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Review

The effects of blinding on the outcomes of psychotherapy and pharmacotherapy for adult depression: A meta-analysis

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ABSTRACT

Background: Randomized trials with antidepressants are often run under double blind placebo-controlled conditions, whereas those with psychotherapies are mostly unblinded. This can introduce bias in favor of psychotherapy when the treatments are directly compared. In this meta-analysis, we examine this potential source of bias.
Methods: We searched Pubmed, PsycInfo, Embase and the Cochrane database (1966 to January 2014) by combining terms indicative of psychological treatment and depression, and limited to randomized trials. We included 35 trials (with 3721 patients) in which psychotherapy and pharmacotherapy for adult depression were directly compared with each other. We calculated effect sizes for each study indicating the difference between psychotherapy and pharmacotherapy at post-test. Then, we examined the difference between studies with a placebo condition and those without in moderator analyses.
Results: We did not find a significant difference between the studies with and those without a placebo condition. The studies in which a placebo condition was included indicated no significant difference between psychotherapy and pharmacotherapy (g = −0.07; NNT = 25). Studies in which no placebo condition was included (and patients and clinicians in both conditions were not blinded), resulted in a small, but significant difference between psychotherapy and pharmacotherapy in favor of pharmacotherapy (g = −0.13; NNT = 14).
Conclusions: Studies comparing psychotherapy and pharmacotherapy in which both groups of patients (and therapists) are not blinded (no placebo condition is included) result in a very small, but significantly higher effect for pharmacotherapy.

1. Introduction

When assessing and comparing the outcomes of psychological and pharmacological antidepressant treatments, there is a fundamental problem regarding blinding of patients and therapists. In trials comparing psychotherapy to control conditions, patients randomized to psychotherapy typically know whether they have been randomized to the psychotherapeutic intervention or to the control condition, and the same is true for the treating therapists [26,28,54]. This may result in expectations of positive effects and hope in the psychological intervention in patients, therapists and researchers, and increases in frustration and despair (nocebo effects) [28] in the patients in the control condition, inflating the effect sizes of psychotherapy [26,59]. These biases are likely to be especially large in studies with waiting lists or care-as-usual control conditions. It is not surprising therefore that the effect sizes of psychotherapy studies are especially large when compared to waiting list controls [47,48].

In contrast, for treatment with antidepressants, blinding of both patients and therapists is possible in principle, and hope induction, activation and other unspecific factors influencing outcome can be controlled. As a consequence, the effect size of antidepressants may to be underestimated compared to those of psychotherapy because the fact that patients know about the risk to receive

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placebo will reduce the hope induced compared to an open treatment. However, it has also been questioned whether typical trials on antidepressants are blinded properly, because usually inert placebos are used instead of active placebos, resulting in many patients who know to which condition they have been assigned [22,35,49].

If this is true, the effects of hope induction and expectancies in patients, clinicians and researchers should be larger in placebo-controlled trials with two active treatments compared to that with one because the chance to get an active treatment is larger. This is supported by a meta-analysis which revealed that placebo response is higher in studies with two active treatments (44,8%) compared to those with one only (34,3%) [63]. The authors also report that the response rate to the antidepressants declined with increasing risk to get placebo only (66,5% with two active drugs without placebo, 55,7% with two active drugs and placebo, 51,7 with one active and one placebo arm). Similar results have been reported by another meta-analysis [64].

A consequence of the effects discussed above is that meta-analytic comparisons of efficacy between psychotherapy and pharmacotherapy may overestimate effects of psychotherapy and underestimate those of pharmacotherapy if a placebo-control group is included [1]. If no placebo control group is included, patients, therapists and researchers in both psychotherapy and pharmacotherapy are not blinded, and the advantage of psychotherapy over pharmacotherapy should not be expected here.

Our earlier meta-analyses of studies directly comparing psychotherapy and pharmacotherapy typically show that there are no significant differences between the two [13,14]. If blinding indeed affects outcome, one could expect a difference between studies with and without a placebo control condition. This question has not been examined in earlier meta-analyses of studies directly comparing psychotherapy and pharmacotherapy.

We therefore decided to perform a new meta-analysis of studies directly comparing psychotherapy and pharmacotherapy for adult depression, and to examine whether studies that also included a placebo condition (blinded pharmacotherapy) differed significantly from the studies in which no placebo condition was included (unblinded pharmacotherapy).

2. Methods

2.1. Identification and selection of studies

This meta-analysis was conducted according to the PRISMA guidelines [39]. We used a database of papers on the psychological treatment of depression that has been described in detail elsewhere [12], and that has been used in a series of earlier published meta-analyses (http://www.evidencebasedpsychotherapies.org). This database has been continuously updated through comprehensive literature searches (covering studies published between 1966 to January 2014). In these searches, we examined 14,902 abstracts from Pubmed, PsycInfo, Embase and the Cochrane Register of Trials. These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). The searches were usually conducted by two independent researchers, but some of the yearly updates were done by only one researcher. Thus, a biased study selection cannot be completely excluded. For this database, we also checked the primary studies from earlier meta-analyses of psychological treatment for depression to ensure that no published studies were missed (http://www.evidencebasedpsychotherapies.org). From the 14,902 abstracts, we retrieved 1613 full-text papers for possible inclusion in the database.

