BMJ Open

Protocol for individual participant data meta-analysis of interventions for post-traumatic stress

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To cite: Wright SL, Karyotaki E, Bisson JI, *et al*. Protocol for individual participant data meta-analysis of interventions for post-traumatic stress. *BMJ Open* 2022;**12**:e054830. doi:10.1136/bmjopen-2021-054830

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-054830).

Received 24 June 2021
Accepted 05 January 2022

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ABSTRACT

Introduction Several evidence-based treatments are effective for post-traumatic stress disorder (PTSD), yet a substantial proportion of patients do not respond or dropout of treatment. We describe the protocol for a systematic review and individual participant data meta-analysis (IPD-MA) aimed at assessing the effectiveness and adverse effects of psychotherapy and pharmacotherapy interventions for treating PTSD. Additionally, we seek to examine moderators and predictors of treatment outcomes.

Method and analysis This IPD-MA includes randomised controlled trials comparing psychotherapy and pharmacotherapy interventions for PTSD. PubMed, Embase, PsycINFO, PTSDpubs and CENTRAL will be screened up till the 11th of January 2021. The target population is adults with above-threshold baseline PTSD symptoms on any standardised self-report measure. Trials will only be eligible if at least 70% of the study sample have been diagnosed with PTSD by means of a structured clinical interview. The primary outcomes of this IPD-MA are PTSD symptom severity, and response rate. Secondary outcomes include treatment dropout and adverse effects. Two independent reviewers will screen major bibliographic databases and past reviews. Authors will be contacted to contribute their participant-level datasets. Datasets will be merged into a master dataset. A one-stage IPD-MA will be conducted focusing on the effects of psychological and pharmacological interventions on PTSD symptom severity, response rate, treatment dropout and adverse effects. Subsequent analyses will focus on examining the effect of moderators and predictors of treatment outcomes. These will include sociodemographic, treatment-related, symptom-related, resilience, intervention, trauma and combat-related characteristics. By determining the individual factors that influence the effectiveness of specific PTSD treatments, we will gain insight into personalised treatment options for PTSD.

Ethics and dissemination Specific ethics approval for an IPD-MA is not required as this study entails secondary analysis of existing anonymised data. The results of this study will be published in peer-reviewed scientific journals and presentations.

Strengths and limitations of this study

- We will conduct an individual participant data meta-analysis (IPD-MA) to examine the available evidence on the effectiveness and adverse effects of psychotherapy and pharmacotherapy interventions for treating post-traumatic stress disorder (PTSD).
- A range of participant-level variables will be examined when available (sociodemographic, treatment-related, symptom-related, resilience, intervention, trauma, and combat-related characteristics), and their role as effect modifiers.
- Within IPD-MAs, statistical power is maximised allowing for the examination of clinically relevant moderators and predictors for treatment effects.
- By gaining insight into which characteristics influence the effectiveness of specific PTSD treatments, time, money and effort can be saved and redirected towards treatments that will be most effective for individual patients.
- However, the IPD-MA is limited to examining factors that are reported similarly across the included individual studies and the availability of primary datasets.

INTRODUCTION

Globally, post-traumatic stress disorder (PTSD) is among the most prevalent of mental illnesses, affecting individuals and communities as a whole.[1] Five to 55% of individuals develop PTSD at some point in their life depending on the type of trauma they are exposed to and the population being studied.[2] While the type of trauma differs, they can all lead to a severe impact on psychological and physical functioning. Enduring PTSD symptoms can place the individual at a higher risk of suicidality, mood and substance use disorders, and increased risk of mortality from medical illnesses.[3–6]

Several leading international organisations provide evidence-based guidelines for the treatment and management of PTSD such as the International Society for Traumatic Stress Studies (ISTSS),[7] WHO,[8] the National Institute for Health and Care Excellence (NICE)[9] and the American Psychological Association.[10] These evidence-based guidelines propose two

first-line treatments for PTSD, namely psychotherapy and/or pharmacotherapy.

