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Effectiveness of psychotherapy for treatment-resistant depression: a meta-analysis and meta-regression

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Review Article

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Abstract

Despite substantial advances in treatment and management strategies for major depression, less than 50% of patients respond to first-line antidepressant treatment or psychotherapy. Given the growing number of controlled studies of psychotherapy for treatment-resistant depression (TRD) and the preference for psychotherapy of depressed subjects as a treatment option, we conducted a meta-analysis and meta-regression analysis to investigate the effectiveness of psychotherapy for TRD. Seven different psychotherapies were studied in 21 trials that included a total of 25 comparisons. In three comparisons of psychotherapy *v.* treatment as usual (TAU) we found no evidence to conclude that there is a significant benefit of psychotherapy as compared with TAU. In 22 comparisons of add-on psychotherapy plus TAU *v.* TAU only, we found a moderate general effect size of 0.42 (95% CI 0.29–0.54) in favor of psychotherapy plus TAU. The meta-regression provided evidence for a positive association between baseline severity as well as group *v.* individual therapy format with the treatment effect. There was no evidence for publication bias. Most frequent investigated treatments were cognitive behavior therapy, interpersonal psychotherapy, mindfulness-based cognitive therapy, and cognitive behavioral analysis system of psychotherapy. Our meta-analysis provides evidence that, in addition to pharmacological and neurostimulatory treatments, the inclusion of add-on of psychotherapy to TAU in guidelines for the treatment of TRD is justified and will provide better outcomes for this difficult-to-treat population.

Introduction

Major depressive disorder (MDD) is a highly prevalent and disabling psychiatric condition. Despite substantial advances in treatment and management strategies for MDD, less than 50% of patients respond to first-line antidepressant treatment or psychotherapy (Cuijpers *et al.*, 2013; Kolovos *et al.*, 2016). MDD that is treatment refractory, mostly described as treatment-resistant depression (TRD), is characterized by marked functional impairment, a large burden on patients and families, and is associated with great direct and indirect healthcare costs (Greden, 2001; Moussavi *et al.*, 2007).

Clinical reviews suggest a prevailing inclination to manage TRD (solely) by pharmacotherapy or other somatic treatments while scarcely mentioning studies into psychotherapy for TRD with little or no discussion of the findings and prospects (e.g. Carvalho *et al.*, 2014; Dold and Kasper, 2016). This may be imprudent because (i) the likelihood of remission is considerably reduced for individuals who require third or fourth-line antidepressant treatment due to non-response in prior steps (Rush *et al.*, 2006), (ii) a majority of depressed individuals seems to prefer psychotherapy over medication (McHugh *et al.*, 2013), and (iii) patients receiving their preferred treatment show better outcomes (Gelhorn *et al.*, 2011; Mergl *et al.*, 2011; Swift *et al.*, 2011; McHugh *et al.*, 2013). Given these considerations, there is a need to thoroughly evaluate psychotherapy as a treatment option for TRD and accordingly formulate recommendations for clinical practice.

High-quality studies that specifically sought to examine the effectiveness of psychotherapeutic treatments for TRD are scarce and virtually absent until the beginning of this millennium. In 2002, Stimpson, Agrawal, and Lewis conducted a systematic review of randomized controlled trials (RCTs) for TRD but no psychotherapy studies met their minimal inclusion criteria at that point. Two more recent reviews, based on seven RCTs and eight uncontrolled

studies, concluded that psychotherapy either as augmentation or substitute therapy could be an effective and reasonable treatment for TRD (McPherson *et al.*, 2005; Trivedi *et al.*, 2011). The authors emphasized the need for more high-quality, controlled trials to effectively judge the utility of psychotherapy for TRD and guide clinical practice.

Moreover, there is considerable variation in and confusion about definitions of TRD and chronic depression (cMDD) in the literature (Ruhe *et al.*, 2012). As a result, many studies into the psychotherapeutic treatment of cMDD appear to be carried out in clinical samples that in the majority consist of participants that already received one or more failed treatments for the index episode, thereby qualifying them, in fact, as studies of psychotherapy for TRD.

Given the considerations above and a growing database of randomized controlled studies treating TRD with psychotherapy, we decided to conduct a meta-analysis and meta-regression. For these analyses, we collected all randomized controlled studies of psychotherapy for adult patients with TRD and/or unsuccessfully treated cMDD in which the effectiveness of psychotherapy was examined as either a substitute for or add-on to treatment as usual (TAU; routine treatments such as clinical management and/or the continuation, optimization or next step pharmacotherapy). We hypothesized (i) that switching to psychotherapy is more effective than TAU, and (ii) psychotherapy as an add-on to TAU to be more effective than TAU only.

Methods

Search strategy and study selection

Two authors (SB and NM) independently performed a comprehensive search through PubMed, Embase and PsychINFO electronic databases combining terms regarding psychotherapy, and TRD/cMDD (online Supplementary Methods I). Publications up until and including 19 December 2016 were reviewed. The search was limited to articles published in English, describing studies with a controlled design in samples of adult participants. References of the selected articles were checked, as well as references of earlier systematic reviews and meta-analyses (McPherson *et al.*, 2005; Cuijpers *et al.*, 2010*c*; Trivedi *et al.*, 2011; Spijker *et al.*, 2013; Kriston *et al.*, 2014; Negt *et al.*, 2016).

The same authors independently assessed articles for inclusion by screening titles and abstracts followed by detailed full-text evaluation if necessary. Disagreements between the reviewers were solved through discussion with a third independent reviewer (FP). We included (i) RCTs that examined the effectiveness of psychotherapy for (ii) adults (⩾18 years of age) with TRD by comparing (iii) psychotherapy *v.* TAU or (iv) add-on psychotherapy and TAU *v.* TAU only. For this meta-analysis, we defined TRD in line with previous reviews (Stimpson *et al.*, 2002; McPherson *et al.*, 2005; Trivedi *et al.*, 2011), as an individual's failure to respond to at least one adequate trial of antidepressants for the current episode irrespective of duration of the current episode. We decided to apply this broad definition to enable comparisons with previous literature and to include a large body of evidence. A failed response was assumed when study sample descriptions mentioned the inclusion of participants not meeting the criteria for clinically significant response or remission to the previous treatment. For the current meta-analyses, we included cMDD studies if the majority of the sample fulfilled our criterion for TRD. Psychotherapy was defined as a face-to-face interaction with a therapist, which was allowed to be delivered either in a group or individual format in both out- and inpatient settings. TAU was defined as treatments that individuals would normally receive in routine (mental) health care, such as clinical management and pharmacotherapy. Pharmacotherapy included continuation, optimization, switching or starting of antidepressant medication. Studies were excluded if they had a maintenance treatment study design or if treatment-resistance was undefined or remained unclear based on the reported information on previously failed response to antidepressant medication.

Quality assessment and data extraction

Two authors (SB and FP) independently evaluated the validity of the studies eligible for the qualitative synthesis. Following recent meta-analyses (Cuijpers *et al.*, 2014, 2015), we examined all included studies on four criteria of the 'Risk of bias' assessment tool, developed by the Cochrane Collaboration (Higgins and Green, 2011): (1) adequate random sequence generation, (2) allocation to treatments by an independent (third) party, (3) blinding of the outcome assessment and (4) the quantity, nature and management of incomplete outcome data. Disagreements between the reviewers were resolved through discussion.