We included (a) randomized trials (b) in which the effects of a psychological treatment (c) was directly compared with the effects of antidepressant medication (d) in adults (e) with a depressive disorder. We included studies with and without a pill placebo condition, but in order to keep the comparison between blinded and not-blinded studies as clear as possible, we excluded studies in which another type of control condition was used (such as care-as-usual or relaxation).

Only studies in which subjects met diagnostic criteria for the disorder according to a structured diagnostic interview (such as the SCID, CIDI, or MINI) were included. Comorbid mental or somatic disorders were not used as an exclusion criterion. Studies on inpatients, adolescents and children (below 18 years of age) were also excluded. We further excluded maintenance studies, aimed at people who had already recovered or partly recovered after an earlier treatment. Language was not used as an exclusion criterion.

2.2. Quality assessment and data extraction

We assessed the validity of included studies using four criteria of the "Risk of bias" assessment tool, developed by the Cochrane Collaboration [29]. This tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence; the concealment of allocation to conditions; the prevention of knowledge of the allocated intervention (masking of assessors); and dealing with incomplete outcome data (this was assessed as positive when intention-to-treat analyses were conducted, meaning that all randomized patients were included in the analyses).

We also coded additional aspects of the included studies, including participant characteristics (recruitment method: community, from clinical samples, or other; target group: adults in general, or more specific target groups such as older adults), intervention characteristics (format: individual, group, or guided self-help; number of sessions; type of psychotherapy: cognitive behavior therapy, interpersonal psychotherapy, or other type; type of medication: SSRI, TCA, or other); and study characteristics (country: United States or other).

2.3. Meta-analyses

For each comparison between a psychotherapy and a pharmacotherapy condition, the effect size indicating the difference between the two groups at post-test was calculated (Hedges's g). Effect sizes were calculated by subtracting (at post-test) the average score of the psychotherapy group from the average score of the pharmacotherapy group, and dividing the result by the pooled standard deviation. Because some studies had relatively small sample sizes, we corrected the effect size for small sample bias [25].

In the calculations of effect sizes, we used only those instruments that explicitly measured symptoms of depression. If means and standard deviations were not reported, we used the procedures of the Comprehensive Meta-analysis software (see below) to calculate the effect size using dichotomous outcomes; and if these were not available either, we used other statistics (such as *t*-value or *P*-value) to calculate the effect size. To calculate pooled mean effect sizes, we used the computer program Comprehensive Meta-Analysis (version 2.2.021; CMA).

We tested whether the effect sizes of the studies with a placebo condition differed from the effect sizes of the studies without placebo with a mixed effects model. In this mixed effects model, studies within subgroups were pooled with the random effects model, while tests for significant differences between subgroups were conducted with the fixed effects model

[7]. Numbers-needed-to-treated (NNT) were calculated using the formulae provided by Kraemer and Kupfer [36]. The NNT indicates the number of patients that have to be treated in order to generate one additional positive outcome [37].

In all analyses, we calculated the I^2-statistic as an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity [30]. We calculated 95% confidence intervals around I^2 [32], using the non-central Chi^2-based approach within the heterogi module for Stata [55].

We tested for publication bias by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's trim and fill procedure [19], which yields an estimate of the effect size after the publication bias has been taken into account (as implemented in CMA). We also conducted Egger's test of the intercept to quantify the bias captured by the funnel plot and test whether it was significant.

Multivariate metaregression analyses were conducted with the effect size as the dependent variable. To decide which variables should be entered as predictors in the regression model, we first defined a reference group within each category of variables. To avoid collinearity among the predictors of the regression model, we first examined whether high correlations were found among the variables that could be entered into the model. Next, we calculated the correlations between all predictors (except the reference variables). Because no correlations were higher than $r = 0.50$, all predictors could be entered in the regression models. Multivariate regression analyses were conducted in STATA MP, version 11 for Mac (Statacorp).

3. Results

3.1. Selection and inclusion of studies

After examining a total of 14,902 abstracts (10,992 after removal of duplicates), we retrieved 1613 full-text papers for further consideration. We excluded 1578 of the retrieved papers. The reasons for excluding studies are given in Fig. 1. Thirty-five studies met inclusion criteria [2–4,5,6,8,15–18,20,21,24,27,31,33,34,40–43,45,46,50–53,56–58,60–62,65,66]. Fig. 1 presents a flowchart describing the inclusion process. These 35 studies were all included in our larger meta-analysis of direct comparisons of psychotherapy and pharmacotherapy for depression and anxiety disorders [14] (except one study that was published after the deadline for inclusion in that meta-analysis) [42].

