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Which patients benefit specifically from short-term psychodynamic psychotherapy (STPP) for depression? Study protocol of a systematic review and meta-analysis of individual participant data.

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ABSTRACT

Introduction: Short-term psychodynamic psychotherapy (STPP) is an empirically supported treatment that is often used to treat depression. However, it is largely unclear if certain subgroups of depressed patients can benefit specifically from this treatment method. We describe the protocol for a systematic review and meta-analysis of individual participant data (IPD) aimed at identifying predictors and moderators of STPP for depression efficacy.

Method and analysis: We will conduct a systematic literature search to identify studies reporting (a) outcomes on standardized measures of (b) depressed (c) adult patients (d) receiving STPP. We will next invite the authors of these studies to share the participant-level data of their trials and combine these data to conduct IPD meta-analyses. The primary outcome for this study is post-treatment efficacy as assessed by a continuous depression measure. Potential predictors and moderators include all socio-demographic variables, clinical variables, and psychological patient characteristics that are measured before the start of treatment and are assessed consistently across studies. One-stage IPD meta-analyses will be conducted using mixed effects models.

Ethics and dissemination: IRB approval is not required for this study. We intend to submit reports of the outcomes of this study for publication to international peer-reviewed journals in the fields of psychiatry or clinical psychology. We also intend to present the outcomes at international scientific conferences aimed at psychotherapy researchers and clinicians. The findings of this study can have important clinical implications, as they can inform expectations of STPP efficacy for individual patients,

and help to make an informed choice concerning the best treatment option for a given patient.

Registration: PROSPERO (registration number currently being assigned).

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Keywords: depression, short-term psychodynamic psychotherapy, predictors, moderators, individual participant data meta-analysis.

Strengths and limitations of this study

- This is the first study that systematically assesses patient characteristics associated with STPP for depression efficacy.
- IPD meta-analysis allows for the examination of predictors and moderators by maximizing statistical power while protecting against ecological bias that presents problems when using conventional meta-analysis techniques.
- The findings of this study can have important clinical implications, as they can inform expectations of STPP efficacy for individual patients, and help to make an informed choice concerning the best treatment option for a given patient.
- IPD meta-analyses rely on variables previously assessed in individual studies and available across multiple trials. Thus, it is possible that not all variables of interest can be examined as potential predictors or moderators.

INTRODUCTION

Depression is a highly prevalent and disabling disorder associated with major personal and societal costs.[1] Affecting more than 300 million people worldwide, depression is ranked as the single largest contributor to global disability by the World Health Organization.[2] Given the tremendous burden of disease, there is a great need for effective and efficient treatments for depression. Antidepressant medications and different psychological therapies constitute the predominant treatments for depressive disorders.[3] Concerning psychological treatments, there is a clinical tradition of short-term psychodynamic psychotherapies (STPPs) being used to treat depression.

Although STPP is a time-honored therapy for depression, its efficacy in this regard has not been studied as extensively as the efficacy of other psychotherapies, such as cognitive behavioral therapy (CBT).[4-5] For this reason, the efficacy of STPP for depression has been debated.[6] This is reflected in treatment guidelines, which typically have not considered STPP a first-choice therapy for depression.[7-8] In recent years, there has been a change with the publication of a number of large-scale and high-quality studies that support the efficacy of STPP for depression.[e.g.,9-10] However, it remains unclear if certain subgroups of depressed patients can benefit specifically from STPP.

Two types of information are relevant to this question: predictors and moderators. Predictors (or prognostic factors) predict outcome to a given treatment and can be used to determine which patients are more likely to respond to STPP relative to other patients. Predictors can inform expectations of STPP efficacy, but are of little use in deciding what treatment to select. On the other hand, moderators (or prescriptive

factors) can detect different patterns of outcomes between different treatments for different types of patients and provide a basis for choosing the best treatment of a given patient.[11]

Some preliminary empirical findings concerning predictors and moderators of STPP efficacy for depression do exist. With regard to predictors, meta-regression analyses alongside a 'conventional' meta-analysis - based on results extracted from publications[12] - showed that mean pre-treatment depression scores were positively associated with pre- to post-treatment depression effect size in STPP. With regard to moderators, Driessen et al.[13] found STPP to be more efficacious than CBT among depressed patients who showed low baseline comorbid anxiety levels. Furthermore, Barber et al.[14] reported that STPP was more efficacious than medication or placebo for ethnic minority males. However, a systematic assessment of which patient characteristics are associated with STPP efficacy is currently lacking.

The main reason why predictors and moderators of STPP for depression have not yet been examined thoroughly is lack of statistical power in individual clinical trials due to relatively small sample sizes. Prediction and moderation analyses can also be conducted alongside conventional meta-analyses. However, since these analyses are usually based on study-level characteristics, they are prone to ecological bias, such that the association between the study-level characteristics may not be representative of the true relationships in the data at the individual level.[15] Thus, current research methods (clinical trials and conventional meta-analyses) have been insufficient to answer the question as to whether certain subgroups of patients can benefit specifically from STPP for depression.

Individual participant data (IPD) meta-analysis is a relatively new technique to examine treatment effects by combining participant-level data of multiple trials. IPD meta-analysis uses the same basic approach as any other well-conducted systematic review and meta-analysis. However, it involves collection of the original data from as many of the relevant trials worldwide as can be accessed. IPD meta-analysis has several advantages over conventional meta-analysis, including increased statistical power to examine predictors and moderators of treatment efficacy.[16] Furthermore, because predictors and moderators are studied at patient-level, ecological bias can be circumvented. For these reasons, IPD meta-analysis is currently considered the 'gold standard' in evidence synthesis[17].

We describe the study protocol for a systematic review and IPD meta-analysis concerning predictors and moderators of STPP for depression efficacy. The aim of this project is to examine which depressed patients benefit specifically from STPP in terms of depressive symptom reduction when compared to other patients (predictors), and which patients benefit specifically from STPP when compared to no-treatment conditions, other psychotherapies, and antidepressant medication (moderators). The goal of this study is to collect the participant-level data of all trials examining the efficacy of STPP for depression identified by a systematic literature search, and to combine these datasets in order to conduct IPD meta-analyses.

METHODS

Design

This study is a systematic review and meta-analysis of individual participant data that is registered in the PROSPERO International prospective register of systematic reviews (identification number is currently being assigned). Important protocol amendments will be documented in this register too. The project started December 1st, 2016 and is expected to be completed November 30th, 2018.

Search strategy

We will use an extensive search strategy including six different search methods in order to retrieve as many relevant studies as possible. These searches have already been performed in 2007 and 2014 for two previous conventional meta-analyses concerning the efficacy of STPP for depression[12,18] and will be updated in 2017.

First, we will systematically search the bibliographic databases PubMed, PsycINFO (via EBSCO), Embase.com, Web of Science (via Elsevier), and Cochrane's Central Register of Controlled Trials (via Wiley). Search terms will include a wide range of synonyms, both in index terms and free-text words, for 1) psychodynamic psychotherapy (e.g., psychotherapy, psychoanalytic), 2) therapy (e.g., psychotherapy), 3) psychodynamic (e.g., dynamic*), and 4) depression (e.g., depressive disorder). These four sets of search terms will be combined as follows: (#1 OR (#2 AND #3)) AND #4. The exact terms for the search in PubMed are presented in Table 1. Complete

search terms for all electronic databases are available on request from the corresponding author. No language or date restrictions will be applied in the searches.

