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Review

The efficacy of adding short-term psychodynamic psychotherapy to antidepressants in the treatment of depression: A systematic review and meta-analysis of individual participant data

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HIGHLIGHTS

- Short-term psychodynamic psychotherapy (STPP) is a treatment for depression.
- Adding STPP to antidepressants results in lower depressive symptom levels.
- This effect is small at post-treatment and moderate at follow-up.
- This effect can be related to STPP's specific treatment components.

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ABSTRACT

Purpose: We examined the efficacy of adding short-term psychodynamic psychotherapy (STPP) to antidepressants in the treatment of depression by means of a systematic review and meta-analysis of individual participant data, which is currently considered the most reliable method for evidence synthesis.
Results: A thorough systematic literature search resulted in 7 studies comparing combined treatment of antidepressants and STPP versus antidepressant mono-therapy ($n = 3$) or versus antidepressants and brief supportive psychotherapy ($n = 4$). Individual participant data were obtained for all these studies and totaled 482 participants. Across the total sample of studies, combined treatment of antidepressants and STPP was found significantly more efficacious in terms of depressive symptom levels at both post-treatment (Cohen's $d = 0.26$, SE $= 0.10$, $p = .01$) and follow-up ($d = 0.50$, SE $= 0.10$, $p < .001$). This effect was most apparent at follow-up and in studies examining STPP's specific treatment efficacy. Effects were still apparent in analyses that controlled for risk of bias and STPP quality in the primary studies.
Conclusions: These findings support the evidence-base of adding STPP to antidepressants in the treatment of depression. However, further studies are needed, particularly assessing outcome measures other than depression

Abbreviations: HAMD, Hamilton Depression Rating Scale; STPP, short-term psychodynamic psychotherapy

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and cost-effectiveness, as well as examining the relative merits of STPP versus other psychotherapies as added to antidepressants.

1. Introduction

Depression is a highly prevalent and potentially disabling disorder associated with major personal and societal costs (Kessler, 2012). Affecting more than 300 million people worldwide, depression is ranked as the single largest contributor to global disability by the World Health Organization (2017). 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 (Marcus & Olfson, 2010). 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 (Driessen et al., 2015).

Findings from 'conventional' meta-analyses suggest that combined treatment of antidepressant medication and psychotherapy in general is more efficacious than antidepressant mono-therapy in terms of depressive symptom reduction (Cuijpers et al., 2014; Karyotaki et al., 2016) and a review concludes that this might also be the case for STPP specifically (Fonagy, 2015). However, conventional meta-analyses, which are based on results extracted from published trial reports, are limited as they depend on the quality of the information in publications in which treatment effects can be overestimated. Therefore, their results can be biased (Stewart & Parmar, 1993).

Alternatively, individual participant data meta-analysis is a technique to examine treatment effects by combining participant-level data of multiple trials. Individual participant data 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. Individual participant data meta-analysis has several advantages over conventional meta-analysis, including the possibility to 1) account for missing data at the individual participant level, so that for instance intent-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 (Riley, Lambert, & Abo-Zaid, 2010). For these reasons, individual participant data meta-analysis provides the least biased and most reliable means of evidence synthesis and is considered the 'gold standard' in this regard (Stewart & Parmar, 1993).

To the best of our knowledge, to date, only one individual participant data meta-analysis has examined the efficacy of adding psychotherapy to antidepressants in the treatment of depression (Furukawa et al., 2018). This network meta-analysis specifically focused on the Cognitive-Behavioural Analysis System of Psychotherapy (CBASP) for persistent depression. It included two studies comparing combined treatment of antidepressants and CBASP versus antidepressant monotherapy and reported a mean difference in depression severity at 12 weeks of 2.6 (1.6 to 4.3) Hamilton Depression Rating Scale (HAMD) points, favoring combined treatment.

We, therefore, conducted a systematic review and meta-analysis of individual participant data to examine the efficacy of adding STPP to antidepressants in the treatment of depression. We aimed to examine two types of comparisons: 1) combined treatment of antidepressants and STPP versus antidepressant mono-therapy, and 2) combined treatment of antidepressants and STPP versus combined treatment of antidepressants and brief supportive psychotherapy. The first comparison relates to the overall additional benefits of STPP added to antidepressants in terms of both specific and non-specific treatment effects. Assuming that the efficacy of brief supportive psychotherapy is mainly determined by non-specific treatment factors as being empathically understood by a therapist or general advises how to deal with depressive symptoms, the second contrast relates to the specific treatment effects of STPP. We aimed to examine the efficacy of adding STPP to antidepressants in the treatment of depression at post-treatment as well as at follow-up.

2. Methods

2.1. Design

This study is part of a large systematic review and individual participant data meta-analysis project that aims to examine different aspects of STPP for depression efficacy and that was registered in the PROSPERO International prospective register of systematic reviews (registration number: CRD42017056029). The study protocol of this project was published too (Driessen et al., 2018).

2.2. Search strategy

We used an extensive search strategy including six different search methods in order to retrieve as many relevant studies as possible. First, we systematically searched 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 included 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 were combined as follows: (#1 OR (#2 AND #3)) AND #4. The exact terms for the search in PubMed are provided in the study protocol (Driessen et al., 2018; Table 1). Complete search terms for all electronic databases are available on request from the corresponding author. No language or date restrictions were applied in the searches.