3.2. Characteristics of included studies

Selected characteristics of the included 35 studies are presented in Table 1. In these studies, 3721 patients were included, 1962 in the psychotherapy conditions, 1759 in the pharmacotherapy conditions. Nine studies included a placebo control condition, 26 studies did not. In six studies, two different types of psychotherapy were examined (and compared with pharmacotherapy), resulting in 41 comparisons between a psychotherapy and pharmacotherapy condition (10 comparisons with placebo, 31 without).

Sixteen studies recruited patients (partly) through the community, 15 exclusively from clinical samples, and three used other methods (one did not report the recruitment method). Twenty-nine studies were aimed at adults in general, three on older adults,

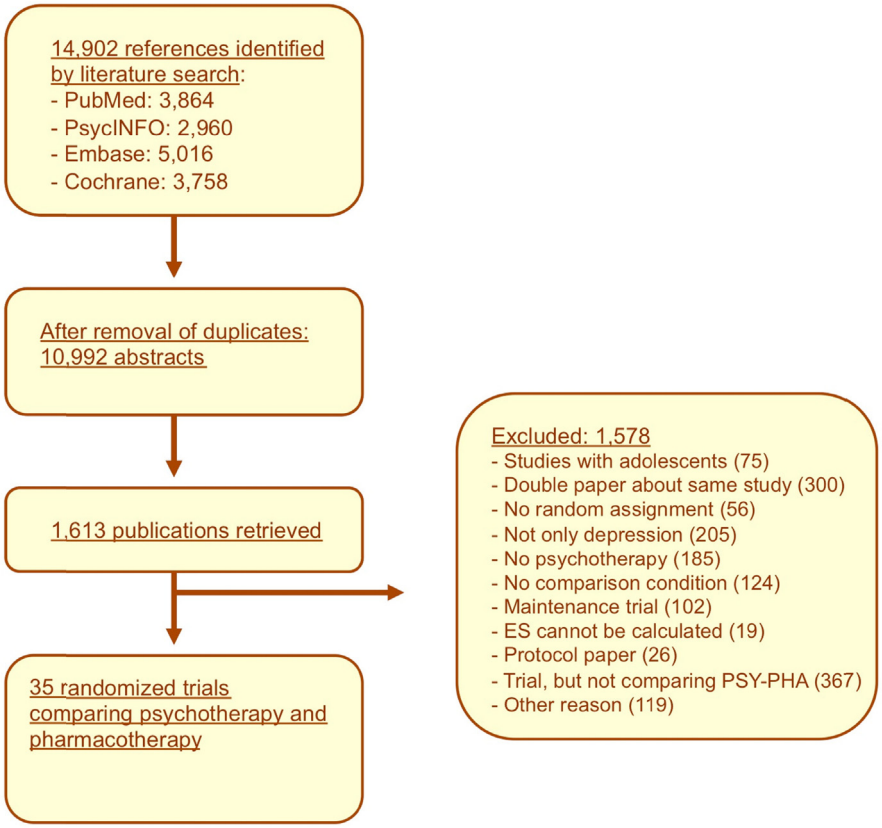

Fig. 1. Flowchart of inclusion of studies.

Table 1
Selected characteristics of studies directly comparing psychotherapy and pharmacotherapy for adult depression.