Two authors (NM and LB) independently extracted the data from the included studies. Data extraction was checked and disagreements were resolved by two other reviewers (FP and SB). For the outcome variable, means and standard deviations (S.D.) of change in depression severity scales from pre- to post-intervention were extracted for both the treatment and TAU condition. Our research questions addressed outcomes of acute-phase treatment specifically. Therefore, the post-treatment endpoint was set a maximum of 16 weeks with a minimum session frequency of once a week. Follow-up measurements were excluded from our analyses. Although the treatment endpoint was set at 16 weeks to target the acute phase, for some studies outcome data were not available at this time point. As a result, the post-intervention depression severity score was assessed at 12.8 weeks on average, varying between 5 and 26 weeks. In addition, we extracted clinical variables, treatment variables and study variables for background information input for sensitivity analyses, and meta-regressions (as described in the 'Statistical Analyses' section). Clinical variables included the male/female ratio, the mean age of the sample, mean depression severity at baseline, prior history (number of previous episodes and mean illness duration in months), mean duration of the current episode and the percentage of participants that did not respond to antidepressants or psychotherapy for the current episode prior to the study. Treatment variables included the type of psychotherapy, treatment duration (number of months and number of treatment sessions), individual or group setting, attrition rates, and treatment integrity. Study variables included the year the study was conducted, the clinical setting (inpatient or outpatient), and an intention to treat approach for the extracted outcome measures.

For each study, we coded the type of comparison: (1) psychotherapy *v.* TAU or (2) add-on psychotherapy plus TAU *v.* TAU. In addition, we specified the type of interventions that were considered TAU. For a few studies comparing the 'add-on psychotherapy plus TAU *v.* TAU', the TAU interventions were slightly different between the two groups. If so, this was coded during our data extraction.

All corresponding authors were contacted to check the data retrieved during our data extraction and were asked to provide

missing data. If those attempts failed and the incomplete data made the calculation of an effect size impossible, studies were excluded from the quantitative but not the qualitative synthesis of evidence.

Statistical analyses

All analyses were done with Stata version 13.1. The primary outcome was the difference between the average depression severity change of treatment and control condition, calculated as Hedges' *g* effect sizes. If multiple instruments were available to assess symptomatic change, the mean effect size was calculated (Borenstein *et al.*, 2009). To test whether studies with multiple depression severity scales affected the overall results of the meta-analyses, sensitivity analyses were performed with only studies using one measurement scale. Since most studies had a small sample size, effects sizes were corrected for small sample bias (Hedges' *g*). If average change scores were not reported, they were calculated using the average pre and post-intervention depression severity score. When unavailable, S.D. of the change scores were calculated using the S.D. of the average pre- and post-intervention depression scores and the correlation coefficient between these scores (calculations were based on the formula presented in online Supplementary Methods II). If this correlation coefficient was not reported, we assumed a correlation of $r = 0.5$, which was based on data from a recent RCT comparing cognitive therapy and interpersonal psychotherapy for MDD (Lemmens *et al.*, 2015). To examine the impact of this assumption, a sensitivity analyses were performed to test whether a reduced ($r = 0.2$) or increased ($r = 0.8$) correlation would change the overall results of the meta-analysis.

Summary effect sizes were pooled using a random-effects model for (i) psychotherapy *v.* TAU or (ii) add-on psychotherapy plus TAU *v.* TAU comparison. To test the homogeneity of the effect sizes, the I^2 statistic was estimated with 95% confidence intervals (Ioannidis *et al.*, 2007). An I^2 value of >50% was assumed to be indicative of heterogeneity. When multiple comparisons of one trial were included, sensitivity analyses were performed to test whether this affected the pooled results by only including the comparison with the smallest effect size. In addition, sensitivity analyses on study quality were conducted by limiting the analyses to the studies meeting all four quality criteria with a low-risk score. For the second comparison, studies with slightly different TAU interventions between the two groups were excluded to see whether this affected the pooled effect size (additional sensitivity analysis). A similar sensitivity analysis was computed for studies with the inclusion of psychotherapy in the TAU interventions. We assessed publication bias by inspecting funnel plots and examining plot asymmetry using the Egger's test (Egger *et al.*, 1997).

A meta-regression was conducted in order to relate specific study-level variables to the statistical heterogeneity between the results of the studies (Thompson and Higgins, 2002). First, we conducted univariate meta-regressions for each of the following a priori selected variables: mean depression severity at baseline, mean illness duration (number of months and number of previous episodes), mean duration of the current episode, the percentage of participants that did not respond to antidepressants for the current episode, mean treatment duration (number of months and number of treatment sessions), attrition rates, the clinical setting (inpatient or outpatient), individual or group format, clinician-rated or self-reported outcomes (or a combination), and whether the extracted outcomes were based on intention to treat data. When variables had at least a p value <0.10, they were included in a multivariate meta-regression. Correlations between the variables that were included in the multivariate meta-regression were examined to check if collinearity could influence the results.

Results

Selection and inclusion of trials

We identified 1044 potentially relevant citations through database searching and 16 additional records through other sources. After removing duplicates and excluding non-relevant citations based on abstract examination, we retrieved 32 full-text papers for further consideration. Finally, 22 trials met our inclusion criteria for the meta-analysis, however, 1 trial was only included in the qualitative analysis as a result of reporting incomplete data. The PRISMA flow chart describing the inclusion process and exclusion reasons is presented in Fig. 1.

Characteristics of included trials

The 21 trials included in the meta-analyses provided a total of 25 comparisons; three comparisons (three studies) pertained to psychotherapy *v.* TAU (Table 1), and 22 (20 studies) to a comparison of add-on psychotherapy plus TAU *v.* TAU only (Table 2). A total of 3539 patients were enrolled (293 in psychotherapy only, 1588 in add-on psychotherapy plus TAU and 1638 in TAU). Sample sizes varied between 11 and 235 participants per treatment arm.

All trials (22 with the inclusion of the one study that was retained in the qualitative analysis only) recruited participants in secondary or tertiary care facilities except for one that was conducted in primary care (Wiles *et al.*, 2013). Two trials were conducted in an inpatient setting. Eight trials were conducted in North- and South America, nine in the UK, four in other European countries, and one in East Asia.

In total, 11 different psychotherapeutic treatments were investigated. In the 25 comparisons, six examined cognitive behavior therapy (CBT), six cognitive behavioral-analysis system of psychotherapy (CBASP), two interpersonal psychotherapy (IPT), four mindfulness-based cognitive therapy (MBCT). The number of treatment sessions varied from 8 to 60 (although treatment endpoint for further analyses was set at 16 weeks to target the acute phase which restricted the range between treatments, see method section). Fourteen comparisons used an individual format, 10 employed a group format, and one utilized a mixed individual and group approach.