Second, in order to identify relevant studies from the so-called 'grey literature' produced by organizations outside of the traditional academic publishing and distribution channels, we searched GLIN, a Dutch electronic database for grey literature, and UMI database ProQuest for digital dissertations. Third, a prospective trial register was searched for unpublished ongoing research (http://www.controlled-trials.com). The grey literature and prospective trial register searches were conducted using the search strategy described above. Fourth, we searched an Internet database of controlled and comparative outcome studies on psychological treatments of depression (http://www.psychotherapyrcts.org) 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 were screened for relevant references not located by means of the other search methods. Sixth, we contacted an email list of researchers in the field of psychodynamic therapy to ask for ongoing or unpublished studies. Literature searches were performed according to this strategy in 2007 and 2014 for two previous conventional meta-analyses concerning the efficacy of STPP for depression (Driessen et al.,

Table 1
Characteristics of the included studies.

Study	Target group	Depression diagnosis	*N*	HAMD version	Follow-up
Antidepressants + STPP versus *antidepressant mono-therapy*					
1. de Jonghe et al., 2001	Adults	Major Depression (DSM-III-R); HAMD ≥14	167	17-item	1 year
2. Lopez Rodriguez et al., 2004	Adults	Mild to moderate depression (DSM-IV and ICD-10)	20	21-item	10 months
3. Maina et al., 2010	Adults with comorbid OCD	Major Depressive Disorder (DSM-IV); HAMD ≥15	57	17-item	1 year
Antidepressants + STPP versus *antidepressants + brief supportive psychotherapy*					
4. Burnand et al., 2002	Adults	Major depressive episode (DSM-IV); HAMD ≥20	81	17-item	–
5. Maina et al., 2007	Adults	Major Depressive Disorder (DSM-IV-TR); HAMD ≥15	35	17-item	1 year
6. Martini et al., 2011	Adults with comorbid panic disorder	HAMD ≥7	35	17-item	1 year
7. Vitriol et al., 2009	Women with childhood trauma	Severe depression (ICD-10); HAMD ≥21	87	17-item	6 months

	STPP model	STPP duration	N sessions	Antidepressants
1.	de Jonghe et al., 1994	24 weeks	16	Step 1: fluoxetine 20 mg/day (SSRI), Step 2: amitriptyline 50–150 mg/day (TCA), Step 3: moclobemide 300–600 mg/day (RIMA)
2.	Bellak, 1993/1994	26 weeks	26	fluoxetine 20 mg/day (SSRI)
3.	Malan, 1976	16 weeks	10–16	fluvoxamine 300 mg/day or sertraline 200 mg/day (SSRIs)
4.	Safran & Muran, 2000 Andreoli, 1999	10 weeks		Step 1: clomipramine 125 mg/day (TCA), Step 2: citalopram 20–40 mg/day (SSRI)
5.	Malan, 1963	26 weeks	15–30	paroxetine or citalopram 20–60 mg/day (SSRIs)
6.	Malan, 1963	16 weeks	10–30	citalopram 20–60 mg/day, escitalopram 10–20 mg/day, fluoxetine 20–40 mg/day, or sertraline 50–150 mg/day (SSRIs)
7.	Vitriol, 2005	13 weeks		Chilean Ministry of Health practice guideline algorithm for prescription of SSRI/SNRIs, mood stabilizers, and second-generation antipsychotics

Note. DSM = Diagnostic and Statistical Manual; HAMD = Hamilton Depression Rating Scale; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th edition; N = number of subjects; N sessions = number of sessions; OCD = obsessive-compulsive disorder; RIMA = Reversible Inhibitor of Monoamine-oxydase A; SNRI = Serotonine Noradrenaline Reuptake Inhibitors; SSRI = Selective Serotonin Reuptake Inhibitor; STPP = short-term psychodynamic psychotherapy; TCA = Tricyclic Antidepressant.

2010, 2015) and were updated June 19th, 2017 for this study using the same search strategy.

To make sure that we did not miss any studies published after the June 19th, 2017 literature search update, we searched an existing database of randomized clinical trials examining the efficacy of psychological treatments for depression that has been described in detail elsewhere (Cuijpers, van Straten, Warmerdam, & Andersson, 2008) and that has been used in a series of published meta-analyses (www.evidencebasedpsychotherapies.org). This database is annually updated through comprehensive literature searches in the bibliographic databases PubMed, PsycINFO, Embase.com, and the Cochrane Library. The search strings use a combination of index terms and free-text words for psychological treatments and depression. We searched this database for additional studies meeting the inclusion criteria for this review published between January 1st, 2017 and January 1st, 2020.

2.3. Selection of studies

We included studies if they reported (a) outcomes on standardized measures of (b) depressed (c) adult participants (d) receiving STPP. Participants were considered depressed if they met specified criteria for major depressive disorder or another unipolar mood disorder as assessed by means of a semi-structured interview or clinicians' assessment, or if they presented an elevated score above the 'no depression' cut-off on a standardized measure of depression. Participants needed to be at least 18 years old, and studies concerning older adults (mean age $>$ 55) were included as well. We included studies in which STPP (a) was based on psychoanalytic theories and practices, (b) was time-limited from the onset (i.e., not a therapy that was brief only in retrospect), and (c) applied verbal techniques (e.g., therapies applying art as expression form were not considered STPP). Studies needed to include at least 10 participants.