	Recr	Target group	Depression	Psychotherapy	N psy	N sess	Format	Pharmacotherapy	N pha	Pla	FU paper	Pha fu	Long-term outcome	FU	Quality[a]	Country
Barber et al., 2012 [2]	Comm	Adults	MDD	DYN	51	20	Ind	Mix/Oth	55	+	No FU				– – + +	US
Barrett et al., 2001 [3]	Clin	Adults	Mood	PST	80	6	Ind	SSRI	80	+	No FU				+ + + +	US
Bedi et al., 2000 [4]	Clin	Adults	MDD	Couns	39	NR	Ind	Mix/Oth	44	–	No FU				+ + – –	EU
Blackburn et al., 1981 [5]	Comm	Adults	MDD	CBT	7	15	Grp	TCA	9	–	Blackburn, 1986	N	Rel	24	– – – –	US
Blackburn and Moore 1997 [6]	Clin	Adults	MDD	CBT	24	16	Ind	Mix/Oth	43	–	No FU				– – – +	EU
Browne et al., 2002 [8]	Comm	Adults	DYS	IPT	122	10	Ind	SSRI	117	–	No FU				+ + + –	CA
David et al., 2008 [15]	Comm	Adults	MDD	CBT	56	20	Ind	SSRI	57	–	David, 2008	Y	Rel/Rem	6	– – + +	EU
				REBT	57	20	Ind				David, 2008	Y	Rel/Rem	6		
Dekker et al., 2008 [16]	Clin	Adults	MDD	DYN	59	16	Ind	Mix/Oth	44	–	No FU				– – + –	EU
Dunlop et al., 2012 [17]	Comm	Adult	MDD	CBT	41	16	Ind	SSRI	39	–	No FU				+ + + +	US
Dunner et al., 1996 [18]	NR	Adults	DYS	CBT	9	16	Ind	SSRI	11	–	No FU				– – + –	US
Elkin et al., 1989 [20]	Clin	Adults	MDD	IPT	61	16	Ind	TCA	57	+	Shea, 1992	N	Rel/Rec	18	+ + + +	US
				CBT	59	16	Ind				Shea, 1992	N	Rel/Rec	18		
Finkenzeller et al., 2009 [21]	Other	Stroke patients	MDD	IPT	23	12	Grp	SSRI	24	–	No FU				+ – + +	EU
Frank et al., 2011 [24]	Clin	Adults	MDD	IPT	160	12	Ind	SSRI	158	–	No FU				– – + +	US
Hegerl et al., 2010 [27]	Clin	Adults	Mood	CBT	52	10	Grp	SSRI	76	+	No FU				+ + + +	EU
Hollon et al., 1992 [31]	Clin	Adults	MDD	CBT	25	20	Ind	TCA	57	–	Evans, 1992	N	Rel	24	– – + +	US
Jarrett et al., 1999 [33]	Comm	Adults	MDD	CBT	36	20	Ind	MAOI	36	+	No FU				+ + + +	US
Keller et al., 2000 [34]	Clin	Chronic	MDD	CBASP	226	18	Ind	SNRI	220	–	No FU				+ + + +	US
Markowitz et al., 2005 [40]	Comm	Adults	DYS	IPT	23	17	Ind	SSRI	24	–	No FU				– – + +	US
				Couns	26	17	Ind				No FU					
Marshall et al., 2008 [41]	Comm	Adults	MDD	CBT	37	16	Ind	Mix/Oth	30	–	No FU				– – – –	CA
				IPT	35	16	Ind				No FU					
Martin et al., 2001 [42]	Comm	Adults	MDD	IPT	13	16	Ind	SNRI	15	–	No FU				– – – +	EU
McBride et al., 2007 [43]	Comm	Adults	MDD	CBT	21	16	Ind	Mix/Oth	21	–	No FU				– – – –	CA
McKnight et al., 1992 [45]	Comm	Adults	MDD	CBT	12	8	Ind	TCA	11	–	No FU				– – – –	US
Mohr et al., 2001 [46]	Other	MS patients	MDD	CBT	20	16	Ind	SSRI	15	–	Mohr, 2001	N	Bdi/Hamd	6	– – – +	US
				Supp Ex	19	16	Grp				Mohr, 2001	N	Bdi/Hamd	6		
Moradveisi et al., 2013 [50]	Comm	Adults	MDD	BAT	50	16	Ind	SSRI	50	–	Moradvesi, 2013	N	Rel/Rem/Resp	12	+ + + +	Iran
Murphy et al., 1984 [51]	Clin	Adults	MDD	CBT	24	20	Ind	TCA	24	–	Simons, 1986	N	Rel/Resp	12	+ + – +	US
Mynors-Wallis et al., 1995 [53]	Clin	Adults	MDD	PST	29	6	Ind	TCA	27	+	No FU			–	+ + + +	EU
Mynors-Wallis et al., 2000 [52]	Clin	Adults	MDD	PST gp	39	6	Ind	SSRI	36	–	Mynors-Wallis, 2000	N	Rec	12	+ + + +	EU
				PST n	41	6	Ind				Mynors-Wallis, 2000	N	Rec	12		
Ravindran et al., 1999 [56]	Comm	Adults	DYS	CBT	24	12	Grp	SSRI	22	+	No FU			–	+ + + –	CA
Reynolds et al., 1999 [57]	Comm	Elderly	MDD	IPT	16	16	Ind	TCA	25	+	No FU			–	– – + +	US
Rush et al., 1977 [58]	Clin	Adults	MDD	CBT	19	20	Ind	TCA	22	–	No FU			–	– – + +	US
Salminen et al., 2008 [60]	Clin	Adults	MDD	DYN	26	16	Ind	SSRI	25	–	No FU			–	– – – +	EU
Shamsaei et al., 2008 [61]	Clin	Adults	MDD	CBT	40	8	Ind	SSRI	40	–	No FU			–	+ – + –	Iran
Sharp et al., 2010 [62]	Other	PPD	Mood	Couns	112	6	Ind	Mix/Oth	106	–	No FU			–	+ + + +	EU
Thompson et al., 2001 [65]	Comm	Elderly	MDD	CBT	36	18	Ind	TCA	33	–	No FU			–	– – – +	US
Williams et al., 2000 [66]	Comm	Elderly	Mood	PST	113	6	Ind	SSRI	106	+	No FU			–	+ + + +	US