In the psychotherapy *v.* TAU comparison, TAU conditions included starting of (Keller *et al.*, 2000; Schramm *et al.*, 2015) and switching to (Thase *et al.*, 2007) different types of antidepressant medication. TAU interventions in the add-on psychotherapy plus TAU *v.* TAU comparison included clinical management, and starting, augmenting, optimizing, and continuing pharmacotherapy. Changes in antidepressant medication (starting, augmenting and optimizing) were guided by a study protocol (Barker *et al.*, 1987; Keller *et al.*, 2000; Kennedy *et al.*, 2003; Schramm *et al.*, 2007; Thase *et al.*, 2007; Kocsis *et al.*, 2009) or left to the decision of clinicians (Murray *et al.*, 2010; Wiles *et al.*, 2013; Wiersma *et al.*, 2014; Fonagy *et al.*, 2015; Michalak *et al.*, 2015; Eisendrath *et al.*, 2016; Souza *et al.*, 2016). For a few studies comparing add-on psychotherapy plus TAU *v.* TAU, TAU conditions involved psychotherapy options (not for all participants) (Murray *et al.*, 2010; Watkins

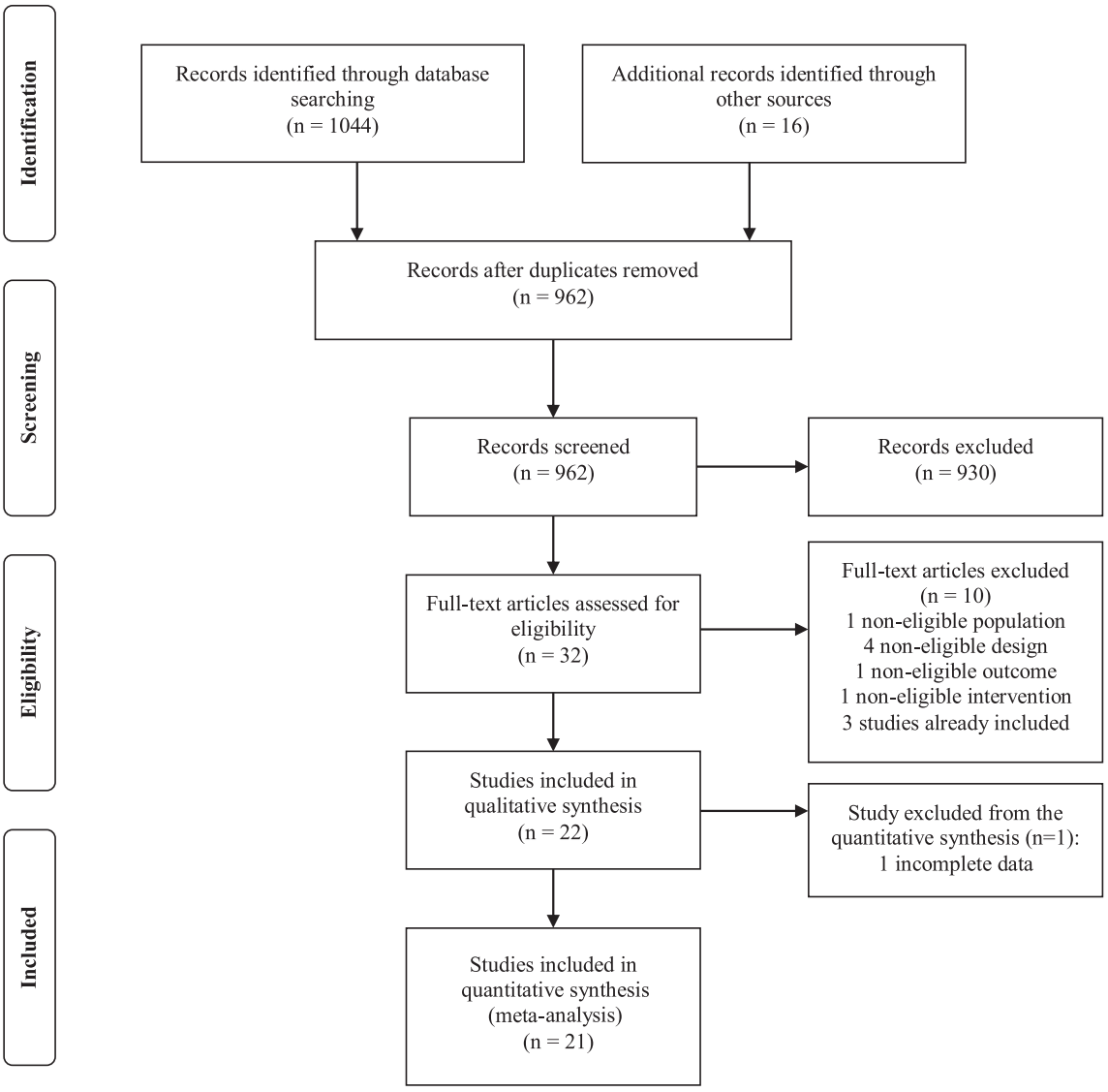

Fig. 1. Study selection process.

et al., 2011; Wiles *et al.*, 2013; Wiersma *et al.*, 2014; Fonagy *et al.*, 2015; Michalak *et al.*, 2015), psycho-education (Chiesa *et al.*, 2015), a health enhancement program (Eisendrath *et al.*, 2016) or other health care services (Harley *et al.*, 2008; Barnhofer *et al.*, 2009; Wiersma *et al.*, 2014). In nine of 22 'psychotherapy plus TAU *v.* TAU' comparisons, the TAU interventions were slightly different between the two groups (Kennedy *et al.*, 2003; Schramm *et al.*, 2007; Thase *et al.*, 2007; Murray *et al.*, 2010; Watkins *et al.*, 2011; Wiersma *et al.*, 2014; Chiesa *et al.*, 2015; Fonagy *et al.*, 2015; Eisendrath *et al.*, 2016).

Studies used various instruments to examine depression severity, including clinician-rated measures (Hamilton Rating Scale for Depression Scale, Montgomery-Asberg Depression Rating Scale, Quick Inventory of Depressive Symptomatology) and self-report measures (Inventory of Depressive Symptomatology, Beck Depression Inventory, Quick Inventory of Depressive Symptomatology).

Quality of included trials

Thirteen of the 22 studies met all four quality criteria with a 'low risk' score. A total of 18 studies reported an adequate random sequence generation. In 19 studies, it was reported that the treatment allocation was done by an independent party. In 23 studies, the outcome assessors were blinded to the treatment allocation. A total of 15 studies used intention-to-treat analyses and had a balanced number of missing outcome data across interventions.

Treatment integrity

Two of the 22 studies did not report information on the therapist's competence in and adherence to the specific treatment type (Barker *et al.*, 1987; Kennedy *et al.*, 2003). Of the remaining 20 studies, seven trials provided extra training for the therapists prior to the study. Therapists received supervision (individual and/or group) in 17 studies, and sessions were video or audio recorded in 13 studies. Adherence was systematically rated in eight studies, of which two used 'checklists' and the remaining six used standardized instruments. Competence was systematically assessed in five studies with standardized instruments. Detailed information about treatment integrity for each study is provided in online Supplementary Results I.