The screening process consisted of three phases. At first, the selection criteria were applied to the citations generated from the searches independently by two raters. Disagreements were discussed and resolved by consensus. Unless they could be definitely excluded, titles identified as potentially relevant were requested in full text. During the second screening phase, two independent raters applied the selection criteria to the full-text papers. Disagreements were discussed and resolved by consensus. During the third phase, two expert STPP researcher-clinicians checked that the therapies described were psychodynamic in nature to make sure that the treatments examined were actual STPPs. Again, disagreements were discussed and resolved by consensus. When disagreements could not be resolved in this way, a third rater was consulted. From the resulting set of studies, we finally identified randomized comparisons of combined treatment of antidepressants and STPP versus antidepressant mono-therapy or versus antidepressants and brief supportive psychotherapy, provided individually in an outpatient setting.

2.4. Data collection

Next, authors of the included studies were contacted and invited to contribute the participant-level data of their studies. Researchers who shared their data were offered co-authorship for publications based on their study's data, given that they would meet standard criteria for authorship of scientific publications according to internationally accepted criteria (www.icmje.org). In addition, researchers who shared their data were offered use of the collective database to examine other research questions provided that the primary investigators of the original trials approved the use of their data for this purpose.

Contact details of all first authors were collected from the relevant publications, or if not reported there, through Internet searches or personal contacts with other researchers. First authors were then 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 did not respond after three weeks, a second and third email were sent. In case of non-response to email, a letter was sent (again with three attempts). If still no response was received, we tried to contact the author by telephone. If all these attempts failed, the last, second, third, fourth, etc. author of the study (in this order) were contacted in the same way. If none of the authors responded to these efforts, other ways were sought to contact one of the authors (e.g., via colleagues or anyone who might know them). Study data were considered unavailable only if all these attempts failed, or in the event that an author indicated that the participant-level data had not been retained or declined sharing these data.

If the author was willing and able to share the individual participant data of his/her trial, the author transferred the anonymized participant-level dataset, including all outcome variables assessed during and after treatment, both in the combined antidepressants and STPP condition as well as in the comparison condition included in the study.

2.5. Data integrity check

After transfer of the dataset, the file was checked to examine whether the data received matched the data reported in the publication. For both 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 were calculated from the dataset received and checked against the published article for this purpose. Discrepancies were resolved with the authors. In addition, the data were checked for invalid, out-of-range, or inconsistent items. Furthermore, we checked the integrity of the randomization by inspecting baseline differences in depression severity across treatment arms.

For each study, we then listed all outcome variables, intermediate, and follow-up assessments. We also extracted multiple study design characteristics (e.g., target group, depression inclusion criteria) and treatment characteristics (e.g., STPP model, antidepressant type), as well as three STPP quality criteria (therapist training, use of a treatment manual, and verification of treatment integrity). In addition, we extracted study validity criteria according to the Cochrane risk of bias assessment tool (Higgins, Altman, & Sterne, 2011) for random sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessment (detection bias), and incomplete outcome data (attrition bias). Blinding of participants and personnel (performance bias) was not rated, as it is considered not possible to blind participants and therapists to treatment in psychotherapy research. Selective reporting (reporting bias) was also not rated. This was considered not applicable, as the authors shared their datasets including all outcome measures assessed.

After checking the data, the datasets were standardized. For this purpose, a copy of each trial's raw data file was recoded into a data file that matched the individual participant data meta-analysis database in terms of variables. Next, the individual study data files were concatenated in one database structured by study and individual participant ID. After all data files were recoded and entered, the data for each study was checked against the original data file received for accuracy.

2.6. Outcome measures

The primary outcome for this study was treatment efficacy as assessed by a continuous depression outcome measure at post-treatment. The secondary outcome was treatment efficacy as assessed by a continuous depression outcome measure at follow-up. For each trial, we identified the primary continuous depression outcome as defined by the study authors. All instruments explicitly measuring depression qualified in this regard. Because different depression measures were used, we standardized the depression outcomes by converting the depression scores into z-scores within each study. Sensitivity analyses were

conducted using unstandardized scores for each depression measure that was assessed in the majority of studies included in the meta-analysis.

2.7. Data-analysis

We conducted individual participant data meta-analyses according to the one-stage approach, because that provides a more exact likelihood in the case of small studies (Burke, Ensor, & Riley, 2017). We conducted individual participant data meta-analyses using mixed model analyses with a three-level structure (study, participant, repeated measures) to take into account between-study heterogeneity. A restricted maximum likelihood estimation was used, because this is recommended when there are few studies in the meta-analysis or studies have small sample sizes (Higgins, Whitehead, Turner, Omar, & Thompson, 2001). The analyses were based on the intent-to-treat samples, including all participants randomized.

We started with a basic model including a main effect for time and a time-by-treatment interaction. This approach is recommended by Twisk et al. (2018), because it adequately accounts for baseline values of depression and because of its favorable properties with regard to missing data (i.e., participants with only a baseline value but missing post-treatment and follow-up assessments are still included in the analyses). Time was treated as a categorical variable, to facilitate the assessment of treatment effects at the different time points. The basic model had a random intercept and fixed slopes. We examined whether adding a random slope to the time-by-treatment interaction resulted in a model improvement. If this was the case, the model that included a random slope was used for effect estimation.