Table 1. PubMed search strategy

Search	PubMed Query 19-06-2017	Items found
#8	Search **#7 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type])**	2285
#7	Search **#6 AND #4**	2350
#6	Search **#1 OR #5**	39841
#1	Search **"Psychoanalytic Therapy"[Mesh] OR "Psychotherapy, Psychodynamic"[Mesh] OR psychodynamic*[tiab]** Sort by: **Relevance**	20177
#5	Search **#2 AND #3**	21435
#4	Search **Depressive disorder[Mesh] OR depression[Mesh] OR ((depress*[tiab] OR melancholia*[tiab] OR dysphoria*[tiab] OR dysthymi*[tiab] OR "seasonal affective disorder"[tiab]) NOT medline[sb])**	223737
#3	Search **dynamic*[tiab] OR STPP[tiab] OR BDT[tiab] OR DIT[tiab] OR insight*[tiab] OR interpretive[tiab] OR interpretative[tiab] OR analytic*[tiab] OR psychoanalytic*[tiab]**	1073217
#2	Search **("Psychotherapy"[Mesh:noexp] OR "Animal Assisted Therapy"[Mesh] OR "Art Therapy"[Mesh] OR "Bibliotherapy"[Mesh] OR "Psychotherapy, Group"[Mesh] OR "Psychotherapy, Brief"[Mesh] OR "Psychotherapy, Multiple"[Mesh] OR "Counseling"[Mesh:NoExp] OR "Directive Counseling"[Mesh:NoExp] OR ((psychotherap*[tiab] OR therap*[tiab] OR counseling[tiab]) NOT medline[sb]))**	380901

Second, in order to identify relevant studies from the so-called 'grey literature', we will search GLIN, a Dutch electronic database for grey literature, and UMI database ProQuest for digital dissertations. Third, a prospective trial register will be searched for unpublished ongoing research (http://www.controlled-trials.com). The grey literature and prospective trial register searches will be conducted using the search strategy described above. Fourth, we will search an Internet database of controlled and comparative outcome studies on psychological treatments of depression (http://www.psychotherapyrcts.org[19]) for studies examining STPP. Fifth, reviews and meta-analyses concerning the efficacy of psychodynamic treatments for depression or for psychiatric disorders in general retrieved from the first search method will be screened for relevant references not located by means of the other search methods. Sixth, we will contact an email list of researchers in the field of psychodynamic therapy to ask for ongoing or unpublished studies.

Selection of studies

We will include studies if they report (a) outcomes on standardized measures of (b) depressed (c) adult patients (d) receiving STPP. Participants are considered depressed if they meet specified criteria for major depressive disorder or another mood disorder, or if they present an elevated score on a standardized measure of depression. Participants need to be at least 18 years old, and studies concerning older adults (mean age >55) will be included as well. We will include studies in which STPP (a) is based on psychoanalytic theories and practices, (b) is time-limited from the onset (i.e. not a therapy that is brief only in retrospect), and (c) applies verbal techniques (e.g., therapies

applying art as expression form are not considered STPP). Studies need to include at least 10 subjects. Case studies will therefore be excluded. We will also include naturalistic studies with a heterogeneous study sample, if these studies include more than 10 participants diagnosed as depressed, as these subgroups also meet the inclusion criteria specified previously. For these studies, the authors will be contacted with a request for subgroup data.

The screening process will consist of three phases. At first, the selection criteria will be applied to the citations generated from the searches independently by two raters. Disagreements will be discussed and resolved by consensus. Unless they can be definitely excluded, titles identified as potentially relevant will be requested in full text. During the second screening phase, two independent raters will apply the selection criteria to the full-text papers. Disagreements will be discussed and resolved by consensus. During the third phase, two expert STPP raters will confirm that the included papers meet criteria for STPP. Again, disagreements will be discussed and resolved by consensus. When disagreements cannot be resolved in this way, a third rater will be consulted.

Data collection

Authors of the included studies will be contacted and invited to contribute the participant-level data of their studies. Researchers who share their data will be offered co-authorship for all publications that are based on their study's data (group-authorship), given that they meet standard criteria for authorship of scientific publications according to internationally accepted criteria (www.icmje.org). In addition,

the collected data will be made available to investigators who contribute data to examine other research questions in the combined dataset. This strategy has been used in previous IPD meta-analyses concerning depression treatments[20-21] and has been successful in convincing researchers to share their data.

Contact details of all first authors will be collected from the relevant publications, or if not reported there, through Internet searches or personal contacts with other researchers. First authors will be contacted by email with a letter of invitation outlining the project's goals and asking if they would be willing to collaborate by sharing the participant-level data of their trial. If an author does not respond after three weeks, a second and third email will be sent. In case of non-response to email, a letter will be sent (again with three attempts). If still no response is received, we will try to contact the author by telephone. If all these attempts fail, the last, second, third, fourth, etc. author of the study (in this order) will be contacted in the same way. If none of the authors respond to these efforts, other ways will be sought to contact one of the authors (e.g., via colleagues or anyone who might know them). Study data will be considered unavailable only if all these attempts fail, or in the event that an author indicates that the participant-level data have not been retained or declines sharing these data.

If the author is willing and able to share the individual participant data of his/her trial, both parties will sign a data sharing agreement. The author will then transfer the participant-level dataset, including all potential predictors and moderators assessed before the start of treatment, as well as all outcome variables assessed during and after treatment, both in the STPP condition as well as in any comparison condition included in the study. The author will anonymize the data, so that the dataset is transferred

without containing personal information that can lead back to individuals. Data can be submitted to the project in any format, and will then be converted to Stata.

Data integrity check

After the dataset has been transferred, the file will be checked to examine whether the data received match the data reported in the publication. For all treatment conditions included in the study, sample size, number of females, mean age, observed mean pre-treatment depression scores, observed mean post-treatment score for the primary depression outcome, and the number of missing cases for the latter will be calculated from the dataset received and checked against the published article for this purpose. Discrepancies will be resolved with the authors. In addition, the data will be checked for invalid, out-of-range, or inconsistent items. Furthermore, we will check the integrity of the randomization for randomized studies by inspecting the balance of the potential predictor/moderator variables across treatment arms.

For each study, we will list all predictor/moderator variables that were assessed, as well as all outcome variables, intermediate, and follow-up assessments. We will also extract multiple STPP characteristics and study design characteristics (for an overview see[12]) as well as study validity criteria according to the Cochrane risk of bias assessment tool[22].

After checking the data, the datasets will be standardized. For this purpose, a copy of each trial's raw data file will be recoded into a data file that matches the IPD meta-analysis database in terms of variables. Next, the individual study data files will be concatenated in one database structured by study and individual participant ID. After all

data files have been recoded and entered, the data for each study will be checked with the original data file received for accuracy. A codebook document will be made that includes the coding of the individual studies as well as the coding of the combined study database. Coding for the database will be finalized when all data have been received from the study authors.

Measures

The primary outcome for this study is treatment efficacy as assessed by a continuous depression outcome measure at post-treatment. We have chosen depressive symptom status as the main outcome for this study as we consider this to be the primary target of STPP for depression. We chose continuous symptom level as the primary outcome, because we expect that the increased variance relative to dichotomous outcomes might facilitate the search for predictors and moderators. We have chosen post-treatment assessment as the primary end-point as it is difficult to control additional treatment in the follow-up period in psychotherapy efficacy studies (e.g.,[23]).