Psychotherapeutic treatments for PTSD have been broadly classified as being either trauma-focused (TF) or non-trauma focused (NTF).[11] TF psychotherapies focus on the thoughts, emotions and memories centred around the traumatic event.[11] Using cognitive, emotional and behavioural techniques, the therapist aims to bring about a positive change in the meaning, interpretation and processing of the traumatic event itself.[12]

Evidence-based TF therapies for PTSD include cognitive–behavioural therapy (CBT) with a trauma focus (CBT-TF), and eye movement desensitisation and reprocessing (EMDR).[13–16] CBT-TF is a broad category of psychotherapies for treating PTSD.[17] These include brief eclectic psychotherapy (BEP),[18–22] cognitive processing therapy (CPT),[23–26] cognitive therapy (CT),[27 28] narrative exposure therapy (NET),[29–31] prolonged exposure (PE),[32 33] reconsolidation of traumatic memories (RTM)[34 35] and virtual reality exposure therapy (VRET).[36–40] Other TF therapies that have been investigated include dialogical exposure therapy (DET),[23] observed and experimental integration (OEI),[40] REM desensitisation (REMD)[41] and written exposure therapy (WET).[26 42 43]

On the other hand, NTF psychotherapies focus on the patient's symptoms without directly focusing on the traumatic event itself.[11] There is evidence for specific NTF psychotherapies such as CBT without a TF (CBT-NTF; involving a combination of the following techniques: stress management, emotional stabilisation, relaxation training, breathing retraining, positive thinking and self-talk, assertiveness training, thought stopping and stress inoculation training), presented centred therapy (PCT),[33 44] emotional freedom technique (EFT)[15 45] and supportive counselling (SC).[28]

Several pharmacological treatments can also be effective in treating PTSD.[46] Pharmacotherapy refers to treatment using pharmacological agents.[47] While it is recommended by the United States Department of Veteran Affairs (VA) as monotherapy for PTSD, the American Psychological Association and NICE do not recommend it as a first-line treatment option. The Australian Centre for Posttraumatic Mental Health and NICE recommends that pharmacotherapy be used as a second-line treatment for patients who do not respond to psychotherapy, or if psychotherapy is not available.

Several selective serotonin reuptake inhibitors (SSRIs) can be beneficial for treating PTSD symptoms such as fluoxetine,[48–52] paroxetine[53–56] and sertraline[57–60] for the treatment of PTSD symptoms. There is also evidence for the serotonin–norepinephrine reuptake inhibitor venlafaxine.[61] Additionally, the atypical antipsychotics quetiapine[62] and risperidone[63 64] can also be effective. To date, there is still insufficient evidence for amitriptyline,[65] imipramine,[66] phenelzine,[66] ketamine,[67] lamotrigine,[68] mirtazapine,[60] brofaromine,[69] neurokinin-1 receptor antagonist,[70] olanzapine,[71] tiagabine[72] and topiramate.[73]

A systematic review of 21 pharmacological interventions found significant improvements for fluoxetine, paroxetine and venlafaxine, compared with placebo control groups.[46] A meta-analysis limiting study inclusion to active control groups, found sertraline and venlafaxine to outperform other drug treatments.[74] Venlafaxine can have positive short-term benefits on PTSD symptoms, but these benefits do not appear to be maintained over time.[61 75 76]

Despite the availability of evidence-based psychotherapy and pharmacotherapy treatments for PTSD, approximately 30%–35% of patients do not respond to treatment.[77 78] Therefore, the identification of individual factors that influence PTSD treatment outcomes is important. Identifying factors that contribute to the success or failure of a specific treatment for PTSD may help to allocate individuals to the right treatment at the right time. Personalised medicine has become a key focus across other medical fields.[79 80]

Researchers have sought to examine which individual factors influence treatment responsiveness. While individual studies have investigated the potential moderators and predictors for treatment response, factors such as age,[81–84] gender,[81–89] marital status,[82 83 90] employment status,[81–83] ethnicity,[90] household income,[89 90] refugee status,[88] intelligence,[91] therapy type,[83] time spent on psychotherapy homework,[92 93] past trauma,[81 94] time since trauma[27 81 83] and type of trauma[83] had no significant effect on treatment outcomes, although that may be related to low statistical power of many studies.