Using this approach, treatment effects can be directly obtained from the regression coefficients of the time-by-treatment interactions (Twisk et al., 2018). The regression coefficients of the time-by-treatment interactions at post-treatment and follow-up represent the treatment comparisons at these assessment moments and can be interpreted as Cohen's *d* effect sizes for analyses with z-scores as outcome measure and as point differences for analyses with unstandardized scores as outcome

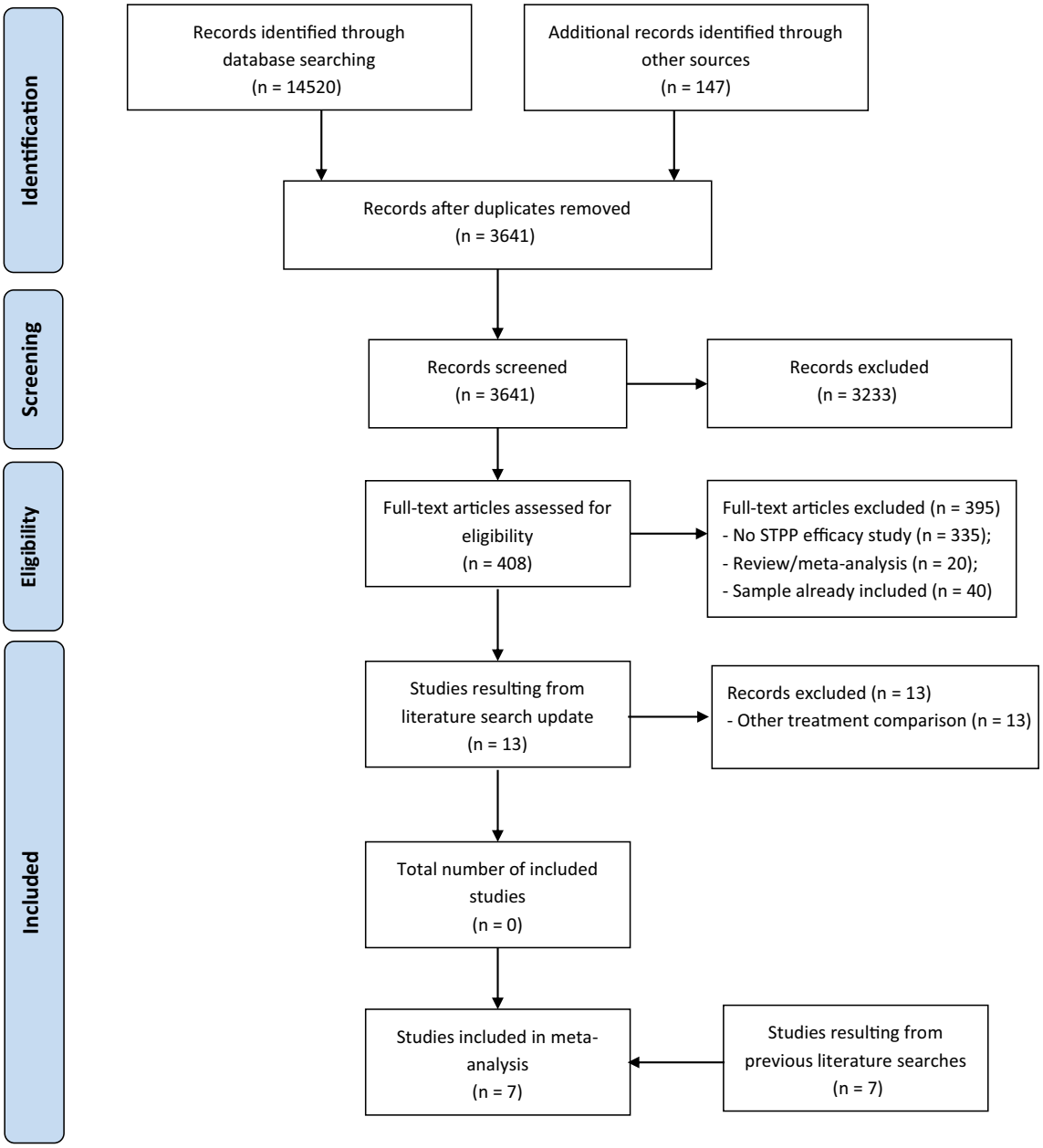

Fig. 1. PRISMA flow diagram of literature search update.

measure. For the analyses of post-treatment outcomes, we excluded follow-up data in which additional help-seeking could not be controlled. We assessed heterogeneity with the I^2 statistic, which describes the variance between studies as a proportion of the total variance.

We visually inspected histograms of residuals and standardized residuals to address the assumption of normally distributed data. To examine the impact of risk of bias, we added the risk of bias items as dichotomous covariates to the mixed model analyses (Higgins, Thompson, & Spiegelhalter, 2009). Furthermore, we conducted sensitivity analyses including only studies that scored negative on all four risk of bias criteria assessed. Similarly, we examined the impact of STPP quality by adding these items as dichotomous covariates to the mixed model analyses and by conducting sensitivity analyses that only included studies scoring positive on all three STPP quality criteria assessed. Finally, we conducted sensitivity analyses only including those studies that enrolled participants meeting diagnostic criteria for depression (rather than presenting an elevated score on a standardized measure of depression). Mixed model analyses were performed with MLwiN (version 2.26).