For each trial, we will identify the primary continuous depression outcome as defined by the study authors. All instruments explicitly measuring depression qualify in this regard. Different depression measures have probably been used and, therefore, we will standardize the depression outcomes by converting the depression scores into Z-scores. Sensitivity analyses will be conducted using unstandardized scores for each depression measure that is assessed in the majority of studies included in the meta-analysis (e.g., Hamilton Depression Rating Scale[24], Beck Depression Inventory[25]).

The secondary outcomes for this study are dichotomous depression outcomes for 1) response (a 50% reduction in symptoms from pre- to post-treatment), and 2) remission (maximum absolute post-treatment scores reflecting normalization). In addition, outcome measures other than depression will be collected (e.g., anxiety symptoms, quality of life, interpersonal functioning). These can be considered tertiary outcomes.

Potential predictors and moderators include socio-demographic variables (e.g., gender, age, education level, marital status, employment status, ethnicity), clinical variables (e.g., number of previous depressive episodes, previous exposure to treatment, comorbid Axis I and II psychopathology, global assessment of functioning), and psychological patient characteristics (e.g., personality organization, attachment, interpersonal styles, childhood maltreatment). These are likely assessed differently in individual studies and will be standardized as well, for instance by converting scores into Z-scores for continuous variables or by recoding variables into similar categories for categorical variables. In the latter case, we will consult study authors to confirm correctness of the recoding.

Missing data

All datasets received that contain individual participant data, at least one relevant outcome measure, and at least one predictor/moderator variable will be considered for quantitative synthesis. We will examine the possibility of complete-case analyses by evaluating the extent of missing data as well as the possible reasons for missing data, and by comparing patients with complete data to patients with missing data. We will also assess whether the missing data can be considered missing at random.[26] If

complete-case analysis is not justifiable and data can be considered missing at random, we will impute missing data using multiple imputation, which is currently considered to be the most sophisticated method for handling missing data.[27]

We will generate one imputed dataset for each percent of missing data (e.g., when 30% of the data is missing, we will create 30 imputed datasets). We will impute missing data by means of hierarchical imputation with fully conditional specification (FCS-GLM),[28] which allows for preserving the heterogeneity across studies, non-normal distributions of variables, and imputing systematically missing variables. FCS-GLM has shown to be a reliable procedure with advantageous properties for IPD meta-analyses with limited numbers of studies or studies with small sample sizes.[29] FCS-GLM will be conducted in R. To ensure congeniality, imputation will be based on all variables that will be included in the meta-analysis model including their interactions as well as any variables that were identified to be predictive of missing values.[29] If multiple imputation is pursued, we will conduct sensitivity analyses restricted to complete cases and compare the results. We will not pursue efforts to combine IPD with aggregate data from studies for which no IPD is available,[30] since the requisite treatment-covariate interactions are seldom reported in publications.

Data-analysis

We will conduct IPD meta-analyses according to the one-stage approach, because that accounts for the correlation amongst model parameters when modelling interactions, offers the highest degree of flexibility for making the necessary assumptions when detecting treatment-covariate interactions,[31] and provides a more exact likelihood in

the case of small studies.[32] We will conduct IPD meta-analyses using mixed models with restricted maximum likelihood to estimate between-study heterogeneity, which is recommended when there are few studies in the meta-analysis or studies have small sample sizes.[33] Analyses will be conducted in Stata 'mixed'. We will apply the Kenward-Roger denominator-degrees-of-freedom adjustment for confidence intervals,[34] because it more adequately accounts for uncertainty than the standard Dersimonian-Laird estimator when the number of studies is small or when heterogeneity is present.[35] To account for clustering of patients within studies and to preserve randomization, we will include a random intercept for study and a random slope for baseline depression. We assume that these random effects will be normally distributed and this assumption will be assessed. We will assess heterogeneity by examining the standard deviation of the predictor or moderator parameter estimates.

Separate analyses will be conducted for the identification of predictors and the identification of moderators of STPP efficacy. With regard to predictors, IPD from STPP conditions across all studies will be combined, regardless of study type (randomized controlled study, non-random comparative study, naturalistic study). For each of the potential predictors, a model will be estimated with baseline depression and the predictor's main effect. A random slope will be added to the predictor to examine if this results in a model improvement. If so, this predictor variable will be included with a random slope in subsequent analyses. Next, all predictors will be modeled simultaneously. Backward selection based on p-value will be conducted until a final prediction model is obtained consisting of statistical significant predictors only. This prediction model will be validated in a held-out sample of the data.

With regard to moderators, analyses will be conducted separately for each comparison (e.g., STPP versus control conditions, STPP versus other psychotherapy, STPP versus antidepressant medication). These analyses will only include IPD from randomized studies. For each of the potential moderators, a model will be estimated with baseline depression as well as the moderator's main effect and interaction with treatment. Next, to examine ecological bias, within-study and across-study interaction effects will be separated.[30] If within-study and across-study interactions differ, ecological bias may be at play, and only the within-trial interaction will be interpreted in subsequent analyses. Finally, all significant treatment-covariate interactions, their main effects, and higher order interactions will be modeled simultaneously. The resulting prediction model will be validated in a held-out sample of the data.

A number of sensitivity analyses will be conducted to examine the robustness of the findings. To examine the impact of study quality, we will conduct sensitivity analyses including only studies that score high on all quality criteria. In addition, we will conduct analyses in which we add the risk of bias items as covariates to the mixed effects models, centered at a value indicating freedom of bias.[36] We will also conduct sensitivity analyses to control for the effects of additional non-study treatment during the trial and in the follow-up period by adding collected data in this regard as covariates to the mixed effects models. Finally, we will examine the impact of STPP delivery mode (individual versus group STPP) by adding this variable to the mixed effects models too.

Furthermore, to examine possible data availability bias, t-tests and chi-square analyses will be conducted comparing the included studies with studies for which no participant-level data was obtained with regard to the extracted study characteristics.

Conventional meta-analysis techniques will be utilized to examine differences in effect sizes between studies that contributed data and studies that did not. We will assess potential publication bias by assessing asymmetry in contour enhanced funnel plots for meta-analyses including 10 or more trials, as is recommended by Sterne and colleagues.[37] The confidence in the cumulative body of evidence will be assessed according to GRADE.

In addition, we will conduct explorative analyses using tree-based statistical learning. More specifically, we will use the generalized linear mixed effects regression trees algorithm (glmertree[38]) in R to detect predictors and moderators of continuous and binary treatment outcomes. These analyses offer several advantages over more traditional mixed-effects modeling approaches, as they allow for the detection of non-linear and higher-level interactions, allow for specifying a large number of potential predictor and moderator variables and involve less stringent assumptions about the distribution of the data. Furthermore, the result of applying glmertree consists of a decision tree that graphically depicts the effects of the relevant predictor and moderator variables. Such a tree can easily be interpreted, and applied in clinical decision-making. However, it should be noted that such tree-based analyses are exploratory by nature. We will assess the expected predictive accuracy on new data using *k*-cross validation[39] and the stability of the resulting decision trees using subsampling methods.[40] The glmertree analyses will be performed using observed, non-imputed data only, as it is currently unclear how to best specify the model for generating imputed data in tree-based analyses for clustered data.