Other research has found that higher education,[84] marital status,[89] higher guilt symptoms,[91] therapeutic alliance[95] and psychotherapy homework completion[96] were associated with a better PTSD treatment response. Some studies have found that comorbid psychiatric disorders have been found to reduce the beneficial effects of treatment on PTSD outcomes.[97 98] In contrast, other studies have found that psychiatric comorbidity did not affect PTSD treatment outcomes.[81 91 95 99] PTSD severity has also been found to moderate the effectiveness of PTSD treatments in some studies[98 100] but no association was found in others.[27 81 83 84 88 101]

Investigating and gaining insight into treatment dropout could lead to better treatment response for PTSD. For example, patients who attend more treatment sessions tend to have a better response to treatment.[77 102 103] A potential concern with TF treatment is dropout.[17 104 105] A recently published meta-analysis examined the individual factors that influence treatment dropout and found 14%–18% of patients receiving psychotherapy for PTSD prematurely end their treatment.[17] They also found a greater number of dropouts for TF psychotherapy compared with NTF psychotherapy treatments.[17] In an earlier meta-analysis investigating treatment dropout across PTSD treatments, the average dropout across all active treatments was 18.28% (95% CI 14.84% to 21.75%).[106] In the latter review, the average dropout rate for TF treatments was 36% while for present

centred therapy it was 22%. No significant difference was found in the proportion of dropouts between group and individual formats; recruitment within clinical settings and by advertisements; only female and mixed gender studies; and sexual assault victims and all trauma types.[17]

Adverse effects of psychotherapy treatments for PTSD are not commonly reported.[11] Pharmaceutical agents are commonly used to treat PTSD symptoms yet the number of recent clinical trials investigating the effectiveness and adverse effects of these treatments is limited. An investigation of the VA medical centre and clinic records between 2003 and 2004 revealed that 80% of patients with PTSD were prescribed psychotropic medications.[107] While a survey of ClinicalTrials.gov from 2006 till December 2016 identified only one phase III, four phase II and no phase I clinical trials for the treatment of PTSD.[108] Sexual dysfunction is a common adverse effect of SSRI treatment which has been identified as a leading cause of medication non-adherence.[109–111] Some other potential adverse effects of specific pharmaceutical treatments for PTSD include sedation,[60 62 112 113] increased anxiety,[60 114] weight gain,[60 61 112] somnolence,[62] nasal stuffiness,[114] blurred vision,[114] dizziness,[113] vertigo,[114] gastrointestinal disturbances such as constipation or diarrhoea, oedema,[114] palpitations,[114] dyspnoea,[114] increased depression[114] and priapism.[114]

As adverse events can occur in any form of treatment, it is important to be aware of the nature and frequency of adverse consequences of each modality. Strategies for managing treatment-related adverse effects include reducing the individual's dosage, adding additional medication to treat it, ruling out other possible causes, and switching medications.[109] Overall, there is limited literature on the adverse effects of both psychotherapy and pharmacotherapy treatments for PTSD.

A problem in the field is that it is premature to draw conclusions or provide recommendations based on currently available studies that have examined predictors or moderators of treatment response. Randomised controlled trials (RCTs) and meta-analyses that pool study-level data usually do not have sufficient statistical power to detect clinically relevant moderators or predictors of treatment effects.[115] Therefore, researchers are not likely to find significant predictors in their RCTs and if they do it may well be a chance finding.

Unlike a conventional meta-analysis, which extracts aggregate-level data from published reports (secondary data), an individual participant data meta-analysis (IPD-MA) synthesises raw participant level data (primary data) from the authors. The raw data from all the included psychotherapy and pharmacotherapy RCTs are combined, creating one large master dataset.[116] Within IPD-MA, statistical power and precision are maximised, leaving room for detecting clinically relevant moderators of treatment effects. This makes the IPD-MA one of the most powerful tools to identify clinically important treatment moderators and prognostic factors.[117] IPD-MAs are crucial to either identify or rule out such effects. Currently, no IPD-MA focused on treatments for PTSD has been published.