3. Results

3.1. Included studies

For detailed results of the 2007 and 2014 literature searches, we refer the reader to Driessen et al. (2010, 2015). These searches identified 7 randomized comparisons of combined treatment of antidepressants and STPP versus antidepressants with or without brief supportive psychotherapy (Burnand, Andreoli, Kolatte, Venturini, & Rosset, 2002; de Jonghe, Kool, van Aalst, Dekker, & Peen, 2001; Lopez Rodriguez, Lopez Butron, Vargas Terrez, & Villamil Salcedo, 2004; Maina, Rosso, Crespi, & Bogetto, 2007; Maina, Rosso, Rigardetto, Chiadò Piat, & Bogetto, 2010; Martini, Rosso, Chiodelli, De Cori, & Maina, 2011; Vitriol, Ballesteros, Florenzano, Weil, & Benadorf, 2009). Results of the literature search update that was performed June 19th, 2017 using the same search strategy are presented in Fig. 1. After removing duplicates, this literature search update resulted in 3641 records, of which the majority (3233) was excluded in the first screening phase. A total of 408 titles were reviewed in full-text. Of these, none met the inclusion criteria for the present review. Finally, the database included 166 randomized clinical trials examining the efficacy of psychological treatments for depression published between January 1st, 2017 and January 1st, 2020. These were all reviewed in full-text, but none were identified as randomized comparisons of combined treatment of antidepressants and STPP versus antidepressants with or without brief supportive psychotherapy.

Thus, 7 studies met the inclusion criteria for the present review. Individual participant data were obtained for all these 7 studies (100.0%). The characteristics of the 7 included studies are described in Table 1. Three (42.9%) studies compared combined treatment of antidepressants and STPP with antidepressant mono-therapy, while the other four studies (57.1%) compared combined treatment of antidepressants and STPP with combined treatment of antidepressants and brief supportive psychotherapy. In all studies, participants were recruited from clinical samples (who actively sought help for depression first and were then asked to participate in the study). Depression inclusion criteria typically consisted of a DSM or ICD-10 depression diagnosis combined with an elevated HAMD score, though in one study an elevated HAMD score constituted the sole inclusion criterion for depression. In four studies (57.1%), the target group was adults with depression in general, while three studies (42.9%) included participants with specific anxiety disorder comorbidities. The study samples ranged from 20 to 167 participants. Follow-up assessments were conducted in 6 (85.7%) studies, with follow-up periods ranging from 6 months to 1 year post-baseline. All studies used the HAMD as primary outcome measure, with 6 (85.7%) studies assessing the 17-item version and 1 (14.3%) study assessing the 21-item version.

STPP was based on the principles described by Safran and Muran (2000), Andreoli (1999), de Jonghe, Rijnierse, and Janssen (1994), Bellak (1993, 1994), Malan (1963, 1976), and Vitriol (2005). Treatment periods ranged from 10 to 26 weeks. Antidepressants included various selective serotonin reuptake inhibitors, though one study focused on a tricyclic antidepressant. In terms of the STPP quality criteria, therapists were adequately trained and treatment integrity was verified in all of the included studies. STPP was conducted according to a treatment manual in all but one study (85.7%; Lopez Rodriguez et al., 2004).

The 7 included studies totaled 482 participants, 238 (49.4%) in the combined antidepressants and STPP treatment conditions and 244 (50.6%) in the comparison conditions. The majority of the participants (70.0%) was female, with a mean age of 35.3 (SD = 9.9) years. The mean baseline 17-item HAMD score was 22.9 (SD = 7.9), indicating moderate symptom levels.

An overview of the risk of bias assessment is provided in Table 2. As can be seen in this table, all studies employed adequate random sequence generation and allocation concealment procedures. However, outcome assessors were not blind to treatment condition in two studies (28.6%) and for one other study (14.3%) the complete intent-to-treat data were not retained. Four studies (57.1%) scored negative on all four risk of bias criteria assessed.

3.2. Efficacy outcomes

Regression coefficients of the time-by-treatment interactions are reported in Table 3 for each of the included studies and in Table 4 for all meta-analyses. Across the total sample of 7 studies, combined treatment of antidepressants and STPP was found to be significantly more efficacious than antidepressants with/without brief supportive

Table 2
Risk of bias assessment of the included studies.

Study	Selection bias		Detection bias	Attrition bias
	Random sequence generation	Allocation concealment	Blinding of HAMD assessment	Incomplete outcome data
Antidepressants + STPP versus *antidepressant mono-therapy*				
de Jonghe et al., 2001	+	+	+	+
Lopez Rodriguez et al., 2004	+	+	+	−
Maina et al., 2010	+	+	+	+
Antidepressants + STPP versus *antidepressants + brief supportive psychotherapy*				
Burnand et al., 2002	+	+	−	+
Maina et al., 2007	+	+	+	+
Martini et al., 2011	+	+	+	+
Vitriol et al., 2009	+	+	−	+

Note. HAMD = Hamilton Depression Rating Scale; STPP = short-term psychodynamic psychotherapy.

Table 3
Cohen's *d* effect sizes of adding STPP to antidepressants at post-treatment and follow-up in each of the included studies.