Table 1. Psychotherapy for TRD when substituted for TAU; study and treatment variables

Author, year	Treatment resistance		Psychotherapy	TAU	No. of sessions, duration	Sample size (treatment, control)	Measurement scales	Setting	Group or individual therapy	Study quality[a]
	Definition of treatment resistance or chronicity	Rates of non-response to ADM or other treatments								
Keller *et al.* (2000)	Chronic forms of major depressive disorder	ADM: 60.2%; PT: 65.2%; ADM + PT: 45.1%.	CBASP	Starting NFN treatment + CM	16–20 sessions; 12 weeks	228, 226	HAM-D_{24}	Outpatient	Individual	1: + 2: + 3: + 4: +
Thase *et al.* (2007)	Inadequate benefit from an initial CTM treatment (level 1 of the STAR-D trial).	ADM: 100%	CBT	Switching to BUP, SER or VLX treatment	16 sessions; 12 weeks	36, 86	HAM-D_{17}; QIDS-C	Outpatient	Individual	1: – 2: + 3: + 4: –
Schramm *et al.* (2015)	Chronic major depressive disorder	ADM:56.9% PT: 67.80% ADM + PT: 47.0%	CBASP	Starting ECM treatment	12 sessions; 8 weeks	29, 31	MADRS; IDS-SR	Outpatient	Individual	1: + 2: + 3: + 4: +

TRD, treatment-resistant depression; TAU, treatment as usual; ADM, antidepressant medication; PT, psychotherapy; CBASP, Cognitive Behavioral Analysis System of Psychotherapy; NFN, Nefazodon; CM, clinical management; HAM-D_{24}, 24-item Hamilton Rating Scale for Depression; CTM, Citalopram; CBT, cognitive behavioral therapy; BUP, bupropion; SER, sertraline; VLX, venlafaxine; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; QIDS-C, clinician-administered version of the 16-item Quick Inventory of Depressive Symptomatology; ECM, Escitalopram; MADRS, Montgomery-Asberg Depression Rating Scale; IDS-SR, self-report version of the Inventory of Depressive Symptomatology.

[a]Study quality was examined using four criteria of the ''Risk of bias'' assessment tool, developed by the Cochrane Collaboration (Collaboration 2015). A positive (low risk) or negative sign (high risk or unclear) is given to each of the criteria respectively: (1) adequate random sequence generation, (2) allocation to treatments by an independent (third) party, (3) blinding of the outcome assessment and (4) the quantity, nature and management of incomplete outcome data.

Table 2. Add-on psychotherapy plus TAU *v.* TAU; study and treatment variables

Author, year	Treatment resistance		Psychotherapy plus TAU	TAU	No. of sessions; duration	Sample size (treatment, control)	Measurement scales	Setting	Group or individual therapy	Study quality[a]
	Definition of treatment resistance or chronicity	Rates of non-response to ADM or other treatments								
Barker *et al.* (1987)	Depression for at least 2 years with failure to respond to recognized treatment regimes.	Recognized treatment regimes: 100%	CBT + starting 5-HT cocktail + low vanadium regime	5-HT cocktail + starting low vanadium regime	15 sessions, 12 weeks	Unclear	HAM-D, BDI	Outpatient	Individual	1: – 2: – 3: – 4: –
Paykel *et al.* (1999); Scott *et al.* (2000)	Residual depression symptoms lasting 2–18 months (after a depressive episode within the last 18 months), despite ADM for at least the 8 weeks prior to the study, with at least 4 weeks at an adequate dose (a minimum equivalent to 125 mg per day of AMI), or to have refused explicitly to increase the dosage.	ADM:100%	CBT + continuation of PHT + CM	Continuation of PHT + CM	16 sessions; 20 weeks	80, 78	HAM-D_{17}; BDI	Outpatient	Individual	1: + 2: + 3: + 4: +
Keller *et al.* (2000)	Chronic forms of major depressive disorder	ADM: 60.2%; PT: 65.2%; ADM + PT: 45.1%.	CBASP + starting NFN treatment + CM	Starting NFN treatment + CM	16–20 sessions;12 weeks	227, 226	HAM-D_{24}	Outpatient	Individual	1: + 2: + 3: + 4: +
Kennedy *et al.* (2003)	Partial response after receiving 1 of 4 standard ADM (MOC, PAR, SER, VLX) to maximum tolerated doses for 8 to 14 weeks.	ADM: 100%	CBT + continuation of PHT	Lithium augmentation + continuation of PHT	12 session; 8 weeks	23, 21	HAM-D_{17}; BDI	Outpatient	Individual	1: – 2: – 3: + 4: +
Thase *et al.* (2007)	Inadequate benefit from an initial CTM treatment (level 1 of the STAR-D trial).	ADM: 100%	CBT + continuation of CTM	Augmentation medication (BUP, BUS) + continuation of CTM	16 sessions;12 weeks	65, 117	HAM-D_{17}; QIDS-SR	Outpatient	Individual	1: – 2: + 3: + 4: –
Schramm *et al.* (2007)	Not defined.	ADM: 50,8% Outpatient treatment: 83.0% Previous hospitalization: 44%	IPT + starting PHT	Starting PHT + CM	23 sessions; 5 weeks	65, 65	HAM-D_{17}; BDI	Inpatient	Individual and group	1: + 2: + 3: + 4: +
Wong, (2008)	Ongoing major depressive disorder despite ADM with mild to severe depressive symptoms despite ADM treatment	ADM:100%	CBT + continuation of PHT	Continuation of PHT	10 sessions; 10 weeks	48, 48	BDI	Outpatient	Group	1: – 2: – 3: + 4: –
Harley *et al.* (2008)	Ongoing major depressive disorder despite ADM	ADM: 100%	DBTST + continuation of PHT and other	Continuation of PHT and other mental health treatments as usual	16 sessions;16 weeks	13, 11	HAM-D_{17}, BDI-II	Outpatient	Group	1: + 2: –

	treatment (i.e. at least the standard effective dosage of a given antidepressant defined in the consensus of 2 senior psychiatrists, and no change in dosage for at least 6 weeks prior to the study)		mental health treatments as usual							3: + 4: –
Kocsis *et al.* (2009)	Chronic forms of the major depressive disorder. Inadequate benefit (less than remission) from an initial standardized PHT (phase 1 of the REVAMP trial).	ADM: 100%	A: BSP + switching PHT + CM B: CBASP + switching PHT + CM	Switching PHT + CM	A. 16–20 session; 12 weeks B:16 sessions;12 weeks	BSP: 195 CBASP: 200 TAU:96	HAM-D_{24}; QIDS-C	Outpatient	Individual	1: + 2: + 3: + 4: +
Barnhofer *et al.* (2009)	Chronic major depressive disorder	ADM: 60% at the start of the trial (80% previously) PT: >2/3 had received PT or counselling, more than half of them had received CBT	MBCT + continuation of PHT and other mental health treatments as usual (except individual PT)	Continuation of PHT and other mental health treatments as usual (except individual PT or meditation practice)	8 sessions; 8 weeks	16, 15	BDI-II	Outpatient	Group	1: + 2: + 3: + 4: +
Murray *et al.* (2010)	Chronic forms of major depressive disorder	ADM: on average 3 failed medication trials PT: 85.7% ECT: 28.1%	Re-ChORD: optimizing PHT, IPT and occupational therapy	Treated with available services based on a detailed recommendations on optimizing PHT and PT interventions	26–28 sessions; 4 months	34, 30	BDI-II	Outpatient	Group	1: + 2: + 3: + 4: –
Watkins *et al.* (2011)	Residual depression symptoms despite ADM treatment (at a therapeutic dose as recommended by the British National Formulary and/or equivalent to 125 mg of AMI) for at least 8 weeks continuously during the current episode and within the 2 months prior to the study	ADM:100%	IRCBT + continuation of PHT + CM	Continuation of PHT + CM + PT (for n = 7)	12 sessions; 6 months	21, 21	HAM-D_{17}, BDI-II	Outpatient	Individual	1: + 2: + 3: + 4: +
Strauss *et al.* (2012)	Chronic forms of major depressive disorder	ADM:88% PT: 84%	PBCT + continuation of PHT + CM	Continuation of PHT + CM	12 sessions; 12 weeks	14, 14	BDI-II	Outpatient	Group	1: – 2: – 3: + 4: +
Wiles *et al.* (2013)	Ongoing depressive symptoms despite at least 6 weeks of ADM treatment at an adequate dose	ADM:100%	CBT + optimizing PHT + CM by a general practitioner (no restrictions on referring to other mental health services including PT)	Optimizing PHT + CM by a general practitioner (no restrictions on referring to other mental health services including PT)	12–18 sessions; 6 months	234, 235	BDI-II	Outpatient	Individual	1: + 2: + 3: + 4: +
Rohricht *et al.* (2013)	Chronic forms of the major depressive disorder	ADM: 100%; an average of 4 ADM trials at an adequate dose (range 2–7)	GBOPT + continuation of PHT + CM by community psychiatric services	Continuation of PHT + CM by community psychiatric services	20 sessions; 10 weeks	16,15	HAM-D_{21}	Outpatient	Group	1: + 2: + 3: + 4: –