The aims of this study are to (1) investigate the effectiveness of different types of psychological and pharmacological treatments for PTSD, (2) identify sociodemographic, clinical and psychological predictors and moderators for treatment effects across different types of psychological and pharmacological treatments for PTSD, (3) examine the proportion of treatment dropouts in intervention and control arms, and (4) identify adverse effects of psychological and pharmacological PTSD treatments.

METHODS

This systematic review and IPD-MA is following the guidelines recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*.[118] This study will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[119 120]

Eligibility criteria

Types of studies

Only RCTs are included.

Type of participants

The population being studied comprises of adults (18 years and older). All participants are required to have above-threshold symptoms on any standardised self-report PTSD questionnaire (eg, PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[121]) or a clinical diagnosis of PTSD. At least 70% of the study sample within each RCT are required to have been diagnosed with PTSD by means of a structured clinical interview according to DSM-III,[122] DSM-IIIR,[123] DSM-IV,[124] DSM-5,[125] International Classification of Diseases 9th Revision (ICD-9),[126] ICD-10[127] or ICD-11[128] criteria. No restrictions are placed on psychiatric or physical comorbidities due to the high rates of comorbidity in this disorder.[129]

Types of interventions

This study includes all psychotherapy and pharmacotherapy based on RCTs primarily aimed at reducing PTSD symptoms. Psychotherapy studies will be analysed separately from the pharmacotherapy studies. For example, psychotherapy interventions will be categorised into EMDR, TF-CBT, TF-CBT (NET), TF-CBT (BEP), CBT-TF (CPT), CBT-TF (CT), CBT-TF (PE), CBT-TF (RTM), CBT-TF (VRET), CBT-TF (DET), WET, OEI, REMD, CBT-NTF, PCT, EFT and SC. Sensitivity analysis for these individual types of psychotherapy alone will be undertaken when there are at least three studies of a particular psychotherapeutic intervention. This analysis will explore whether moderators are specific to certain types of psychotherapies. The interventions are required to have begun no sooner than 1 month after the traumatic event. Studies are excluded if they are primarily aimed at relapse prevention or maintenance treatment.

Interventions delivered by clinicians or lay health workers who had received appropriate training and supervision are included.[74] No restrictions are placed on the route of administration.

Comparison groups

Eligible control conditions for the psychotherapy trials include inactive control conditions (such as waiting list control; minimal contact group), active control conditions (treatment as usual groups; psychoeducation; complementary therapies), and other psychotherapy treatment groups. Pharmacotherapy control conditions will include placebo groups, other active medication comparators or other inactive controls.

Types of outcome measures

The primary outcomes are PTSD symptom severity and PTSD treatment response (symptom reduction of at least 50% from pre-treatment to post-treatment assessment). The PTSD symptom severity score will be based on validated and established PTSD outcome measures. Preference will be given to the measures that are listed as primary outcome measures in the study protocol or the published RCT manuscript. In instances where more than one primary outcome measure is used in the same RCT, we will prioritise blinded clinical interviews followed by blinded self-report instruments, and lastly non-blinded interviews. Secondary outcome measures will include treatment dropout and adverse effects. In line with the definition used in the meta-analysis which formed part of an update of the ISTSS treatment guidelines, we considered the number of participants who left the study by post treatment as an indicator of dropout.[17]