BAT: behavioral activation therapy; CA: Canada; CBASP: cognitive behavioral analysis system of psychotherapy; CBT: cognitive behavior therapy; Clin: recruitment from clinical samples only; Comm: (part of the) sample recruited from the community; Couns: non-directive supportive counseling; DYN: psychodynamic therapy; DYS: dysthymic disorder; EU: Europe; Grp: group format; Ind: individual format; IPT: interpersonal psychotherapy; Maoi: Monoamine oxidase inhibitor; MDD: major depressive disorder; Mix/oth: other antidepressant/mix of antidepressants or protocolized treatment with antidepressants; Mood: mixed mood disorder; MS: multiple sclerosis; N sess: number of sessions; Npha: number of patients in the pharmacotherapy conditions; Npsy: number of patients in the psychotherapy condition; NR: not reported; PPD: post-partum depression; PST gp: PST by a general practitioner; PST n: PST by a nurse; PST: problem-solving therapy; REBT: rational emotive behavior therapy; Recr: recuitment; Snri: Serotonin–norepinephrine reuptake inhibitor; Ssri: selective serotonin reuptake inhibitor; Supp Ex: supportive-expressive therapy; Tca: tricyclic antidepressant; US: United States.

[a] In this column, a positive or negative sign is given for four quality criterias, respectively: allocation sequence; concealment of allocation to conditions; blinding of assessors; and intention-to-treat analyses.

and three on other target groups (women with post-partum depression, multiple sclerosis patients, and stroke patients). Most studies (27) were aimed at patients with a major depressive disorder, four were aimed at unipolar mood disorders in general, and four were exclusively aimed at patients with dysthymia. Of the 41 psychotherapies that were examined, 19 were cognitive behavior therapy, eight interpersonal psychotherapy, five problem-solving therapy, four non-directive counseling, three psychodynamic therapy and two others. Thirty-six delivered the treatment in an individual format and five in group format. The number of treatment sessions ranged from 6 to 20 (in 26 comparisons, the number of sessions ranged from 16 to 20). In 16 of the 35 studies, a SSRI was used, nine used a TCA, and the remaining 10 used another medication (MAOI, SNRI) or a protocol with a mix of medications. Eighteen studies were conducted in the US, 11 in Europe, 4 in Canada, and 2 in Iran.

The quality of the included studies varied. Seventeen of the 35 studies reported an adequate sequence generation. Fifteen studies reported allocation to conditions by an independent (third) party. Twenty-four studies reported blinding of outcome assessors and in 25 studies, intention-to-treat analyses were conducted. Eleven studies met all four-quality criteria, 13 met 2 or 3 criteria; and the remaining 11 studies had a lower quality (0 or 1 of the 4 criterias).

3.3. Difference between studies with and without a placebo condition

The overall effect size indicating the difference between psychotherapy and pharmacotherapy in all studies (regardless of the presence of a placebo control condition) was non-significant with g = −0.07 (95% CI: −0.21∼0.07; NNT = 25) in favor of pharmacotherapy (I^2 = 37%; 95% CI: 1∼57), which is very much in line with earlier meta-analyses of studies directly comparing psychotherapy with pharmacotherapy [13,14].

When we compared studies with and without a placebo condition, we found no significant differences (P = 0.15). The 10 comparisons between psychotherapy and pharmacotherapy with a placebo condition resulted in a non-significant effect size of g = 0.02 (95% CI: −0.15∼0.18), with zero heterogeneity (I^2 = 0; 95% CI: 0–62). This corresponds with a NNT of 83. The results are summarized in Table 2 and in Fig. 2. The 31 comparisons in which no placebo control condition was used resulted, in line with the hypothesis, in a small, but significant effect in favor of pharmacotherapy with g = −0.13 (95% CI: −0.23∼−0.03; NNT = 14) with moderate heterogeneity (I^2 = 43; 95% CI: 13∼63).

There was one study that could be considered as an outlier, because the 95% CI around the effect size did not overlap with the 95% CI of the pooled effect size [58]. After removal of this outlier, the difference between the studies with a placebo condition and those without, approached significance (P = 0.09; g = −0.15; NNT = 12).

In the analyses, we included six studies in which two psychological treatments were compared with the same pharmacotherapy group. This means that multiple comparisons from these studies were included in the same analysis, that are not independent of each other, which may have resulted in an artificial reduction of heterogeneity and may have affected the pooled effect size. We examined the possible effects of this by conducting an analysis in which we included only one effect size per study. First, we included only the comparison with the largest effect size from these studies and then, we conducted another analysis in which we included only the smallest effect size. As can be seen from Table 2, the resulting effect sizes did not affect the overall mean effect size very much, nor did it affect heterogeneity considerably.

When we limited the analyses to the effect sizes based on the HAM-D-17 only (Table 2), we found that the difference between the two groups of studies became smaller.

