Adding Psychotherapy to Pharmacotherapy in the Treatment of Depressive Disorders in Adults: A Meta-Analysis

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Objective: A considerable number of studies has examined whether adding psychotherapy to pharmacotherapy results in stronger effects than pharmacotherapy alone. However, earlier meta-analyses in this field have included only a limited number of available studies and did not conduct extended subgroup analyses to examine possible sources of heterogeneity.

Data Sources: We used a database derived from a comprehensive literature search in PubMed, PsycINFO, EMBASE, and the Cochrane Central Register of Controlled Trials for studies published from 1966 to January 2008 that examined the psychological treatment of depression. The abstracts of these studies were identified by combining terms indicative of psychological treatment and depression.

Study Selection: We included randomized trials in which the effects of a pharmacologic treatment were compared to the effects of a combined pharmacologic and psychological treatment in adults with a depressive disorder.

Data Extraction: For each of the studies, we calculated a standardized mean effect size indicating the difference between pharmacotherapy and the combined treatment at posttest. We also coded major characteristics of the population, the interventions, and the quality and design of the study.

Data Synthesis: Twenty-five randomized trials, with a total of 2,036 patients, were included. A mean effect size of $d = 0.31$ (95% CI, 0.20 ~ 0.43) was found for the 25 included studies, indicating a small effect in favor of the combined treatment over pharmacotherapy alone. Studies aimed at patients with dysthymia resulted in significantly lower effect sizes compared to studies aimed at patients with major depression, a finding that suggests that the added value of psychotherapy is less in patients with dysthymia. The dropout rate was significantly lower in the combined treatment group compared to the pharmacotherapy only group (OR = 0.65; 95% CI, 0.50 ~ 0.83).

Conclusions: Psychotherapy seems to have an additional value compared to pharmacotherapy alone for depression.

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Both pharmacologic[1] and psychological treatments[2] for depression in adults have been examined in a considerable number of studies. The combination of the 2 treatments has been less well-examined, however. A growing body of evidence that combined treatment is more effective than psychotherapy alone[3–5] suggests that adding pharmacotherapy has an independent, cumulative effect on depression. Research is less conclusive, however, on the question of whether combined treatment is more effective than pharmacotherapy alone. Some studies do find support for this,[6–8] but others do not.[9–11] Because it can be expected that the difference between psychological and combined treatments is small, large sample sizes are required to find significant differences. When small effect sizes are expected in individual studies, meta-analytic techniques can be used to integrate the results of individual studies and to increase the statistical power.[12]

Although 2 earlier meta-analytic studies[4,13] have examined the difference between pharmacologic and combined treatments, these studies suffer from several limitations. Both reviews included only a limited number of currently available studies, included studies in which no strict diagnostic criteria were established, and did not conduct extended subgroup analyses to examine possible sources of heterogeneity. Each of the 2 meta-analyses included less than half of the studies we identified in our searches (the 2 meta-analyses included 10 and 12 studies of the 25 studies we included using the specific inclusion criteria specified below), and our literature searches resulted in 13 studies that were not included in either of the 2 earlier meta-analyses. Furthermore, these earlier meta-analyses did not examine possible sources of heterogeneity. For example, in an earlier meta-analysis,[12] we found that pharmacotherapy was significantly more effective than psychotherapy in the treatment of dysthymia and that selective serotonin reuptake inhibitors (SSRIs) were more effective than psychotherapy. Subgroup analyses of this kind were not conducted in the

2 earlier meta-analyses. These 2 earlier meta-analyses did, however, find indications that combined treatment is more effective than pharmacotherapy alone.

We decided to conduct a new comprehensive meta-analysis of studies in which pharmacotherapy was compared to the combination of pharmacotherapy and psychotherapy. Our hypothesis was that we would confirm that combined treatment is more effective than pharmacotherapy alone. We also wanted to explore whether study characteristics were related to the relative effects of pharmacologic and combined treatment.