(*Continued*)

Table 2. (*Continued.*)

Author, year	Treatment resistance		Psychotherapy plus TAU	TAU	No. of sessions; duration	Sample size (treatment, control)	Measurement scales	Setting	Group or individual therapy	Study quality[a]
	Definition of treatment resistance or chronicity	Rates of non-response to ADM or other treatments								
		PT: 100%; one or two courses of individual psychotherapy (CBT, PDP)								
Wiersma *et al.* (2014)	Chronic forms of the major depressive disorder	ADM: 64.1% Previous mental health treatment (secondary or tertiary care): 82.3%	CBASP + optimizing PHT + CM	Optimizing PHT + CM + psychotherapy (CBT, IPT, short psycho-analytic supportive therapy and supported/structured therapy)	24 sessions: 12 months[b]	69, 73	IDS	Outpatient	Individual	1: + 2: + 3: + 4: +
Michalak *et al.* (2015)	Chronic forms of the major depressive disorder	ADM:53.8% PT: 29.2%	A. MBCT + continuation and starting PHT + CM/PT B. CBASP + continuation and starting PHT + CM/PT	Continuation and starting PHT + CM/PT	MBCT: 8 sessions; 8 weeks CBASP: 10 sessions; 8 weeks	MBCT:36 CBASP:35 TAU:35	$HAM\text{-}D_{24}$ BDI-II	Outpatient	Group	1: + 2: + 3: + 4: +
Fonagy *et al.* (2015)	Ongoing major depressive disorder despite at least two antidepressant treatments, one of which must have included ADM treatment and the other with either ADM or a psychological intervention.	ADM:100%	PDP + optimizing PHT + CM	Optimizing PHT + CM + PT	60 sessions; 18 months[c]	67, 62	$HAM\text{-}D_{17}$; BDI	Outpatient	Individual	1: + 2: + 3: + 4: +
Chiesa *et al.* (2015)	Ongoing major depressive disorder (failure to achieve remission) despite ADM treatment at adequate dosages for at least 8 weeks prior to the study	ADM: 100%	MBCT + continuation of PHT	Psycho-education program + continuation of PHT	8 sessions; 8 weeks	26, 24	$HAM\text{-}D_{21}$ BDI-II	Outpatient	Group	1: + 2: + 3: + 4: +
Eisendrath *et al.* (2016)	Ongoing major depressive disorder despite at least two adequate trials of antidepressant medication during the current episode	ADM:100%	MBCT + continuation or optimizing of PHT	Health Enhancement Program (comparator condition for MBCT) + continuation or optimizing of PHT	8 sessions; 8 weeks	87, 86	$HAM\text{-}D_{17}$	Outpatient	Group	1: + 2: + 3: + 4: –

Souza *et al.* (2016)	Ongoing major depressive disorder despite at least one trial of ADM in an adequate dose (equivalent to ⩾75 mg of AMI) and adequate duration (⩾ 4 weeks)	ADM: 100%	IPT + optimizing PHT + CM	Optimizing PHT + CM	16 sessions; 16–19 weeks,	17, 23	$HAM\text{-}D_{17}$; BDI	Outpatient	Individual	1: + 2: + 3: + 4: –

TRD, treatment resistant depression; TAU, treatment as usual; CBT, Cognitive Behavior Therapy; 5-HT cocktail, combination of phenelzine, L-tryptophan and lithium carbonate; low vanadium regime, a diet low in vanadium and sodium calcium edetat; HAM-D, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; AMI, amitriptyline; ADM, antidepressant medication; PHT, Pharmacotherapy; CM, clinical management; $HAM\text{-}D_{17}$, 17-item Hamilton Rating Scale for Depression; CBASP, Cognitive Behavioral Analysis System of Psychotherapy; NFN, Nefazodon; $HAM\text{-}D_{24}$, 24-item Hamilton Rating Scale for Depression; MOC, moclobemide; PAR, paroxetine; SER, sertraline; VLX, venlafaxine; CTM, Citalopram; BUP, bupropion; BUS, buspirone; QIDS-SR, self-report version of the Inventory of Depressive Symptomatology; DBTST, Dialectic Behaviour Therapy Skills Training; BDI-II, Beck Depression Inventory, second edition; BSP, Brief supportive psychotherapy; QIDS-C, clinician-administered version of the 16-item Quick Inventory of Depressive Symptomatology; MBCT, Mindfulness Based Cognitive Therapy; ECT, electroconvulsive therapy; PDP, Psycho-dynamic psychotherapy; GBOPT, Group body oriented psychological therapy; $HAM\text{-}D_{21}$,21-item Hamilton Rating Scale for Depression; IPT, Interpersonal Therapy; IDS, Self-report version of the Inventory for Depressive Symptomatology.
[a]Study quality was examined using four criteria of the "Risk of bias" assessment tool, developed by the Cochrane Collaboration (Collaboration 2015). A positive (low risk) or negative sign (high risk or unclear) is given to each of the criteria, respectively: (1) adequate random sequence generation, (2) allocation to treatments by an independent (third) party, (3) blinding of the outcome assessment and (4) the quantity, nature and management of incomplete outcome data.
[b]For reasons of adequate comparison results at 12 weeks of acute treatment were used in the analyses.
[c]For reasons of adequate comparison results at 16 weeks of acute treatment were used in the analyses.

Psychotherapy v. *TAU*

We examined three studies consisting of three comparisons (see Table 1). Interventions were CBT and CBASP. The TAUs as described in the trials were mainly a continuation of ongoing pharmacotherapy.

The mean pooled effect size was $g = -0.13$ (95% CI −0.30 to 0.05), heterogeneity was low with a high level of uncertainty given the wide 95% CI interval ($I^2 = 0.00$: 95% CI 0.00–89.60). The effect sizes of the individual trials are plotted in Fig. 2, showing that none of the interventions had significantly higher depression severity change scores on average than TAU. Given the small number of studies, we did not perform an Egger's test (Higgins and Green, 2011). Separate sensitivity analyses (1) examining different correlations between pre- and post-intervention depression scores, (2) excluding studies that used multiple outcome measures, (3) including only the comparison with the smallest effect size, did not change the results, and (4) including only studies meeting all four quality criteria with a low risk score. Given the small number of included studies, we were not able to conduct a meta-regression.