Types of predictor/moderator variables

Eligible studies will be examined to identify valid predictors and moderators. A wide range of participant-level variables will be included, and their role as effect modifiers (variables that have an impact on the relative effects of interventions) will be explored when available. These include sociodemographic characteristics (age; gender; country of origin; country study conducted in; low-middle income/high income countries; religious affiliation; race; education level; marital status: married/not married; relationship status; employment status; aid worker status: yes/no; sexual orientation; population: general population/military/first responder/refugee), treatment-related characteristics (past psychotherapy for PTSD; past pharmacotherapy for PTSD; current pharmacotherapy; clinical setting: inpatient/outpatient; therapeutic alliance quality), symptom-related characteristics (duration of PTSD symptom; re-experiencing symptoms; avoidance symptoms; negative alterations in cognitions and mood; alterations in arousal and reactivity; guilt symptoms; baseline psychiatric comorbidity), characteristics of resilience (post-traumatic growth; coping strategies; life satisfaction; quality of life; level of hope), intervention characteristics (intervention delivery method: individual/group/internet-based; study design; number of participants randomised per group; the number of participant dropouts at post treatment per group; treatment replated adverse events; dosage (frequency); mean end dosage; route of administration; duration of treatment intervention (weeks); session length (minutes); intervention length (weeks); number of sessions completed; intervention provider: non-specialists or paraprofessionals (task shifted)/ mental health provider; intervention involve homework; proportion of assigned homework tasks completed; internet-based: guided or unguided), trauma characteristics (time since index trauma (months); number of past traumatic event/s including index trauma; type of index trauma; delayed onset; physically injured during index trauma; number of traumatic events experienced), and combat-related characteristics (length of deployment; branch of the military; multiple/single deployment).

Timing of outcome assessments

All available post-intervention outcomes will be included despite potential variability in time frames. If the timing of interventions differs extremely, sensitivity analyses will be conducted to explore the effect of length of treatment on treatment outcomes (interventions lasting for less than 6 months compared with those lasting 6 months or more). Additionally, length of treatment will be included as a control variable in regression analyses. Post treatment follow-ups will be included and analysed separately. The follow-up period will be divided into follow-up 1 assessed up to and including 24 weeks after post treatment, and follow-up 2 assessed more than 24 weeks after post treatment.

Search methods for identification of studies

We will use and update an existing search that was developed by the Cardiff University Traumatic Stress Research Group, which has been used as a basis for the ISTSS guidelines.[7] The systematic search strategy was conducted using Cochrane methodology, including trials up until 2018. The search will be updated to include the period from the 1 January 2018 till the 11 of January 2021 using the same search strategy.

The search strategy will include screening major bibliographic databases, namely, PubMed, Embase, PsycINFO, PTSDpubs and CENTRAL (see online supplemental file 1). The searches will combine free and indexed terms indicative of PTSD, trauma, psychotherapy and pharmacotherapy. No restrictions will be placed on study setting or publication status, including poster abstracts and abstracts available from symposia. Past systematic reviews and meta-analyses focusing on psychotherapeutic and/or psychopharmacological PTSD interventions will be screened for any additional articles. Additionally, authors who are contacted for data will be asked to identify any additional unpublished literature. Duplicates will be removed. The titles and abstracts of all potential studies identified will be independently examined by two

members of the review team. The full publications will be screened independently by both reviewers. In the case where no full publication can be located, the authors will be contacted to provide further information. Any uncertainty about study inclusion will be resolved by discussion with a third senior member of the review team.

Data collection

Senior authors of eligible trials will be contacted via email to request permission to use their participant-level data. Reminders will be sent after 1 month to the authors who did not respond. After five attempts to contact the senior author, two additional authors on the publication will be contacted. Four attempts will be made to contact the two additional authors. If no response is received by this point, the participant-level data will be considered unavailable. The aggregate data will be extracted from the publications for unavailable participant-level data. In the case where organisations (eg, drug companies) hold the rights to the data, these parties will be contacted directly. The collected data will be stored in the currently existing encrypted database at the VU Amsterdam. Once the datasets have been received, the variables will be standardised across the studies. Often the coding may not be clear (eg, missing value labels). In these cases, the missing information will be obtained from the primary authors through an iterative process.

Quality assessment

Two independent reviewers will use the Risk of Bias tool by the Cochrane Collaboration to evaluate included studies.[118] Studies are scored as low, high or as unclear risk of bias for each of the six domains. These domains include (1) random sequence generation, (2) allocation concealment, (3) blinding of outcome assessors, (4) incomplete outcome data, (5) selective outcome reporting and (6) other bias.