ETHICS AND DISSEMINATION

IRB approval was not required for this project. IRB approval may be required for the investigators who share their primary data depending on their institution's policies. It is the responsibility of the investigators to obtain IRB approval if their institution's policies require them to do so. We intend to submit reports of the outcomes of this study for publication to international peer-reviewed journals in the fields of psychiatry or clinical psychology. We also intend to present the findings of this study at international scientific conferences aimed at psychotherapy researchers and clinicians.

DISCUSSION

We described the study protocol of a systematic review and meta-analysis of IPD to examine predictors and moderators of STPP efficacy for depression. The goal of this study is to collect the participant-level data of all studies examining the efficacy of STPP for depression identified by a thorough literature search, and to combine these datasets in order to conduct IPD meta-analyses. The proposed study design allows for the examination of predictors and moderators of STPP efficacy with increased statistical power and can thus help to show which subsets of depressed patients specifically benefit from therapies based on psychoanalytic principles.

Clinical and scientific relevance

STPPs are underrepresented in current treatment guidelines for depressive disorders, in contrast to how commonly they are utilized in clinical practice. Further high-quality

research that extends and disseminates knowledge about the effectiveness of STPP is therefore called for. Research showing whether subsets of depressed patients can specifically benefit from this therapy modality, especially when compared to other treatments, is particularly needed. Knowledge of such moderators can have important implications for clinical practice, as it can be used to guide treatment selection and increase the efficiency of treatments for depression by helping patients and clinicians to make an informed choice concerning the best treatment option for a given patient.

Little is known about patient characteristics associated with STPP efficacy, because clinical trials often have relatively small sample sizes and limited statistical power to examine predictors and moderators of change. Moreover, prediction and moderation analyses in conventional meta-analyses are often based on study-level aggregates and are, therefore, prone to ecological bias. By means of individual participant data meta-analyses these critical limitations can be overcome. IPD meta-analyses have been utilized more frequently in the medical field, but are newer in the field of psychiatry and clinical psychology.[41] Although IPD meta-analyses have now been used to examine single moderators of CBT and pharmacotherapy efficacy for depression,[20-21] to date no IPD meta-analysis has been conducted concerning STPP.

Strengths and limitations

Individual participant data meta-analysis has several advantages over conventional meta-analysis, including increased statistical power to examine predictors and moderators.[16] In addition, by collecting the primary data, access to predictor or moderator variables that might not have been reported in the published articles is

gained; increasing the chance that aggregation of these variables across studies is possible. Other advantages of individual participant data meta-analysis over conventional meta-analysis include the possibility to 1) account for missing data at the individual participant level, so that for instance intention-to-treat analyses can be conducted even though the original study reported completers-only analyses, 2) use the same statistical methods for imputing missing data and for conducting statistical analyses, thereby facilitating standardization across studies, 3) standardize outcomes across studies, for instance by using equal cut-off points on a depression outcome measure when the primary studies used different cut-offs, and 4) verify the results presented in the original studies, also by means of more sophisticated statistical techniques that were not available at time of publication in the case of older studies.[42]

IPD meta-analyses involve collection of original data from all the relevant trials worldwide that can be accessed. These data need to be prepared and checked before being included in the meta-analysis, and complex decisions on the data sometimes need to be made in order to ensure the accuracy of the outcomes. Therefore, it takes more time and resources to conduct an IPD meta-analysis than to conduct a conventional meta-analysis based solely on results extracted from published trial reports.[42] However, the IPD approach can improve the quality of both the data and the analyses, and so the reliability of the results. Therefore, it is considered the 'gold standard' of meta-analysis.[17]

IPD meta-analyses can also have a number of limitations. First, although IPD meta-analyses are generally considered the most reliable approach to evidence synthesis,[17] this does not mean that they are bias-free and selection bias, publication

bias, and data availability bias need to be considered.[43] We do so by performing a systematic literature search that also aims to identify grey literature and unpublished work, and by testing for differences between studies for which IPD was and was not obtained. Second, IPD meta-analyses rely on variables previously assessed in individual studies and available across multiple trials. For this reason, it is possible that not all variables of interest can be examined as potential predictors or moderators. Third, and related, it is necessary to standardize predictor/moderator variables for the analyses, but doing so might involve recoding and possibly omitting important information for some variables. Fourth, although combining multiple trials reduces the possibility that predictors/moderators identified are chance findings in single study samples, generalizability of the findings might still be limited to patients who volunteer to participate in scientific outcome research.

Conclusion

We described the study protocol for a systematic review and meta-analysis of IPD aimed at examining if certain subgroups of depressed patients can benefit specifically from STPP. We will collect the participant-level data of all studies examining the efficacy of STPP for depression identified by a thorough literature search. We will combine these datasets and conduct IPD meta-analyses to identify predictors and moderators of STPP efficacy. Knowledge of such predictors and moderators can have important implications for clinical practice, as they can, respectively, inform expectations of treatment efficacy for individual patients, and help patients and clinicians to make an informed choice concerning the best treatment option for a given patient.

AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the study design or the acquisition of individual participant data. ED, EW, and PC drafted the manuscript. All other authors revised it critically for important intellectual content and approved the final version of this manuscript. ED is the guarantor of the review.

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COMPETING INTERESTS STATEMENT

AAA practices and provides training in methods of STPP and receives royalties from a book he wrote on STPP. JPB has given talks on STPP at workshops and conferences for which organizers often have not paid for travel and accommodations. JPB and JJMD receive royalties from books on STPP they have co-authored. JMT has given talks on STPP at workshops and conferences for which organizers have paid for travel and accommodations. PF declares being Chief Executive of the Anna Freud Centre (UK). He teaches mentalization-based treatment trainings and dynamic-interpersonal therapy trainings in the UK and internationally. He is the Co-PI on The IMPACT Study – The Effectiveness of Psychological Treatment for Depressed Adolescents, and Consultant to

the Child and Family Program at the Menninger Department of Psychiatry and Behavioural Sciences at Baylor College of Medicine, Houston, TX, USA. PF also receives royalties from books on interpersonal psychotherapy which he has co-authored with others. HLV and SCMdM are trainers and registered supervisors of short-term psychodynamic supportive psychotherapy. They also receive royalties from books on STPP they have co-authored. SDH reports no financial conflicts, but acknowledges an intellectual passion for the cognitive and behavioral interventions for depression. ED, MBCG, MF, JWRT, EW, and PC declare that they have no known conflicts of interest.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	70
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-42
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	503-507
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	161-162
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	510-513
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	511
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	511-513
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	99-145
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	☒	☐	146-154

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	196-210, 179
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	165-194
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	170-181, Table 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	265-278
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	211-220
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	222-264
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	246-250, 265-269
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	280-300
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	266-269, 377-380
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	313-315
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	337-375
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	☒	☐	376--409

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	376-392
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	392-393

BMJ Open

Which patients benefit specifically from short-term psychodynamic psychotherapy (STPP) for depression? Study protocol of a systematic review and meta-analysis of individual participant data.

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Clinical trials < THERAPEUTICS

Which patients benefit specifically from short-term psychodynamic psychotherapy (STPP) for depression? Study protocol of a systematic review and meta-analysis of individual participant data.

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ABSTRACT

Introduction: Short-term psychodynamic psychotherapy (STPP) is an empirically supported treatment that is often used to treat depression. However, it is largely unclear if certain subgroups of depressed patients can benefit specifically from this treatment method. We describe the protocol for a systematic review and meta-analysis of individual participant data (IPD) aimed at identifying predictors and moderators of STPP for depression efficacy.