Add-on psychotherapy plus TAU v. *TAU*

We examined 20 studies consisting of 22 comparisons for the effectiveness of psychotherapy added to TAU *v.* TAU alone. The psychotherapeutic interventions were IPT, CBASP, CBT, psychodynamic therapy (PDT), body-oriented therapy (BOT), dialectic behavior therapy (DBT) and brief supportive psychotherapy (BSP). The TAUs as described in the trials were mainly a continuation of ongoing pharmacotherapy. Study characteristics are shown in Table 2.

The mean pooled effect size was $g = 0.42$ (95% CI 0.29–0.54), indicating that adding psychotherapy to TAU resulted in higher average depression severity change as compared with treatment with TAU alone (Fig. 3). We found an indication for heterogeneity between studies, with again large uncertainty around this estimate ($I^2 = 52.96$; 95% CI 23.6–71.04). When grouped together by type of treatment, IPT ($g = 0.33$; 95% CI 0.02–0.64), CBASP ($g = 0.42$; 95% CI 0.08–0.76), CBT ($g = 0.26$; 95% CI 0.01–0.51), and MBCT ($g = 0.55$; 95% CI 0.31–0.79) show moderate but significant pooled effect sizes. Within the group of other therapies, BOT, PDT, individual rumination-focused cognitive behavioral therapy, and person-based cognitive therapy showed significant effect sizes (Fig. 3). The funnel plot (Fig. 4) did not indicate publication bias and Egger's test did not indicate asymmetry of the funnel plot (intercept: 0.78; 95% CI −0.79 to 2.35; $p = 0.31$).

Separate sensitivity analyses (1) examining alternative correlations between pre- and post-intervention depression scores, (2) excluding studies that used multiple outcome measures, (3) including only the comparison with the smallest effect size, (4) excluding trials where the TAU in the control group was different from the TAU in the intervention arm, (5) excluding trials where TAU included psychotherapy options, and (6) including only studies meeting all four quality criteria with a low-risk score, did not change the results.

In the univariate meta-regression analyses regarding the set of a priori selected variables, baseline severity ($\beta = 0.16$; S.E. = 0.09; $p = 0.079$); divided into four categories between mild and very severe (Rush *et al.*, 2003), number of sessions ($\beta = -0.12$; S.E. = 0.06; $p = 0.073$), and individual *v.* group format ($\beta = 0.32$; S.E. = 0.14; $p = 0.027$) met our criterion of $p < 0.10$. In a final multivariate

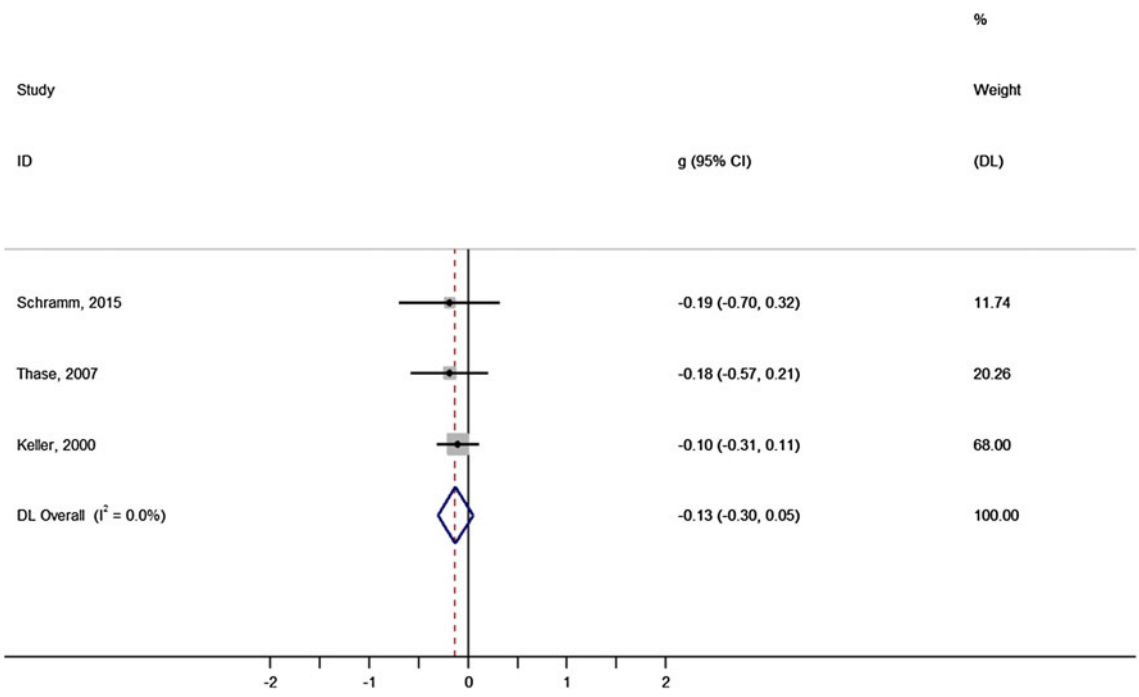

Fig. 2. Effects of psychotherapy for TRD when substituted for TAU. g = Hedges' g effect sizes, 95% CI = 95% confidence interval, DL = DerSimonian-Laird method: between study variation was estimated using the DerSimonian-Laird method.

meta-regression higher baseline severity ($\beta = 0.81$; S.E. = 0.07; $p = 0.032$), and group therapy-format ($\beta = 0.38$; S.E. = 0.20; $p = 0.079$) were associated with a larger effect size. Their correlation was 0.23, indicative of low collinearity.

Discussion

In the present meta-analysis, we investigated the effectiveness of psychotherapy for adult patients with TRD and/or unsuccessfully treated cMDD either as a substitute or as an add-on to TAU. We identified 22 trials of which 21 could be included in the meta-analyses, yielding a total of 25 comparisons. In three comparisons of psychotherapy *v.* TAU we found no significant advantage of psychotherapy over TAU, while in 22 comparisons of add-on psychotherapy plus TAU *v.* TAU only, we found a significant improvement of patients due to psychotherapy with a moderate general effect size of 0.42 (95% CI 0.29–0.55).

Psychotherapy v. *TAU*

Our hypothesis that for acute-phase treatment psychotherapy is more effective than TAU in TRD was not confirmed. Compared with ongoing TAU, psychotherapy, as a substitute for ongoing or recently started TAU, psychotherapy appeared not more effective in TRD (Hedges' $g = -0.02$). We found no indication for publication bias and the heterogeneity between studies was small although this should be interpreted with caution because CI intervals were wide. In a previous meta-analysis (Cuijpers *et al.*, 2010*c*), addressing the effectiveness of psychotherapy for cMDD and dysthymia, the authors reported that pharmacotherapy was more effective than psychotherapy, which seems at odds with our finding. However, it should be kept in mind that our inclusion criteria (aimed at TRD and exclusion of dysthymia) resulted in a selection of different studies. The vast majority of participants in our study selection had not responded to at least one previous trial with an antidepressant that is known to be associated with a less favorable response to subsequent treatments with pharmacotherapy (Ruhe *et al.*, 2006).