We examined possible publication bias in the two groups of studies separately as well as in the full sample of studies, but found no indications that there was significant publication bias. In the full sample as well as in each of the two subsamples, Duvall and Tweedie's trim and fill procedure indicated that there were no missing studies, and the adjusted and unadjusted effect sizes were equal. Egger's test also did not point at significant asymmetry of the funnel plot for any of the samples.

3.4. Sensitivity analyses

We conducted a series of sensitivity analyses to examine the robustness of our findings. In these analyses, we first limited the analyses to the studies meeting all quality criteria. Then, in another analysis, we included only studies examining SSRI as pharmacotherapy, then with only studies examining CBT as psychotherapy. Next, we excluded studies exclusively aimed at dysthymic patients. Finally, we excluded studies aimed at specific target groups.

In these analyses, the results of the main analyses were mostly replicated. The difference between studies with a placebo group did not differ significantly from those without in any of the

Table 2
Effects of studies comparing psychotherapy and pharmacotherapy for adult depression: Hedges' g[a].

	With placebo control						Without placebo control						
	N_{comp}	g	95% CI	I^2	95% CI	NNT	N_{comp}	g	95% CI	I^2	95% CI	NNT	P[b]
All studies	10	0.02	−0.15∼0.18	0	0∼62	83	31	−0.13	−0.23∼−0.03	43	13∼63	14	0.15
One outlier removed [58]	10	0.01	−0.15∼0.16	0	0∼62	167	30	−0.15	−0.25∼−0.05	33	0∼57	12	0.09
One effect size per study (only highest)	9	0.03	−0.14∼0.21	0	0∼65	63	26	−0.10	−0.21∼−0.01	42	8∼64	18	0.21
One effect size per study (only lowest)	9	0.02	−0.16∼0.20	0	0∼65	83	26	−0.12	−0.24∼−0.01	47	15∼66	15	0.20
Only HAM-D	5	−0.05	−0.30∼0.21	0	0∼79	36	25	−0.09	−0.21∼0.03	50	21∼69	20	0.75
Sensitivity analyses													
Only high-quality studies	7	−0.04	−0.18∼0.11	0	0∼71	45	6	−0.17	−0.32∼−0.02	46	0∼79	10	0.21
No combined treatment condition in study	8	−0.04	−0.18∼0.09	0	0∼68	45	18	−0.18	−0.28∼−0.07	22	0∼56	10	0.12
Only SSRI's	4	0.03	−0.17∼0.21	0	0∼85	63	16	−0.16	−0.27∼−0.04	10	0∼47	11	0.10
Only CBT	4	0.01	−0.26∼0.27	0	0∼85	167	15	0.04	−0.12∼0.19	31	0∼63	45	0.85
Studies on dysthymia excluded	9	−0.01	−0.18∼0.15	0	0∼65	167	27	−0.09	−0.20∼−0.02	41	6∼63	20	0.44
Studies aimed at adults in general	8	−0.03	−0.21∼0.15	0	0∼68	63	25	−0.14	−0.26∼−0.03	39	2∼63	13	0.32

CI: confidence interval; N_{comp}: number of comparisons.
[a] According to the random effects model.
[b] The P-values in this column indicate whether the difference between the effect sizes in the group of studies with a placebo condition differs from those without placebo is significant.