Method and analysis: We will conduct a systematic literature search in multiple bibliographic databases (PubMed, PsycINFO, Embase.com, Web of Science, and Cochrane's Central Register of Controlled Trials), 'grey literature' databases (GLIN and UMI ProQuest), and a prospective trial register (http://www.controlled-trials.com). We will include studies reporting (a) outcomes on standardized measures of (b) depressed (c) adult patients (d) receiving STPP. We will next invite the authors of these studies to share the participant-level data of their trials and combine these data to conduct IPD meta-analyses. The primary outcome for this study is post-treatment efficacy as assessed by a continuous depression measure. Potential predictors and moderators include all socio-demographic variables, clinical variables, and psychological patient characteristics that are measured before the start of treatment and are assessed consistently across studies. One-stage IPD meta-analyses will be conducted using mixed effects models.

Ethics and dissemination: IRB approval is not required for this study. We intend to submit reports of the outcomes of this study for publication to international peer-

reviewed journals in the fields of psychiatry or clinical psychology. We also intend to present the outcomes at international scientific conferences aimed at psychotherapy researchers and clinicians. The findings of this study can have important clinical implications, as they can inform expectations of STPP efficacy for individual patients, and help to make an informed choice concerning the best treatment option for a given patient.

Registration: PROSPERO (registration number: CRD42017056029).

Word count abstract: 294

Keywords: depression, short-term psychodynamic psychotherapy, predictors, moderators, individual participant data meta-analysis.

Strengths and limitations of this study

- This is the first study that systematically assesses patient characteristics associated with STPP for depression efficacy.
- IPD meta-analysis allows for the examination of predictors and moderators by maximizing statistical power while protecting against ecological bias that presents problems when using conventional meta-analysis techniques.
- The findings of this study can have important clinical implications, as they can inform expectations of STPP efficacy for individual patients, and help to make an informed choice concerning the best treatment option for a given patient.

- IPD meta-analyses rely on variables previously assessed in individual studies and available across multiple trials. Thus, it is possible that not all variables of interest can be examined as potential predictors or moderators.

INTRODUCTION

Depression is a highly prevalent and disabling disorder associated with major personal and societal costs.[1] Affecting more than 300 million people worldwide, depression is ranked as the single largest contributor to global disability by the World Health Organization.[2] Given the tremendous burden of disease, there is a great need for effective and efficient treatments for depression. Antidepressant medications and different psychological therapies constitute the predominant treatments for depressive disorders.[3] Concerning psychological treatments, there is a clinical tradition of short-term psychodynamic psychotherapies (STPPs) being used to treat depression. STPP is an empirically supported treatment for depression.[4] However, it is unlikely that any treatment will work for equally well for all depressed patients[5] and it remains largely unclear if certain subgroups of patients can benefit specifically from STPP.

Two types of information are relevant to this question: predictors and moderators. Predictors (or prognostic factors) predict outcome to a given treatment and can be used to determine which patients are more likely to respond to STPP relative to other patients. For instance, if age were found to be a positive predictor of STPP efficacy, this might indicate that older patients would be more likely to benefit from STPP than younger patients. Predictors can inform expectations of STPP efficacy, but are of little use in deciding which treatment to select. On the other hand, moderators (or prescriptive factors) can detect different patterns of outcomes between different treatments for different types of patients and provide a basis for choosing the best treatment for a given patient.[6] For instance, if age were found to be a moderator of STPP efficacy versus antidepressant medication, this might indicate that older patients

might benefit more from STPP than from medication, while younger patients might benefit more from medication than from STPP.

Some preliminary empirical findings concerning predictors and moderators of STPP efficacy for depression do exist. With regard to predictors, meta-regression analyses alongside a 'conventional' meta-analysis (based on results extracted from publications[4]) showed that mean pre-treatment depression scores were positively associated with pre- to post-treatment depression effect size, although this effect might not be specific to STPP[7]. With regard to moderators, Driessen et al.[8] found STPP to be more efficacious than CBT among depressed patients who showed low baseline comorbid anxiety levels. Furthermore, Barber et al.[9] reported that STPP was more efficacious than medication or placebo for ethnic minority males. However, a systematic assessment of which patient characteristics are associated with STPP efficacy is currently lacking.

The main reason why predictors and moderators of STPP for depression have not yet been examined thoroughly is lack of statistical power in individual clinical trials due to relatively small sample sizes. Prediction and moderation analyses can also be conducted alongside conventional meta-analyses. However, since these analyses are usually based on study-level characteristics, they are prone to ecological bias, such that the association between the study-level characteristics may not be representative of the true relationships in the data at the individual level.[10] Thus, current research methods (clinical trials and conventional meta-analyses) have been insufficient to answer the question as to whether certain subgroups of patients can benefit specifically from STPP for depression.

Individual participant data (IPD) meta-analysis is a relatively new technique to examine treatment effects by combining participant-level data of multiple trials. IPD meta-analysis uses the same basic approach as any other well-conducted systematic review and meta-analysis. However, it involves collection of the original data from as many of the relevant trials worldwide as can be accessed. IPD meta-analysis has several advantages over conventional meta-analysis, including increased statistical power to examine predictors and moderators of treatment efficacy.[11] Furthermore, because predictors and moderators are studied at patient-level, ecological bias can be circumvented. For these reasons, IPD meta-analysis is currently considered the 'gold standard' in evidence synthesis[12].

We describe the study protocol for a systematic review and IPD meta-analysis concerning predictors and moderators of STPP for depression efficacy. The aim of this project is to examine which depressed patients benefit specifically from STPP in terms of depressive symptom reduction when compared to other patients (predictors), and which patients benefit specifically from STPP when compared to no-treatment conditions, other psychotherapies, and antidepressant medication (moderators). The goal of this study is to collect the participant-level data of trials examining the efficacy of STPP for depression identified by a systematic literature search, and to combine these datasets in order to conduct IPD meta-analyses.

METHODS

Design

This study is a systematic review and meta-analysis of individual participant data that is registered in the PROSPERO International prospective register of systematic reviews (registration number: CRD42017056029). Important protocol amendments will be documented in this register too. The project started December 1st, 2016 and is expected to be completed February 28th, 2019.

Search strategy

We will use an extensive search strategy including six different search methods in order to retrieve as many relevant studies as possible. These searches have already been performed in 2007 and 2014 for two previous conventional meta-analyses concerning the efficacy of STPP for depression[4,13] and will be updated in 2017.

First, we will systematically search the bibliographic databases PubMed, PsycINFO (via EBSCO), Embase.com, Web of Science (via Elsevier), and Cochrane's Central Register of Controlled Trials (via Wiley). Search terms will include a wide range of synonyms, both in index terms and free-text words, for 1) psychodynamic psychotherapy (e.g., psychotherapy, psychoanalytic), 2) therapy (e.g., psychotherapy), 3) psychodynamic (e.g., dynamic*), and 4) depression (e.g., depressive disorder). These four sets of search terms will be combined as follows: (#1 OR (#2 AND #3)) AND #4. The exact terms for the search in PubMed are presented in Table 1. Complete

search terms for all electronic databases are available on request from the corresponding author. No language or date restrictions will be applied in the searches.