Study	Post-treatment			Follow-up		
	d	SE	p	*d*	SE	p
Antidepressants + STPP versus *antidepressant mono-therapy*						
de Jonghe et al., 2001	−0.289	0.202	0.153	−0.221	0.185	0.232
Lopez Rodriguez et al., 2004	−0.488	0.446	0.274	−0.780	0.436	0.074
Maina et al., 2010	−0.036	0.235	0.878	0.043	0.202	0.831
Antidepressants + STPP versus *antidepressants + brief supportive psychotherapy*						
Burnand et al., 2002	−0.109	0.232	0.638			
Maina et al., 2007	0.151	0.356	0.671	−1.427	0.299	< 0.001
Martini et al., 2011	0.068	0.237	0.774	−0.681	0.262	0.009
Vitriol et al., 2009	−0.638	0.206	0.002	−0.659	0.215	0.002

Note. *p* = *p*-value; SE = standard error; STPP = short-term psychodynamic psychotherapy. Negative signs indicate lower depressive symptom levels in the combined antidepressants and STPP treatment condition than in the comparison condition.

psychotherapy with a Cohen's *d* effect size of 0.26 (SE = 0.10; $p = .01$) at post-treatment. In the 6 studies that assessed the 17-item HAMD, a non-significant 1.6 (SE = 1.3; $p = .21$) HAMD point difference favoring combined treatment of antidepressants and STPP was found at post-treatment. At follow-up, combined treatment of antidepressants and STPP was again significantly more efficacious than antidepressants with/without brief supportive psychotherapy, though effects were larger with a Cohen's *d* effect size of 0.50 (SE = 0.10; $p < .001$) and a 3.7 (SE = 1.3; $p = .01$) HAMD point difference. Heterogeneity was low to moderate in these analyses (I^2 = 0.0–45.7%).

A similar pattern of findings was observed in the subset of 4 (57.1%) studies contrasting combined treatment of antidepressants and STPP with combined treatment of antidepressants and brief supportive psychotherapy, with a significant effect size of $d = 0.26$ (SE = 0.13; $p = .04$) and a non-significant 1.6 (SE = 1.5; $p = .30$) HAMD point difference at post-treatment, and with a significant effect size of $d = 0.82$ (SE = 0.15; $p < .001$) and a significant 6.2 (SE = 1.1 $p < .001$) HAMD point difference at follow-up. Heterogeneity was low to moderate in these analyses (I^2 = 0.0–53.9%).

In the subset of 3 (42.9%) studies that compared combined treatment of antidepressants and STPP to antidepressant mono-therapy, no statistically significant time-by-treatment interactions were observed in the analyses with HAMD z-scores as outcome measure (post-treatment: Cohen's $d = 0.24$, SE = 0.15, $p = .11$; follow-up: Cohen's $d = 0.21$, SE = 0.13; $p = .11$), while combined treatment was found to be significantly more efficacious than antidepressant mono-therapy in the analyses with unstandardized 17-item HAMD scores as outcome measure. In these latter analyses, HAMD point differences at post-treatment and follow-up were 2.5 (SE = 0.9; $p = .01$) and 2.4 (SE = 0.9; $p = .01$), respectively. Heterogeneity was low in these analyses (I^2 = 0.0–3.1%).

3.3. Sensitivity analyses

Adding blinding of HAMD assessment and incomplete outcome data as covariates to the analyses including all studies resulted in a similar pattern of findings (Table 4), with a significant effect size of $d = 0.26$ (SE = 0.10; $p = .01$) and a non-significant 1.7 (SE = 1.3; $p = .20$) HAMD point difference at post-treatment, and with a significant effect size of $d = 0.50$ (SE = 0.10; $p < .001$) and a significant 3.3 (SE = 1.4 $p = .02$) HAMD point difference at follow-up. Repeating the analyses in the subset of 4 (57.1%) studies that scored negative on all 4 risk of bias criteria assessed resulted in somewhat smaller effects, with a non-significant effect size of $d = 0.11$ (SE = 0.12; $p = .38$) and a significant 1.5 (SE = 0.7; $p = .04$) HAMD point difference at post-treatment, and with a significant effect size of $d = 0.42$ (SE = 0.11; $p < .001$) and a significant 2.9 (SE = 1.4; $p = .04$) HAMD point difference at follow-up.

Table 4
Treatment effects of adding STPP to antidepressants at post-treatment and follow-up.

Outcome	Post-treatment				Follow-up			
	B	SE	*p*	I^2	B	SE	*p*	I^2
	Main analyses							
	All studies							
HAMD z-score (Cohen's *d*)	**−0.255**	**0.096**	**0.008**	**0.00**	**−0.503**	**0.102**	**< 0.001**	**0.00**
17-item HAMD score	−1.630	1.295	0.208	45.72	**−3.674**	**1.341**	**0.006**	**38.70**
	Antidepressants + STPP versus *antidepressant mono-therapy*							
HAMD z-score (Cohen's *d*)	−0.237	0.146	0.105	0.00	−0.211	0.133	0.113	0.00
17-item HAMD score	**−2.524**	**0.921**	**0.006**	**0.00**	**−2.415**	**0.931**	**0.009**	**3.06**
	Antidepressants + STPP versus *antidepressants + brief supportive psychotherapy*							
HAMD z-score (Cohen's *d*)	**−0.262**	**0.127**	**0.039**	**0.00**	**−0.823**	**0.153**	**< 0.001**	**0.00**
17-item HAMD score	−1.550	1.509	0.304	53.90	**−6.215**	**1.100**	**< 0.001**	**47.67**
	Sensitivity analyses							
	All studies – risk of bias items added as covariates							
HAMD z-score (Cohen's *d*)	**−0.255**	**0.096**	**0.008**	**0.00**	**−0.503**	**0.102**	**< 0.001**	**0.00**
17-item HAMD score	−1.668	1.303	0.201	30.38	**−3.327**	**1.427**	**0.020**	**25.52**
	Low risk of bias studies only							
HAMD z-score (Cohen's *d*)	−0.108	0.122	0.376	0.00	**−0.424**	**0.114**	**< 0.001**	**0.00**
17-item HAMD score	**−1.509**	**0.723**	**0.037**	18.67	**−2.916**	**1.445**	**0.044**	**15.37**
	All studies – STPP quality items added as covariates							
HAMD z-score (Cohen's *d*)	**−0.255**	**0.096**	**0.008**	**0.00**	**−0.503**	**0.102**	**< 0.001**	**0.00**
17-item HAMD score	−1.630	1.295	0.208	45.72	**−3.674**	**1.341**	**0.006**	**38.70**
	High STPP quality studies only							
HAMD z-score (Cohen's *d*)	**−0.247**	**0.098**	**0.012**	**0.00**	**−0.492**	**0.104**	**< 0.001**	**0.00**
17-item HAMD score	−1.630	1.295	0.208	45.72	**−3.674**	**1.341**	**0.006**	**38.70**
	Studies including participants with diagnosed mood disorders only							
HAMD z-score (Cohen's *d*)	**−0.289**	**0.102**	**0.005**	**0.00**	**−0.480**	**0.109**	**< 0.001**	**0.00**
17-item HAMD score	−2.104	1.311	0.109	40.24	**−3.780**	**1.755**	**0.031**	**39.29**