Patient and public involvement

No patients will be directly involved

ANALYSIS

Statistical analyses will be conducted in STATA.[130] After the initial data checks have been completed and the datasets have been standardised, individual datasets will be integrated into one large master dataset.

Conventional meta-analysis

It is unlikely that we will obtain participant-level data for all the included studies. Therefore, in case we are not able to include all eligible trials in our IPD-MA, we will first conduct a conventional MA to compare available with unavailable data which may bias the results of this IPD-MA. Data will be extracted from academic publications to compare the outcomes of the studies for which data were unavailable with the study data collected for this IPD MA. Effect sizes will be used to indicate the differences between comparison treatments. These effect sizes will be compared using a random-effects model because possible heterogeneity between studies is expected. To examine the amount of variation across studies due to heterogeneity, a standard χ^2 test will be conducted. The degree of heterogeneity between studies will be assessed using the I^2 statistic, which gives heterogeneity in percentages. A value of 0%, 50%, 75%, indicating no, low, moderate or high heterogeneity respectively.[131] The 95% CI around I^2 will be calculated. In cases where high heterogeneity is found, subgroup analyses and meta-regression will be conducted to explore possible causes of heterogeneity. A funnel plot will be used to assess small sample bias and publication bias. The estimated effect size after considering bias related to including studies with small samples will be conducted using Duval and Tweedie's trim and fill procedure.[132] Metaregression analyses will be run in STATA to examine differences in outcome between studies that contributed data and those that did not. The standardised effect sizes will be the dependent variable and a variable indicating whether data has or has not been shared by the authors, and other study characteristics as the independent variables.

IPD meta-analysis

Primary PTSD outcome scales and timepoints in each trial will be selected based on information from publications and study authors. In cases where different PTSD outcome measures have been used, the scores will be converted into standardised z-scores to retain continuous scores of PTSD. The continuous PTSD scores will also be converted into response rates per individuals. Response will be defined as a symptom reduction of at least 50% from pretreatment to post treatment. This will allow the outcomes to be compared across studies and different PTSD outcome measures. Missing outcome data at the post-treatment assessment will be estimated using multiple imputation under the missing-at-random assumption.[130] This will generate a 100 imputed data sets based on baseline PTSD symptoms scores, age, sex and group data. The new imputed data sets will include the observed and the imputed standardised PTSD symptoms scores for the missing values. Each will be analysed separately using the selected model, and the results will be averaged according to Rubin's rules for multiple imputation.[133] We will also conduct sensitivity analyses using only participants with complete data after treatment to examine whether there was a difference between those who dropped out of the RCTs and those who provided post-treatment data.

The one-stage IPD MA will then be conducted as it yields less biased estimates and has better performance in terms of power than a two-stage approach.[134] We will merge all participant level data from all studies with participants nested within studies. We will calculate the standardised β coefficient for the examined comparisons. This estimate indicates how many SD the dependent variable (PTSD symptoms severity or the log OR of treatment response) changes per SD increase in the predictor variable. Thus, the higher the β, the greater the effect of the predictor variable on the dependent variable. The

primary analysis will be twofold. First, we will analyse the effects of the interventions on PTSD symptom severity at the end of treatment using a multilevel mixed-effect linear regression (using a random intercepts model with a random effect for each trial and fixed effects for the intervention and the symptoms severity, using STATA's mixed command). The post-treatment PTSD scores will be used as the dependent variable and trial arm condition (treatment vs control) as the independent variable, while controlling for baseline PTSD symptom severity.

Second, we will analyse the effects of the interventions on treatment response at the post-treatment assessment using a multilevel mixed-effect logistic regression (using a random intercepts model with a random effect for each trial and fixed effects for the intervention and the PTSD symptoms severity, using STATA's melogit command). The response (yes or no) will be the dependent variable and condition the independent variable.