Table 1. PubMed search strategy

Search	PubMed Query 19-06-2017	Items found
#1	Search **"Psychoanalytic Therapy"[Mesh] OR "Psychotherapy, Psychodynamic"[Mesh] OR psychodynamic*[tiab]** Sort by: **Relevance**	20177
#2	Search **("Psychotherapy"[Mesh:noexp] OR "Animal Assisted Therapy"[Mesh] OR "Art Therapy"[Mesh] OR "Bibliotherapy"[Mesh] OR "Psychotherapy, Group"[Mesh] OR "Psychotherapy, Brief"[Mesh] OR "Psychotherapy, Multiple"[Mesh] OR "Counseling"[Mesh:NoExp] OR "Directive Counseling"[Mesh:NoExp] OR ((psychotherap*[tiab] OR therap*[tiab] OR counseling[tiab]) NOT medline[sb]))**	380901
#3	Search **dynamic*[tiab] OR STPP[tiab] OR BDT[tiab] OR DIT[tiab] OR insight*[tiab] OR interpretive[tiab] OR interpretative[tiab] OR analytic*[tiab] OR psychoanalytic*[tiab]**	1073217
#4	Search **#2 AND #3**	21435
#5	Search **#1 OR #4**	39841
#6	Search **Depressive disorder[Mesh] OR depression[Mesh] OR ((depress*[tiab] OR melancholia*[tiab] OR dysphoria*[tiab] OR dysthymi*[tiab] OR "seasonal affective disorder"[tiab]) NOT medline[sb])**	223737
#7	Search **#5 AND #6**	2350
#8	Search **#7 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type])**	2285

Second, in order to identify relevant studies from the so-called 'grey literature', we will search GLIN, a Dutch electronic database for grey literature, and UMI database ProQuest for digital dissertations. Third, a prospective trial register will be searched for unpublished ongoing research (http://www.controlled-trials.com). The grey literature and prospective trial register searches will be conducted using the search strategy described above. Fourth, we will search an Internet database of controlled and comparative outcome studies on psychological treatments of depression (http://www.psychotherapyrcts.org[14]) for studies examining STPP. Fifth, reviews and meta-analyses concerning the efficacy of psychodynamic treatments for depression or for psychiatric disorders in general retrieved from the first search method will be screened for relevant references not located by means of the other search methods. Sixth, we will contact an email list of researchers in the field of psychodynamic therapy to ask for ongoing or unpublished studies.

Selection of studies

We will include studies if they report (a) outcomes on standardized measures of (b) depressed (c) adult patients (d) receiving STPP. Participants are considered depressed if they meet specified criteria for major depressive disorder or another mood disorder as assessed by means of a semi-structured interview or clinicians' assessment, or if they present an elevated score above the 'no depression' cut-off on a standardized measure of depression. Participants need to be at least 18 years old, and studies concerning older adults (mean age >55) will be included as well. We will include studies in which STPP (a) is based on psychoanalytic theories and practices, (b) is time-limited from the

onset (i.e. not a therapy that is brief only in retrospect), and (c) applies verbal techniques (e.g., therapies applying art as expression form are not considered STPP). Studies need to include at least 10 subjects. Case studies will therefore be excluded. We will also include naturalistic studies with a heterogeneous study sample, if these studies include more than 10 participants diagnosed as depressed, as these subgroups also meet the inclusion criteria specified previously. For these studies, the authors will be contacted with a request for subgroup data.

The screening process will consist of three phases. At first, the selection criteria will be applied to the citations generated from the searches independently by two raters. Disagreements will be discussed and resolved by consensus. Unless they can be definitely excluded, titles identified as potentially relevant will be requested in full text. During the second screening phase, two independent raters will apply the selection criteria to the full-text papers. Disagreements will be discussed and resolved by consensus. During the third phase, two expert STPP raters will confirm that the included papers meet criteria for STPP. Again, disagreements will be discussed and resolved by consensus. When disagreements cannot be resolved in this way, a third rater will be consulted.

Data collection

Authors of the included studies will be contacted and invited to contribute the participant-level data of their studies. Researchers who share their data will be offered co-authorship for all publications that are based on their study's data (group-authorship), given that they meet standard criteria for authorship of scientific

publications according to internationally accepted criteria (www.icmje.org). In addition, the collected data will be made available to investigators who contribute data to examine other research questions in the combined dataset. This strategy has been used in previous IPD meta-analyses concerning depression treatments[15-16] and has been successful in convincing researchers to share their data.

Contact details of all first authors will be collected from the relevant publications, or if not reported there, through Internet searches or personal contacts with other researchers. First authors will be contacted by email with a letter of invitation outlining the project's goals and asking if they would be willing to collaborate by sharing the participant-level data of their trial. If an author does not respond after three weeks, a second and third email will be sent. In case of non-response to email, a letter will be sent (again with three attempts). If still no response is received, we will try to contact the author by telephone. If all these attempts fail, the last, second, third, fourth, etc. author of the study (in this order) will be contacted in the same way. If none of the authors respond to these efforts, other ways will be sought to contact one of the authors (e.g., via colleagues or anyone who might know them). Study data will be considered unavailable only if all these attempts fail, or in the event that an author indicates that the participant-level data have not been retained or declines sharing these data.

If the author is willing and able to share the individual participant data of his/her trial, both parties will sign a data sharing agreement. The author will then transfer the participant-level dataset, including all potential predictors and moderators assessed before the start of treatment, as well as all outcome variables assessed during and after treatment, both in the STPP condition as well as in any comparison condition included

in the study. The author will anonymize the data, so that the dataset is transferred without containing personal information that can lead back to individuals. Data can be submitted to the project in any format, and will then be converted to Stata.

Data integrity check

After the dataset has been transferred, the file will be checked to examine whether the data received match the data reported in the publication. For all treatment conditions included in the study, sample size, number of females, mean age, observed mean pre-treatment depression scores, observed mean post-treatment score for the primary depression outcome, and the number of missing cases for the latter will be calculated from the dataset received and checked against the published article for this purpose. Discrepancies will be resolved with the authors. In addition, the data will be checked for invalid, out-of-range, or inconsistent items. Furthermore, we will check the integrity of the randomization for randomized studies by inspecting the balance of the potential predictor/moderator variables across treatment arms.

For each study, we will list all predictor/moderator variables that were assessed, as well as all outcome variables, intermediate, and follow-up assessments. We will also extract multiple STPP characteristics (e.g., number of sessions, treatment format, STPP mode) and study design characteristics (e.g., therapist training, treatment integrity check, use of a treatment manual; for a complete overview see[4]). Finally, we will extract study validity criteria according to the Cochrane risk of bias assessment tool[17].

After checking the data, the datasets will be standardized. For this purpose, a copy of each trial's raw data file will be recoded into a data file that matches the IPD meta-

analysis database in terms of variables. Next, the individual study data files will be concatenated in one database structured by study and individual participant ID. After all data files have been recoded and entered, the data for each study will be checked with the original data file received for accuracy. A codebook document will be made that includes the coding of the individual studies as well as the coding of the combined study database. Coding for the database will be finalized when all data have been received from the study authors.

Measures

The primary outcome for this study is treatment efficacy as assessed by a continuous depression outcome measure at post-treatment. We have chosen depressive symptom status as the main outcome for this study as we consider this to be the primary target of STPP for depression. We chose continuous symptom level as the primary outcome, because we expect that the increased variance relative to dichotomous outcomes might facilitate the search for predictors and moderators. We have chosen post-treatment assessment as the primary end-point as it is difficult to control additional treatment in the follow-up period in psychotherapy efficacy studies (e.g.,[18]).