Note. B = regression coefficient; HAMD = Hamilton Depression Rating Scale; *p* = p-value; SE = standard error; STPP = short-term psychodynamic psychotherapy. Negative signs indicate lower depressive symptom levels in the combined antidepressants and STPP treatment condition than in the comparison condition. Numbers printed in bold indicate a statistically significant time-by-treatment interaction ($p < .05$).

Heterogeneity was low in all these analyses (I^2 = 0.0–30.4%).

Adding use of a treatment manual as a covariate to the analyses including all studies did not change the pattern of results, nor did repeating the analyses in the subset of 6 (85.7%) studies that scored positive on all 3 STPP quality criteria assessed (Table 4). Repeating the analyses in the subset of 6 (85.7%) studies that only included participants meeting diagnostic criteria for depression also did not change the pattern of results (Table 4).

4. Discussion

4.1. Findings

We conducted a systematic review and meta-analysis of individual participant data to examine the efficacy of adding STPP to antidepressants in the treatment of depression. Across the total sample of seven studies that were identified by a thorough literature search, combined treatment of antidepressants and STPP was found to be significantly more efficacious than antidepressants with/without brief supportive psychotherapy. The size of this effect was small at post-treatment and moderate at follow-up. These results are in line with previous reviews suggesting increased treatment efficacy when adding psychotherapy in general (Cuijpers et al., 2014; Karyotaki et al., 2016) as well as STPP specifically (Fonagy, 2015) to antidepressant medication.

The overall findings appeared to be mostly driven by the subset of studies that contrasted combined treatment of antidepressants and STPP with combined treatment of antidepressants and brief supportive psychotherapy. Assuming that the efficacy of brief supportive psychotherapy is mainly determined by non-specific treatment factors as being empathically understood by a therapist or general advises how to deal with depressive symptoms, this contrast relates to STPP's specific treatment effects. In this set of studies, combined treatment of antidepressants and STPP was found to be significantly more efficacious than combined treatment of antidepressants and brief supportive psychotherapy with a small effect size at post-treatment and a large effect size at follow-up.

The effect of adding STPP to antidepressants at follow-up was less apparent in the set of studies that contrasted combined treatment of antidepressants and STPP with antidepressant mono-therapy. In this subset of studies, small effects were found at both post-treatment and follow-up that were significantly superior to antidepressant mono-therapy when using unstandardized 17-item HAMD scores as outcome measure, but not when using HAMD z-scores as outcome measure. We think that this effect difference at follow-up is the consequence of the different studies that constitute the two subsets. For example, one of the studies comparing combined treatment of antidepressants and STPP versus antidepressant mono-therapy found no effect of adding STPP at both post-treatment (d = −0.04, SE = 0.24, p = .88) and follow-up (d = 0.04, SE = 0.20, p = .83; Maina et al., 2010). This study focused on comorbid major depression and obsessive-compulsive disorder and concluded that supplemental STPP has no significant clinical effect on such patients who are receiving adequate medications.

4.2. Strengths and limitations

This study has a number of strengths. First, individual participant data were obtained for all included studies. Thus, this meta-analysis did not suffer from data availability bias. Similarly, selection bias appeared to be limited as all studies employed adequate sequence generation and allocation concealment procedures. Second, by using individual participant data meta-analytic methods, we were able to improve the quality of the data and the analyses when compared to conventional meta-analysis methods. For instance, we worked with intent-to-treat samples that were not always reported on in the original study publications, and we facilitated standardization across studies by using the same statistical method for data-analysis, appropriately adjusting for baseline levels of depression in all studies (Twisk et al., 2018). Third, the included studies shared similarities in terms of sample recruitment, depression inclusion criteria, treatment format, and primary outcome measure.