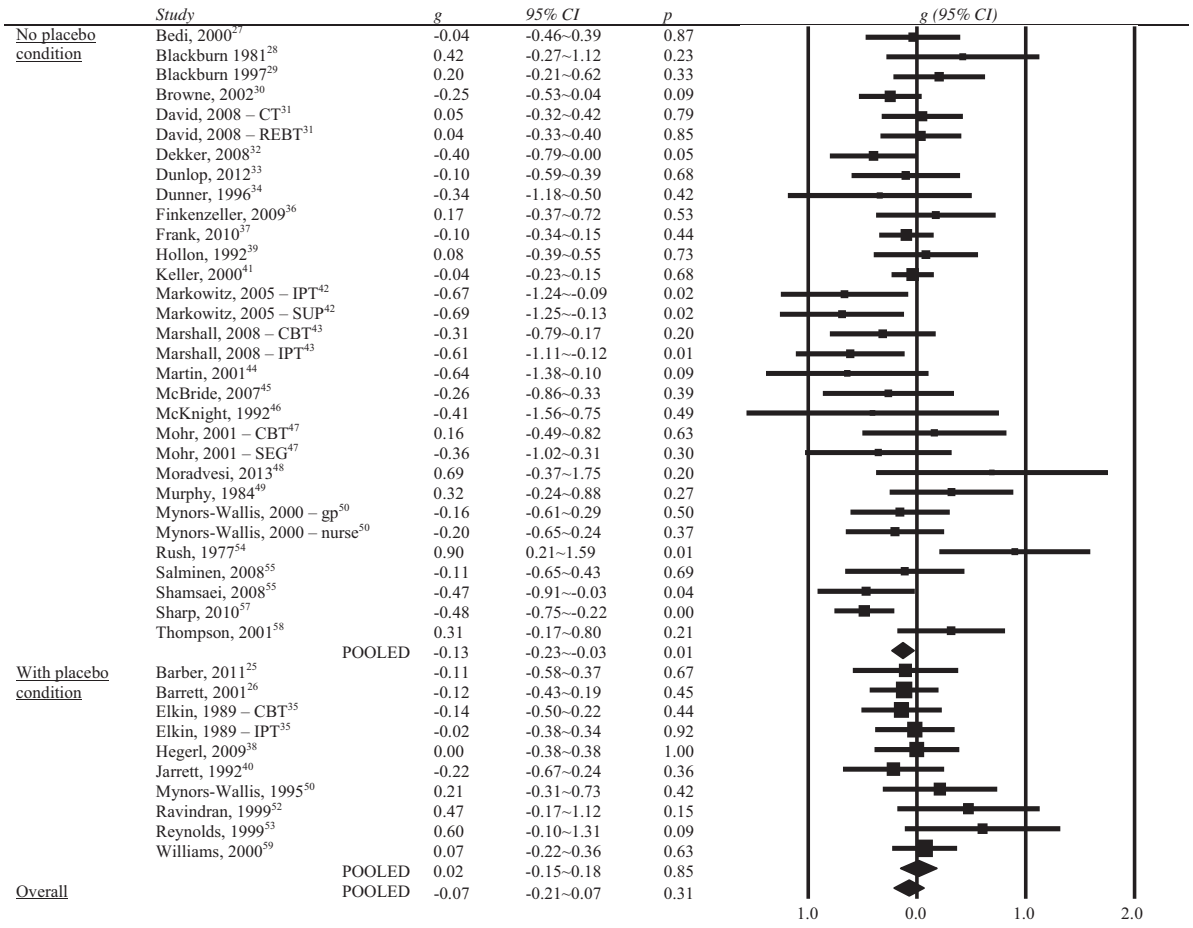

Fig. 2. Forrest plot of studies comparing psychotherapy and pharmacotherapy for adult depression, with and without placebo control condition.

analyses. In all analyses, the studies with a placebo control group indicated no significant difference between psychotherapy and pharmacotherapy (effect sizes ranged from g = 0.03 to g = −0.04). In all analyses of the studies without placebo control group, the difference between psychotherapy and pharmacotherapy was significant, with all analyses pointing at a small but significant difference between psychotherapy and pharmacotherapy in favor of pharmacotherapy (effect sizes ranging from g = −0.09 to −0.17). The only exception was the subsample of studies on CBT. In these studies, no significant difference between psychotherapy and pharmacotherapy was found (g = 0.04; 95% CI: −0.12∼0.19).

3.5. Multivariate metaregression analysis

In order to examine the possible influence of other characteristics of the patients, the therapists, the interventions and the studies, we conducted a multivariate metaregression analysis in which we entered a dummy variable indicating whether or not a placebo condition was used in the study, while adjusting for the major characteristics of the studies.

We first entered all variables simultaneously in the model (Appendix 1), and found that the dummy variable indicating whether the study had a placebo condition or not, was not significantly associated with the effect size ($P = 0.15$).

We then conducted a (manual) back-step metaregression analysis. In this analysis, we dropped the least significant variable in each step, until only significant predictors were retained in the model (Appendix 1). The results of this parsimonious model indicated that there was a trend ($P = 0.06$) indicating that studies with a placebo condition may differ from those without a placebo condition.

We ran these analyses once more while leaving out the potential outlier [58]. The results were comparable to the analyses of the full sample, except that in the parsimonious model, the difference between studies with a placebo and those without was borderline significant ($P = 0.06$).

4. Discussion

In this meta-analysis, we examined the influence of blinding in trials directly comparing psychotherapy and pharmacotherapy for adult depression. We divided these studies into two groups. In the first group of studies, a pill placebo condition was included. In these studies, the patients, therapists and researchers in the pharmacotherapy conditions were blinded for whether the patients received pharmacotherapy or placebo. In the second group of studies, no placebo condition was included, and in these studies, patients, therapists and researchers were not blinded for the fact that the patients received pharmacotherapy. In both groups of studies, the participants in the psychotherapy conditions were not blinded for their assignment to psychotherapy. These studies did not allow us to examine the effects of not being blinded for psychotherapy directly, but they did enable us to test the effects of being blinded or not in the pharmacotherapy conditions. We did not find a significant difference between these groups of studies, although the outcomes were in the expected direction. The studies in which a placebo condition was included indicated no significant

difference between psychotherapy and pharmacotherapy. Studies in which no placebo condition was included, however, resulted in a small, but significant difference between psychotherapy and pharmacotherapy in favour of pharmacotherapy.