For each trial, we will identify the primary continuous depression outcome as defined by the study authors. All instruments explicitly measuring depression qualify in this regard. Different depression measures have probably been used and, therefore, we will standardize the depression outcomes by converting the depression scores into Z-scores. Sensitivity analyses will be conducted using unstandardized scores for each

depression measure that is assessed in the majority of studies included in the meta-analysis (e.g., Hamilton Depression Rating Scale[19], Beck Depression Inventory[20]).

The secondary outcomes for this study are dichotomous depression outcomes for 1) response (a 50% reduction in symptoms from pre- to post-treatment), and 2) remission (maximum absolute post-treatment scores reflecting normalization). In addition, outcome measures other than depression will be collected (e.g., anxiety symptoms, quality of life, interpersonal functioning). These can be considered tertiary outcomes.

Potential predictors and moderators include socio-demographic variables (e.g., gender, age, education level, marital status, employment status, ethnicity), clinical variables (e.g., number of previous depressive episodes, previous exposure to treatment, comorbid Axis I and II psychopathology, global assessment of functioning), and psychological patient characteristics (e.g., personality organization, attachment, interpersonal styles, childhood maltreatment, alexithymia). These are likely assessed differently in individual studies and will be standardized as well, for instance by converting scores into Z-scores for continuous variables or by recoding variables into similar categories for categorical variables. In the latter case, we will consult study authors to confirm correctness of the recoding.

Missing data

All datasets received that contain individual participant data, at least one relevant outcome measure, and at least one predictor/moderator variable will be considered for quantitative synthesis. We will examine the possibility of complete-case analyses by evaluating the extent of missing data as well as the possible reasons for missing data,

and by comparing patients with complete data to patients with missing data. We will also assess whether the missing data can be considered missing at random.[21] If complete-case analysis is not justifiable and data can be considered missing at random, we will impute missing data using multiple imputation, which is currently considered to be the most sophisticated method for handling missing data.[22]

We will generate one imputed dataset for each percent of missing data (e.g., when 30% of the data is missing, we will create 30 imputed datasets). We will impute missing data by means of hierarchical imputation with fully conditional specification (FCS-GLM),[23] which allows for preserving the heterogeneity across studies, non-normal distributions of variables, and imputing systematically missing variables. FCS-GLM has shown to be a reliable procedure with advantageous properties for IPD meta-analyses with limited numbers of studies or studies with small sample sizes.[24] FCS-GLM will be conducted in R. To ensure congeniality, imputation will be based on all variables that will be included in the meta-analysis model including their interactions as well as any variables that were identified to be predictive of missing values.[24] If multiple imputation is pursued, we will conduct sensitivity analyses restricted to complete cases and compare the results. We will not pursue efforts to combine IPD with aggregate data from studies for which no IPD is available,[25] since the requisite treatment-covariate interactions are seldom reported in publications.

Data-analysis

We will conduct IPD meta-analyses according to the one-stage approach, because that accounts for the correlation amongst model parameters when modelling interactions,

offers the highest degree of flexibility for making the necessary assumptions when detecting treatment-covariate interactions,[26] and provides a more exact likelihood in the case of small studies.[27] We will conduct IPD meta-analyses using mixed models with restricted maximum likelihood to estimate between-study heterogeneity, which is recommended when there are few studies in the meta-analysis or studies have small sample sizes.[28] Analyses will be conducted in Stata 'mixed'. We will apply the Kenward-Roger denominator-degrees-of-freedom adjustment for confidence intervals,[29] because it more adequately accounts for uncertainty than the standard Dersimonian-Laird estimator when the number of studies is small or when heterogeneity is present.[30] To account for clustering of patients within studies and to preserve randomization, we will include a random intercept for study and a random slope for baseline depression. We assume that these random effects will be normally distributed and this assumption will be assessed. We will assess heterogeneity by examining the standard deviation of the predictor or moderator parameter estimates.

Separate analyses will be conducted for the identification of predictors and the identification of moderators of STPP efficacy. With regard to predictors, IPD from STPP conditions across all studies will be combined, regardless of study type (randomized controlled study, non-random comparative study, naturalistic study). For each of the potential predictors, a model will be estimated with baseline depression and the predictor's main effect. A random slope will be added to the predictor to examine if this results in a model improvement. If so, this predictor variable will be included with a random slope in subsequent analyses. Next, all predictors will be modeled simultaneously. Backward selection based on p-value will be conducted until a final

prediction model is obtained consisting of statistical significant predictors only. This prediction model will be validated in a held-out sample of the data.

With regard to moderators, analyses will be conducted separately for each comparison (e.g., STPP versus control conditions, STPP versus other psychotherapy, STPP versus antidepressant medication). These analyses will only include IPD from randomized studies. For each of the potential moderators, a model will be estimated with baseline depression as well as the moderator's main effect and interaction with treatment. Next, to examine ecological bias, within-study and across-study interaction effects will be separated.[25] If within-study and across-study interactions differ, ecological bias may be at play, and only the within-trial interaction will be interpreted in subsequent analyses. Finally, all significant treatment-covariate interactions, their main effects, and higher order interactions will be modeled simultaneously. The resulting prediction model will be validated in a held-out sample of the data.

A number of sensitivity analyses will be conducted to examine the robustness of the findings. To examine the impact of study quality, we will conduct sensitivity analyses including only studies that score high on all quality criteria. In addition, we will conduct analyses in which we add the risk of bias items as covariates to the mixed effects models, centered at a value indicating freedom of bias.[31] We will also conduct sensitivity analyses to control for the effects of additional non-study treatment during the trial and in the follow-up period by adding collected data in this regard as covariates to the mixed effects models. Finally, we will examine the impact of STPP characteristics (e.g., STPP type, delivery mode) and study design characteristics (e.g., therapist

training, use of a treatment manual) by adding these variables to the mixed effects models too.

Furthermore, to examine possible data availability bias, t-tests and chi-square analyses will be conducted comparing the included studies with studies for which no participant-level data was obtained with regard to the extracted study characteristics. Conventional meta-analysis techniques will be utilized to examine differences in effect sizes between studies that contributed data and studies that did not. We will assess potential publication bias by assessing asymmetry in contour enhanced funnel plots for meta-analyses including 10 or more trials, as is recommended by Sterne and colleagues.[32] The confidence in the cumulative body of evidence will be assessed according to GRADE.[33]

In addition, we will conduct explorative analyses using tree-based statistical learning. More specifically, we will use the generalized linear mixed effects regression trees algorithm (glmertree[34]) in R to detect predictors and moderators of continuous and binary treatment outcomes. These analyses offer several advantages over more traditional mixed-effects modeling approaches, as they allow for the detection of non-linear and higher-level interactions, allow for specifying a large number of potential predictor and moderator variables and involve less stringent assumptions about the distribution of the data. Furthermore, the result of applying glmertree consists of a decision tree that graphically depicts the effects of the relevant predictor and moderator variables. Such a tree can easily be interpreted, and applied in clinical decision-making. However, it should be noted that such tree-based analyses are exploratory in nature. We will assess the expected predictive accuracy on new data using *k*-cross

validation[35] and the stability of the resulting decision trees using subsampling methods.[36] The glmertree analyses will be performed using observed, non-imputed data only, as it is currently unclear how to best specify the model for generating imputed data in tree-based analyses for clustered data.