However, this study also has a number of limitations. First, even though individual participant data could be obtained for all studies, the total number of participants included in this meta-analysis is modest (n = 482). Relatively few studies examined the efficacy of adding STPP to antidepressants. We think this reflects that psychodynamic therapy in general has been studied less extensively than other forms of psychotherapy for depression, such as cognitive behavioural therapy (CBT; e.g., Cuijpers et al., 2014). Second, and related, we cannot rule out the possibility that we have missed additional studies meeting the inclusion criteria, although we have tried to minimize this possibility by using an extensive search strategy and we were able to include a study that did not report the requisite data for effect size calculation in its publication and was therefore excluded from previous conventional meta-analyses (Driessen et al., 2010, 2015). Third, not all studies were free from detection bias and attrition bias. However, effects were still apparent in the sensitivity analyses that controlled for risk of bias in the primary studies. Fourth, although the studies shared similarities, they also differed, for instance, with regard to the STPP model used, the type of antidepressant examined, length of follow-up, and their focus on specific comorbidities. Therefore, this meta-analysis' results might not generalize to all STPP modes, antidepressant types, and participant groups. Fifth, this meta-analysis used depression level as the sole outcome measure. Although depression symptom level was specified a priori as the primary outcome measure (Driessen et al., 2018), examining additional outcome measures (e.g., anxiety, interpersonal functioning, quality of life) would have been desirable as these are important aspects of participant functioning too. In addition, examining cost-effectiveness would have been desirable as well to investigate whether the benefits in terms of efficacy outweigh the costs of adding STPP to antidepressant medication. However, this was not possible as outcome measures other than depression were not assessed consistently across the trials.

4.3. Clinical and research implications

The findings of this study suggest that people suffering from depression and their clinicians might expect lower depressive symptom levels when adding STPP to antidepressant medication. These benefits might be small at post-treatment and the largest benefits might be expected at follow-up. The finding that these benefits might be related to STPP's specific treatments effects as opposed to non-specific treatment factors, implicate the need for proper therapist training and supervision in order to capitalize on these specific STPP treatment effects. Collectively, these findings add to the evidence-base of adding STPP to antidepressants in the treatment of depression.

However, the findings of this study cannot be taken to imply that combined treatment of antidepressants and STPP should be considered the first choice treatment for individuals with depression, as this study does not speak to comparative efficacy with other depression treatments. Examining the relative merits of STPP versus other psychotherapies as added to antidepressants requires randomized comparisons of combined treatment of antidepressants and STPP versus combined treatment of antidepressants and another psychotherapy. The literature searches for our larger STPP for depression individual participant data meta-analysis project identified only one such study. This was a pilot study comparing combined treatment of antidepressants and STPP versus combined treatment of antidepressants and CBT, which pooled the two treatment conditions in its report because of the small sample size (n = 12; Perry, Banon, & Bond, 2020). One other study compared STPP and CBT as mono-therapies, but offered additional treatment with antidepressants to severely depressed participants

(n = 129; Driessen et al., 2013). No significant treatment differences were found in this subgroup of severely depressed participants receiving combined treatment (post-treatment: Cohen's d = 0.21, 95% CI = −0.23 to 0.64, follow-up: d = 0.32, 95% CI = −0.15 to 0.79), but favored combined treatment with CBT and were large enough to be significant if replicated in a larger sample.

Considering the limitations of this study mentioned previously and the clinical importance of the research question, the field would benefit from further study of the efficacy of adding STPP to antidepressants in the treatment of depression. In our opinion, comparisons of combined treatment of antidepressants and STPP versus combined treatment of antidepressants and brief supportive psychotherapy are most relevant in this regard as they relate to STPP's specific treatment effects. Comparisons of combined treatment of antidepressants and STPP versus combined treatment of antidepressants and other psychotherapies (e.g., CBT) are also needed. Preferably, future study constitutes large-scale rigorously conducted randomized clinical trials that also assess outcome measures other than depression, including measures that facilitate cost-effectiveness analyses. As STPP might not be available for all people with depression due to scarcity of treatment resources and because the addition of psychotherapy to antidepressant medication requires a financial investment, future research examining which participants benefit specifically from adding STPP to antidepressants in the treatment of depression is also needed.

5. Conclusion

We examined the efficacy of adding STPP to antidepressants in the treatment of depression by means of a systematic review and meta-analysis of individual participant data, which is currently considered the most reliable method for evidence synthesis. Across the total sample of seven studies that were identified by a thorough systematic literature search, adding STPP to antidepressants was found to be significantly more efficacious than antidepressants with/without brief supportive psychotherapy in terms of depressive symptom level at both post-treatment and follow-up. Effects were most apparent at follow-up and in studies that assessed STPP's specific treatment effects by including brief supportive psychotherapy in the comparison condition. Effects were still apparent in analyses that controlled for risk of bias and STPP quality in the primary studies. Although further study is needed, particularly assessing cost-effectiveness and outcome measures other than depression, these findings support the evidence-base of adding STPP to antidepressants in the treatment of depression.

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Contributors

Ellen Driessen, Jack J. M. Dekker, Henricus L. Van, Jos W. R. Twisk, and Pim Cuijpers designed the study and wrote the protocol. Ellen Driessen conducted literature searches and statistical analyses, and wrote the first draft of the manuscript. Jack J. M. Dekker, Jaap Peen, Henricus L. Van, Giuseppe Maina, Gianluca Rosso, Sylvia Rigardetto, Francesco Cuniberti, Veronica G. Vitriol, Ramon U. Florenzano, Antonio Andreoli, Yvonne Burnand, Jaime López-Rodríguez, and Valerio Villamil-Salcedo collected the individual participant data. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

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