Add-on psychotherapy plus TAU v. *TAU*

We found that psychotherapy added to ongoing TAU has a moderate and significant effect size (Hedges' $g = 0.42$) in comparison with TAU alone in TRD. Again, there was no evidence for publication bias, however there was some indication of heterogeneity between studies with wide CI intervals. The results from this meta-analysis suggest that, in line with a previous meta-analysis (Cuijpers *et al.*, 2010*c*) and recent clinical recommendations (Jobst *et al.*, 2016) about the treatment of cMDD, several psychotherapeutic approaches may be of value in the treatment of TRD when added to TAU, with some evidence for more effectiveness in patients with more severe depressive symptomatology. However, some considerations may apply. First, studies of the effectiveness of CBT were done in samples with relatively low levels of TRD (mostly one unsuccessful trial with an antidepressant), which may restrict its applicability in patients with more advanced TRD. Second, some studies (e.g. Keller *et al.*, 2010) excluded participants displaying high levels of TRD, like non-response to three previous adequate trials of different classes of antidepressants or electroconvulsive therapy, again limiting generalizability to patients with more advanced levels of TRD. Third, based on these findings one cannot rule out that TAU and psychotherapy interfere and that the combination of the two interventions leads to a greater impact than the sum of each treatment effect separately. However, a recent meta-analysis on combination therapy (pharmacotherapy and psychotherapy) for depression and anxiety disorders has shown equal and independent effects of pharmacotherapy and psychotherapy (Cuijpers *et al.*, 2014).

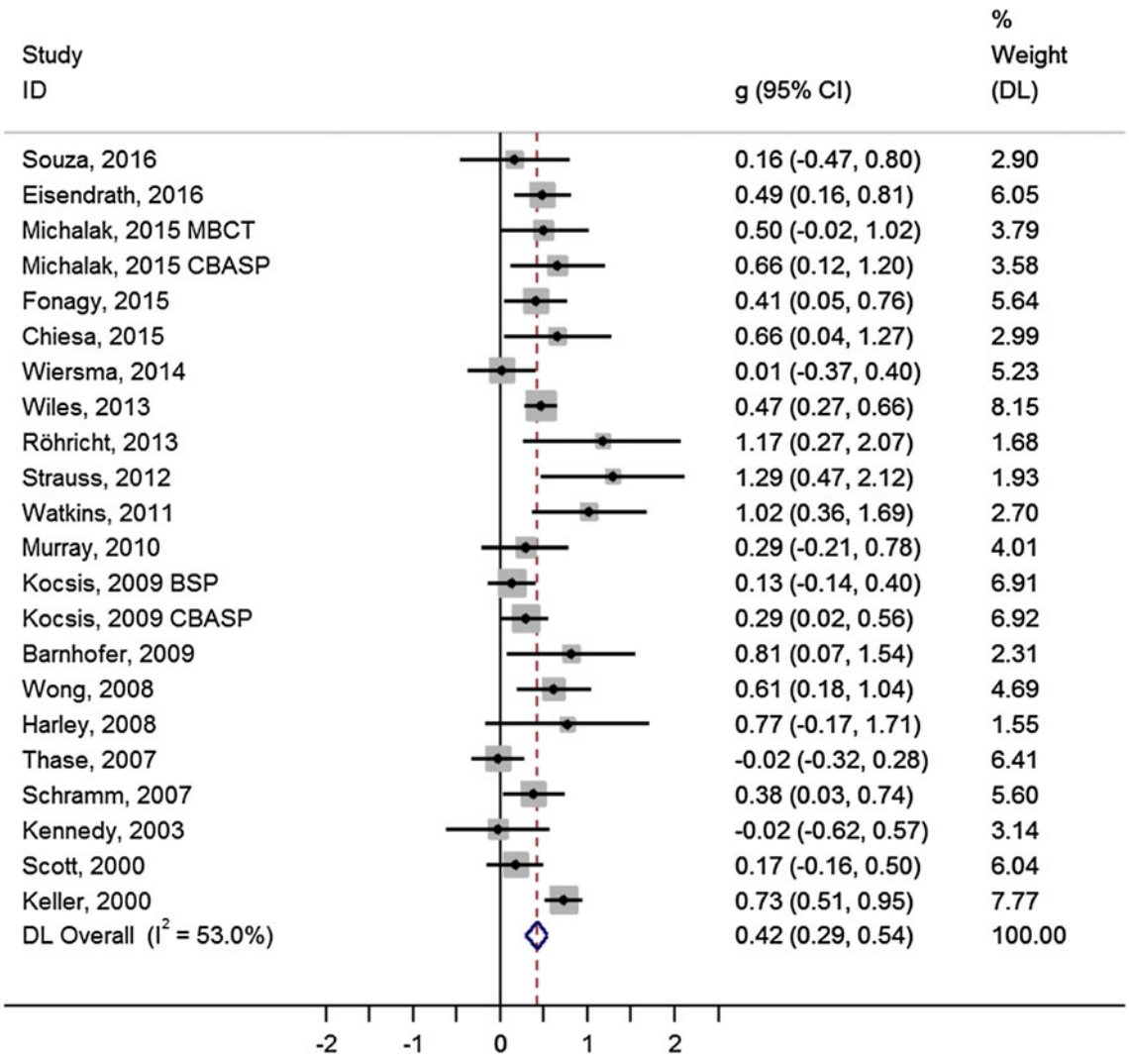

Fig. 3. Effects of add-on psychotherapy plus TAU *v.* TAU for TRD. g = Hedges' g effect sizes, 95% CI = 95% confidence interval, DL = DerSimonian-Laird method: between study variation was estimated using the DerSimonian-Laird method, MBCT = Mindfulness Based Cognitive Therapy, CBASP = Cognitive Behavioral Analysis System of Psychotherapy, BSP = Brief supportive psychotherapy.

Fourth, since no active and structural equivalent placebo condition was included, the current design is insufficient to examine if the specific components of psychotherapy are responsible for the moderate effect size (Baskin *et al.*, 2003).

Meta-analyses of psychotherapy for non-TRD typically report effect-sizes, that are comparable with the overall effect-size of g = 0.42 for psychotherapy as an add-on to TAU for TRD that we have found (Cuijpers *et al.*, 2008, 2010*b*). This is also commensurate with the results from a meta-analysis that examined the effectiveness of psychotherapy for cMDD and dysthymia (Cuijpers *et al.*, 2010*c*).

In the current meta-analysis, the most frequently investigated treatments are CBT, CBASP, MBCT, and to a lesser extent IPT, all with small to moderate overall effect sizes. No significant differences in the efficacy between the treatments emerged from the meta-regression. This result should be interpreted with caution since for each therapy a different number of comparisons was included (ranging between one and five studies). In addition, one could argue that aggregated results from RCTs are not suited to isolate effects of specific psychotherapies (Budd and Hughes, 2009).