ETHICS AND DISSEMINATION

IRB approval was not required for this project. IRB approval may be required for the investigators to share their primary data depending on their institution's policies. It is the responsibility of the investigators to obtain IRB approval if their institution's policies require them to do so. By signing the data sharing agreement, the authors who share their data declare that those data were collected and transferred to our research group according to all applicable local and international laws and regulations, including but not limited to local IRB approval.

We intend to submit reports of the outcomes of this study for publication to international peer-reviewed journals in the fields of psychiatry or clinical psychology. We also intend to present the findings of this study at international scientific conferences aimed at psychotherapy researchers and clinicians.

DISCUSSION

We described the study protocol of a systematic review and meta-analysis of IPD to examine predictors and moderators of STPP efficacy for depression. The goal of this

study is to collect the participant-level data of studies examining the efficacy of STPP for depression identified by a thorough literature search, and to combine these datasets in order to conduct IPD meta-analyses. The proposed study design allows for the examination of predictors and moderators of STPP efficacy with increased statistical power and can thus help to show which subsets of depressed patients specifically benefit from therapies based on psychoanalytic principles.

Clinical and scientific relevance

In contrast to how commonly STPPs are utilized in clinical practice, they are underrepresented in current treatment guidelines for depressive disorders. Further high-quality research that extends and disseminates knowledge about the effectiveness of STPP is therefore called for. Research showing whether subsets of depressed patients can specifically benefit from this therapy modality, especially when compared to other treatments, is particularly needed. Knowledge of such moderators can have important implications for clinical practice, as it can be used to guide treatment selection and increase the efficiency of treatments for depression by helping patients and clinicians to make an informed choice concerning the best treatment option for a given patient.

Little is known about patient characteristics associated with STPP efficacy, because clinical trials often have relatively small sample sizes and limited statistical power to examine predictors and moderators of change. Moreover, prediction and moderation analyses in conventional meta-analyses are often based on study-level aggregates and are, therefore, prone to ecological bias. By means of individual participant data meta-analyses these critical limitations can be overcome. IPD meta-analyses have been

utilized more frequently in the medical field, but are newer in the field of psychiatry and clinical psychology.[37] Although IPD meta-analyses have now been used to examine single moderators of CBT and pharmacotherapy efficacy for depression,[20-21] to date no IPD meta-analysis has been conducted concerning STPP.

Strengths and limitations

Individual participant data meta-analysis has several advantages over conventional meta-analysis, including increased statistical power to examine predictors and moderators.[11] In addition, by collecting the primary data, access to predictor or moderator variables that might not have been reported in the published articles is gained; increasing the chance that aggregation of these variables across studies is possible. Other advantages of individual participant data meta-analysis over conventional meta-analysis include the possibility to 1) account for missing data at the individual participant level, so that for instance intention-to-treat analyses can be conducted even though the original study reported completers-only analyses, 2) use the same statistical methods for imputing missing data and for conducting statistical analyses, thereby facilitating standardization across studies, 3) standardize outcomes across studies, for instance by using equal cut-off points on a depression outcome measure when the primary studies used different cut-offs, and 4) verify the results presented in the original studies, also by means of more sophisticated statistical techniques that were not available at time of publication in the case of older studies.[38]

IPD meta-analyses involve collection of original data from all the relevant trials worldwide that can be accessed. These data need to be prepared and checked before

being included in the meta-analysis, and complex decisions on the data sometimes need to be made in order to ensure the accuracy of the outcomes. Therefore, it takes more time and resources to conduct an IPD meta-analysis than to conduct a conventional meta-analysis based solely on results extracted from published trial reports.[38] However, the IPD approach can improve the quality of both the data and the analyses, and so the reliability of the results. Therefore, it is considered the 'gold standard' of meta-analysis.[12]

IPD meta-analyses also have a number of limitations. First, although IPD meta-analyses are generally considered the most reliable approach to evidence synthesis,[12] this does not mean that they are bias-free and selection bias, publication bias, and data availability bias need to be considered.[39] We try to overcome this limitation by performing a systematic literature search that also aims to identify grey literature and unpublished work, and by testing for differences between studies for which IPD was and was not obtained. Second, IPD meta-analyses rely on variables previously assessed in individual studies and available across multiple trials. For this reason, it is possible that not all variables of interest can be examined as potential predictors or moderators. Third, and related, it is necessary to standardize predictor/moderator variables for the analyses, but doing so might involve recoding and possibly omitting important information for some variables. Fourth, although combining multiple trials reduces the possibility that predictors/moderators identified are chance findings in single study samples, generalizability of the findings might still be limited to patients who volunteer to participate in scientific outcome research. Fifth, the predictors and moderators identified in this study can either apply specifically to STPP or can be

more general factors associated with depression treatment efficacy. We intend to address this distinction in this study's outcome reports in the context of the predictors/moderators identified.

Conclusion

We described the study protocol for a systematic review and meta-analysis of IPD aimed at examining if certain subgroups of depressed patients can benefit specifically from STPP. We will collect the participant-level data of studies examining the efficacy of STPP for depression identified by a thorough literature search. We will combine these datasets and conduct IPD meta-analyses to identify predictors and moderators of STPP efficacy. Knowledge of such predictors and moderators can have important implications for clinical practice, as they can, respectively, inform expectations of treatment efficacy for individual patients, and help patients and clinicians to make an informed choice concerning the best treatment option for a given patient.

AUTHORS' CONTRIBUTIONS

ED, AAA, JPB, JJMD, MF, SDH, EPJ, SCMdM, JMT, JWRT, HLV, EW, and PC made substantial contributions to the study design. ED, AAA, JPB, MBCG, JJMD, PF, SDH, JMT, HLV, and PC made substantial contributions to the acquisition of individual participant data. ED, EW, and PC drafted the manuscript. ED, AAA, JPB, MBCG, JJMD, MF, PF, SDH, EPJ, SCMdM, JMT, JWRT, HLV, EW, and PC revised it critically for

important intellectual content and approved the final version of this manuscript. ED is the guarantor of the review.

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COMPETING INTERESTS STATEMENT

AAA practices and provides training in methods of STPP and receives royalties from a book he wrote on STPP. JPB has given talks on STPP at workshops and conferences for which organizers often have not paid for travel and accommodations. JPB and JJMD receive royalties from books on STPP they have co-authored. JMT has given talks on STPP at workshops and conferences for which organizers have paid for travel and accommodations. PF declares being Chief Executive of the Anna Freud Centre (UK). He teaches mentalization-based treatment trainings and dynamic-interpersonal therapy trainings in the UK and internationally. He is the Co-PI on The IMPACT Study – The Effectiveness of Psychological Treatment for Depressed Adolescents, and Consultant to the Child and Family Program at the Menninger Department of Psychiatry and Behavioural Sciences at Baylor College of Medicine, Houston, TX, USA. PF also receives royalties from books on interpersonal psychotherapy which he has co-authored

with others. HLV and SCMdM are trainers and registered supervisors of short-term psychodynamic supportive psychotherapy. They also receive royalties from books on STPP they have co-authored. SDH reports no financial conflicts, but acknowledges an intellectual passion for the cognitive and behavioral interventions for depression. ED, MBCG, MF, JWRT, EW, and PC declare that they have no known conflicts of interest.

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