Third, we will run a two-stage IPD-MA to analyse the participant-level data separately in each study and then combine the estimates to calculate the pooled effect sizes (Hedges' g) for PTSD symptom severity. A two-stage IPD-MA facilitates analysis standardisation across the included studies and estimation of outcomes that are not available in the published reports (eg, treatment response).[135]

We will calculate the OR of treatment response and numbers needed to treat, which will allow us to compare the results of the present MA with those reported in earlier MA. Two-stage IPD-MA will also allow us to examine the moderation effect of study-level variables. Thus, subgroup moderator analyses will be conducted using a mixed-effect model in which the random-effects model will be used to pool studies within subgroups, while between-subgroup differences will be tested as fixed effects. We will also run metaregression analyses to examine the association between treatment duration and treatment outcomes (severity of PTSD symptoms and treatment response).

Sensitivity analysis

Several sensitivity analyses will be conducted to examine the robustness of the IPD-MA findings. We will test whether available demographic and clinical characteristics moderated the effect of psychotherapy and pharmacotherapy interventions on PTSD outcomes (PTSD symptoms severity and treatment response). To examine moderators, we will add the interaction between each potential moderator and treatment outcome on PTSD severity into the multilevel mixed-effect linear regression model. We similarly will add the interaction between each potential moderator and treatment response into the multilevel mixed-effect logistic regression model. Each potential moderator will be included in a separate model as a main effect.

ETHICS AND DISSEMINATION

Specific ethics approval for an IPD-MA is not required as this study entails secondary analysis of existing anonymised data. Data collection and storage will follow the requirements set out in the European General Data Protection Regulation.[136] Our findings will be published in peer-reviewed scientific publications. Before submission for publication, the articles from this study will be sent to all the authors who have contributed data. This will allow them to provide feedback and recommendations. Other than publishing the findings in academic journals, the results will be presented at international conferences related to the treatment of PTSD (such as the ISTSS and the European Society for Traumatic Stress Studies). We will also disseminate the findings through Vrije Universiteit Amersterdam and Stellenbosch University social media platforms.

DISCUSSION

Targeted allocation of treatment resources may contribute to that each patient gets appropriate and timely treatment. For this to be possible, we need to know which specific treatments are best for which people. By maximising statistical power and precision using IPD-MA, we can examine data that are rarely reported by primary studies, detect overall effects, and test moderators of treatment outcomes. This allows for a better understanding of the effects of patient level characteristics on PTSD outcomes, as well as greater precision in treatment decision-making. Thus, gaining insight into how patient-level characteristics moderate PTSD severity outcomes and treatment dropout, can increase the likelihood that each patient gets the treatment that suits him/her most. This has the additional benefit of meeting unmet treatment needs. For example, if certain people benefit more (or as well) from community-based interventions or interventions carried out by non-professional helpers (task-shifting), then the resources for individual psychotherapy can be allocated to others who need it and who may not respond well to community-based interventions. This might be beneficial in low-middle-income countries where mental health resources were already very limited before the COVID-19 pandemic.[137 138] Potential limitations of this study are (1) the pooling of different types of therapies may lead to high heterogeneity between studies. These possible sources of heterogeneity will be investigated and discussed, (2) relevant moderators associated with PTSD outcomes may not be included in many studies, (3) inability to obtain participant level data for some studies at all, as there may be obstacles in gaining access to some of the datasets. However, like with a traditional MA, if the overall patterns are consistent, we may assume that the results of the IPD-MA are representative for all studies, and (4) pooling of interventions and control conditions that may be very heterogeneous could result in a risk of bias in the included studies. The impact of these biases will be considered when we examine comparability between treatment groups by assessing subgroup effects and heterogeneity. This analysis will also explore whether moderators are specific to certain types of psychotherapies, in comparisons of different psychotherapies with

each other as well as in comparisons (of psychotherapies and pharmacotherapies, respectively) with control conditions (placebo, waitlist, care-as-usual, etc). Other sensitivity analyses may be necessary and will be determined after all accessible data have been collected and examined.

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Funding This research is funded by the NRF-NUFFIC scholarship, grant number 115977.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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