These results could suggest that in the acute treatment of depression, pharmacotherapy is somewhat more effective than psychotherapy, and this may be a reason for clinicians and patients to prefer pharmacotherapy over psychotherapy. Although the difference is significant, it is also small, however, as effect sizes of $d < 0.20$ are usually considered to be small [9]. There is no generally accepted threshold for what a clinically significant effect is, with some suggesting that an effect size of d = 0.5 may be such a threshold [23]. But it has also been suggested that this threshold is indeed lower (d = 0.24) [11]. The effect sizes found in this paper are all very small and probably can not be considered to be clinically relevant.

But the results of this study do indicate that blinding in the pharmacotherapy conditions reduces the effects and makes it probable that the effects of psychotherapies, which can not be blinded properly [26,54], are also in part the result of the hope and expectations in patients, therapists and researchers related to knowing that they are assigned to an active treatment. Earlier meta-analyses of direct comparisons between psychotherapy and pharmacotherapy have not examined the effects of the presence of a placebo condition on the differential effects of the two treatments [13,14].

The best way to assess clinical significance for the relative effects of psychotherapy and pharmacotherapy, so when they are directly compared with each other, is probably when they are both not blinded for therapists and patients (so no placebo condition is included), but use blinded raters. This means that the effects of blinding are not present in both conditions, and the exact contributions of the treatments cannot be discerned from the expectations and hope associated with not being blinded. But because blinding is not possible for most forms of psychotherapy, it seems reasonable not to do that in pharmacotherapy either when comparing the effects of the two.

On the other hand, the absence of blinding in a trial in which both psychotherapy and pharmacotherapy conditions are not blinded could influence the outcomes also considerably. Furthermore, such a trial would also require a non-inferiority design, which would increase the number of participating patients considerably. So, there is probably no perfect design for trials comparing psychotherapy and pharmacotherapy, but each design has its own advantages and disadvantages [47,48].

It is also important to examine the comparative effects of psychotherapy and placebo, for example by comparing psychotherapy plus placebo with psychotherapy alone or with placebo alone. Although a few of these studies have been conducted [38,57], the number is so small that no meta-analysis of these studies is yet possibly.

This study has several important limitations. First, the quality of the studies was not optimal and the risk of bias in several aspects is considerable. Second, the number of studies for several comparisons was small, resulting in too little power to examine core questions. Especially, the number of studies in which a pill placebo condition was included was small. Third, it was not possible to verify from the papers whether the treatments (both psychotherapy and pharmacotherapy) were conducted adequately. This may have influenced the outcomes considerably. Fourth, we focused exclusively on depressive symptoms as outcome. However, other outcomes, such as social functioning, quality of life, effects of work status, are also highly relevant, but the number of studies reporting such outcomes was too low to be included in the analyses. We also did not consider patient preferences, which typically show that most patients prefer psychotherapy over pharmacotherapy [44]. Nor did we examine long-term effects [10]. Finally, it is the racial and cultural diversity of participants in the trials was quite limited, so the results may not be generalized to these groups.

Despite these limitations, we found clear indications that at the short term, the effects of pharmacotherapy are probably somewhat better than those of psychotherapy, when both conditions are not blinded.

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Disclosure of interest

Prof. Hegerl was an advisory board member for Lilly, Lundbeck, Takeda Pharmaceuticals, Servier and Otsuka Pharma; a consultant for Nycomed; and a speaker for Bristol-Myers Squibb, Medice Arzneimittel, Novartis and Roche Pharma. Dr. Mergl reports a Consultancy Agreement with Nycomed, a Takeda company. Drs Cuijpers, Karyotaki, Andersson and Li declare that they have no conflicts of interest concerning this article.

Appendix 1. Standardized regression coefficients of characteristics of studies directly comparing psychotherapy and pharmacotherapy for adult depression: Multivariate metaregression analyses.

	Full model			Parsimonious model		
	Coef.	SE	*P*	Coef	SE	*P*
Placebo condition present (y/n)	0.22	0.15	0.15	0.18	0.09	0.06
Combined treatment is included	0.12	0.13	0.36	0.20	0.09	0.02
Aimed at adults in general (y/n)	−0.25	0.16	0.12			
Exclusively aimed at dysthymia patients (y/n)	−0.18	0.20	0.38	−0.37	0.13	0.01
Only clinical samples	0.11	0.12	0.40			
Psychotherapy						
CBT	Ref.					
IPT	−0.14	0.12	0.27			
Other	−0.12	0.13	0.35			
Individual treatment format (y/n)	−0.18	0.17	0.92			
Number of sessions (continuous)	0.02	0.01	0.12	0.02	0.01	0.03
Pharmacotherapy						
SSRI	Ref.					
TCA	0.06	0.14	0.68			
Other	−0.27	0.12	0.04	−0.23	0.08	0.01
Quality (continuous)	−0.01	0.04	0.77			
Conducted in the US (y/n)	−0.11	0.12	0.35			
Constant	−0.06	0.25	0.82	−0.35	0.12	0.01

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