Clinical features and study characteristics

In our meta-regression we found no evidence, other than baseline severity and group of individual treatment format, for an association between variables such as mean duration of the current episode, mean treatment duration (number of months and number of treatment sessions), attrition rates, clinician-rated or self-reported outcomes, and an intention to treat approach for the outcome measures. The lack of an association between effect size and treatment duration or a number of sessions should be interpreted with caution since we used results from acute-phase treatment with an endpoint at approximately 16 weeks treatment for sake of comparison and absence of long-term follow-up data in many studies. Therefore, in the current study, we did not demonstrate that more treatment sessions would result in significant larger effect sizes like previously reported in a meta-analysis examining the effectiveness of psychotherapy for cMDD and dysthymia (Cuijpers *et al.*, 2010*c*). However, we found comparable effects sizes between recent studies of MBCT and treatments of longer duration, suggesting that the reported association between a number of sessions and effect size may be not as strong as

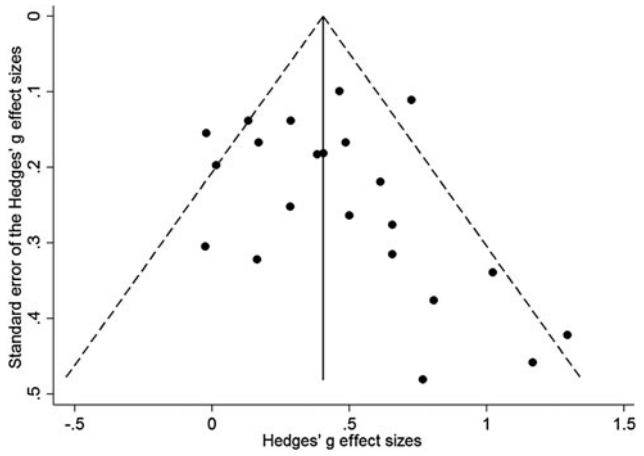

Fig. 4. Add-on psychotherapy plus TAU *v.* TAU for TRD: Funnel plot.

previously reported. It cannot be ruled out that some elements of MBCT (e.g. daily application of exercises after treatment termination) have enduring effects beyond the typically 8 weeks duration of training. In contrast to previous findings (Cuijpers *et al.*, 2010*a*), we did not find an effect of clinician-rated *v.* self-reported instruments on our results. This result should also be interpreted with caution since we used a combination of clinician-rated and self-reported outcomes (average effect size) for 11 of the included comparisons.

Studies that included participants with more baseline depression severity showed a larger effect-size. This is in line with previous findings that reported more efficacy of antidepressants in more severely depressed subjects (Turner *et al.*, 2008; Fournier *et al.*, 2010). An unexpected finding from the meta-regression was the larger effect-size in studies that employed a group instead of an individual treatment format. Several speculative explanations can be put forward. First, group formats consist of longer sessions than typical for individual treatment thereby increasing therapy exposure, although the literature does not support this speculation as there is no indication for greater efficacy of group format compared with individual therapy (Huntley *et al.*, 2012). Additionally, one of the group therapies (MBCT) consists of daily exercises outside of the strict session context thereby increasing exposure to therapeutic interventions. Another explanation may be that the group format also provides additional peer support in subjects demoralized after unsuccessful previous treatment.

In the last decade, both the number and quality of psychotherapeutic trials in the field have increased considerably. The former is illustrated by the small number of studies that were included in previous reviews and meta-analyses (Stimpson *et al.*, 2002; McPherson *et al.*, 2005; Trivedi *et al.*, 2011). Quality improved because recent studies relied on solid randomization procedures, well-described treatments, and well-trained therapists, used blinded outcome assessments, and reported intention-to-treat instead of completers-only analyses. We consider this a positive development given the preference for psychotherapy of many patients and the association between receiving a preferred treatment and clinical outcome.

Generally, one of the problems in interpreting study results of treatments for TRD is the lack of a uniform definition of TRD which may range from non-response to only one treatment trial, mostly with an antidepressant, to non-response following intensive consecutive treatments including ECT (Ruhe *et al.*, 2012). Subsequently, non-response to only one treatment trial might not be considered as a relevant level of TRD in clinical practice. These different levels of treatment resistance impede interpretation of the results from this meta-analysis and its applicability in daily practice. A recommendation for future studies would be to include detailed information on previous failed treatments and include this in data-analysis. This can facilitate clinical decision-making based on the level of treatment resistance.

Strengths and limitations

To our knowledge, this is the largest meta-analysis to date of studies into the effectiveness of psychotherapeutic treatments when applied for the treatment of individuals with TRD. Although studies specifically aimed at this clinically very important population have been carried out in recent years, we were able to enlarge the database by adding studies in cMMD that in fact included a majority of patients with TRD. This enabled us to address the clinically relevant question whether psychotherapy for TRD is indeed effective. In addition, we extended this meta-analysis with a meta-regression to relate specific study-level variables to the statistical heterogeneity between the study results.

Some limitations apply to this meta-analysis. First, one of the problems in interpreting study results of treatments for TRD is the lack of a uniform definition of TRD which may range from non-response to only one treatment trial (mostly with an antidepressant) to non-response following intensive consecutive treatments including ECT (Ruhe *et al.*, 2012). This is also illustrated by the fact that the majority of the studies included participants that were resistant to pharmacotherapy, no studies investigated specifically the efficacy of psychotherapy after previous treatment with some other form of psychotherapy. This impedes interpretation of the results from this meta-analysis and its applicability in daily practice. A recommendation for future studies would be to include more detailed information on previous failed treatments and include this in data-analysis and/or use validated tools to quantify TRD (Peeters *et al.*, 2016). Second, although effect-sizes were roughly of equal magnitude, differences in content between experimental interventions were large, which may limit guidance for daily clinical practice; clinicians are confronted with many remaining options. Third, the impact of treatment integrity and therapists effects on the effectiveness of psychotherapy was not evaluated, since standardized instruments to assess therapy adherence and therapist's competence were often lacking and information of therapists effect was not included. Fourth, the number of studies in the comparison between psychotherapy and TAU was limited. Fifth, type and quality of the TAU conditions (mostly pharmacotherapy and clinical management) were variable, which may affect their validity as comparison intervention resulting in an overestimation of effect sizes of the experimental conditions. However, given their presumed reflection of common clinical practice in these patients, this variability might improve the generalizability of the results. Sixth, although we performed meta-regression analyses to address the impact of potentially relevant variables on outcome differences between studies, we did not find significant results apart from baseline depression severity and group/individual format. It should be noted that meta-regression is an analysis of the influence at the level of differences between and not within studies. Therefore, including variables at this level, has its limitations because only sample means are used, while ignoring the range in scores in the individual study populations (i.e. ecological bias; Thompson and Higgins, 2002). This

limits adequate subgroup analyses and better examination of heterogeneity between subjects for which individual patient data would be needed. Another limitation of our meta-regression is the missing information on some variables, limiting the power of our analyses. Eighth, we included studies of cMDD when a majority of the participants were reported to have failed to respond to at least one treatment trial for the current episode. This might have resulted in the inclusion of some subjects who were, in fact, true cMDD patients without qualifying for TRD, which may have influenced the results. However, it should be kept in mind that the majorities of non-responding patients in the included studies were large. Additionally, we examined this potential bias in the meta-regressions; the percentage of participants that did not respond to antidepressants for the current episode was not significantly associated with effect sizes. We, therefore, feel that our results represent an accurate approximation of the effect size in TRD. Finally, as outlined earlier, we were not able to pool long-term data from the few studies that relied on treatments with longer duration and/or more treatment sessions which may obscure additional beneficial results.

Conclusion

Our meta-analysis provides evidence that, in addition to pharmacological and neurostimulatory treatments, add-on of psychotherapy to TAU in guidelines for the treatment of TRD is justified and will provide better outcomes for this difficult-to-treat population.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329171800199X.

Conflict of interest. None.

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