOD across treatment models.

Aim 4: Examine individual-, treatment-, and study-level moderators to identify for whom each treatment model works best.

Relevant PH 1.0 publications include:

Hien et al. (2024), Psychological Bulletin (systematic review and network meta-analysis).

Hien et al. (2023), American Journal of Psychiatry (IPD comparative effectiveness analysis).

Saavedra et al. (2021), Contemporary Clinical Trials (design and methodology of the Virtual Clinical Trial).

Project Harmony 2.0 represents a direct continuation and expansion of this program by incorporating additional datasets into the established PH 1.0 framework.

Review conflict of interest

Declared individual interests are recorded under team member details.. No additional interests are recorded for this review.

Medical Subject Headings

Comorbidity; Ethanol; Humans; Stress Disorders, Post-Traumatic; Substance-Related Disorders; Alcohol-Related Disorders; Marijuana Abuse; Clinical Trial Protocols as Topic; Cognitive Behavioral Therapy; Naltrexone; Network Meta-Analysis; Topiramate; Trauma and Stressor Related Disorders; Implosive Therapy; Opioid-Related Disorders; Analgesics; Buprenorphine; Buprenorphine, Naloxone Drug Combination; Methadone; Heroin Dependence; Morphine Dependence; Opium Dependence; Opiate Overdose; Psychotherapy; Medication Adherence

SIMILAR REVIEWS

Check for similar records already in PROSPERO

PROSPERO identified a number of existing PROSPERO records that were similar to this one (last check made on 9 December 2025). These are shown below along with the reasons given by that the review team for the reviews being different and/or proceeding.

- Project Harmony: A systematic review and meta-analysis of individual patient data of behavioral and pharmacologic trials for comorbid posttraumatic stress, alcohol and other drug use disorders [published 5 December 2019] [CRD42019146678]. The review was acknowledged as **similar** but the authors opted to continue because *the review looks at additional or different outcomes*, *the review will be more up to date*
- Psychological interventions for PTSD and comorbid substance use disorder [published 15 November 2020] [CRD42020207840]. The review was judged **not to be similar**
- Individual patient data meta-analysis for posttraumatic stress disorder [published 28 April 2020] [CRD42020138638]. The review was judged **not to be similar**

PROSPERO version history

- Version 1.0, published 23 Dec 2025

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