METHOD

Identification and Selection of Studies

First, we used a database of 832 studies on the psychological treatment of depression in general. This database has been described in detail elsewhere[14] and has been used in a series of earlier meta-analyses (www.evidencebasedpsychotherapies.org). It was developed through a comprehensive literature search (articles published from 1966 to January 2008) in which we examined 6,947 abstracts in PubMed (1,244 abstracts), PsycINFO (1,736), EMBASE (1,911), and the Cochrane Central Register of Controlled Trials (2,056). These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). For this database, we also collected the primary studies from 42 meta-analyses on psychological treatment for depression (www.evidencebasedpsychotherapies.org). For the current study, we examined the abstracts of these 832 studies.

We included (1) randomized trials (2) in which the effects of a pharmacologic treatment (3) were compared to the effects of a combined pharmacologic and psychological treatment (4) in adults (5) with a depressive disorder. No language restrictions were applied. Only studies in which the subjects met diagnostic criteria for a depressive disorder (major depression, dysthymia) were included. Studies aimed at subjects with elevated levels of depressive symptoms (as measured by self-report measures) but no indication of diagnosis were excluded, as were studies on inpatients, studies on adolescents or children (below 18 years of age), and studies aimed at relapse prevention or maintenance treatments. Comorbid general medical or psychiatric disorders were not used as an exclusion criterion.

Quality Assessment

We assessed the validity of included studies by using a number of basic criteria, as suggested in the Cochrane Handbook[15]: allocation to conditions conducted by an independent (third) party, blinding of assessors to outcomes, and completeness of follow-up data. We did not use the fourth criterion for validity (adequacy of random allocation concealment to respondents) because it was not possible in these studies to conceal the randomization to patients.

Meta-Analyses

For each comparison between pharmacologic and combined treatments, we calculated the effect size (Cohen's *d*) indicating the difference between the 2 types of treatment at posttest. We calculated the effect sizes by subtracting (at posttest) the mean score of the combined treatment group from the mean score of the pharmacotherapy group, and dividing the result by the pooled standard deviations of the 2 groups. Effect sizes of 0.8 can be assumed to be large, while effect sizes of 0.5 are moderate, and effect sizes of 0.2 are small.[16] When psychological treatments are compared to control groups, effect sizes of 0.6 or larger are usually found.[2,17] In our meta-analysis, effect sizes of zero were assumed to indicate that there was no difference between the effects of pharmacotherapy and those of the combined treatment.

In the calculations of effect sizes, we used only those instruments that explicitly measured symptoms of depression. If more than 1 depression measure was used, the mean of the effect sizes was calculated, so that each study (or contrast group) provided only 1 effect size. If means and standard deviations were not reported, we used other statistics that were reported about the test between the 2 conditions at posttest (*P* or *t* value). If these were not reported, we used the procedures of the software program Comprehensive Meta-Analysis (version 2.2.021; Biostat, Englewood, New Jersey) to calculate the effect size by using dichotomous outcomes.

We used only the effect sizes indicating the differences between pharmacologic and combined treatments at posttest. We decided not to examine the differential effects at follow-up because the number of effect sizes was relatively low. In addition, the follow-up period differed considerably among these studies, and, in several studies, treatments were continued and others discontinued.

To calculate pooled mean effect sizes, we used the computer program Comprehensive Meta-Analysis (version 2.2.021). As we expected considerable heterogeneity among the studies, we decided to calculate mean effect sizes with the random-effects model. In the random-effects model, it is assumed that the included studies are drawn from populations of studies that differ from each other systematically (heterogeneity). In this model, the effect sizes resulting from included studies differ not only because of the random error within studies (as in the fixed-effects model) but also because of true variation in effect size from one study to the next.

To indicate homogeneity, we calculated the I^2 statistic, which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity.[18] We also calculated the *Q* statistic but only report whether or not this was statistically significant.

Subgroup analyses were conducted according to the mixed-effects model. In this model, studies within subgroups

are pooled with the random-effects model, while tests for statistically significant differences between subgroups are conducted with the fixed-effects model. For continuous variables, we used metaregression analyses to test whether there is a statistically significant relationship between the continuous variable and the effect size, as indicated by a *Z* value and an associated *P* value.

Publication bias was tested by inspecting the funnel plot on primary outcome measures and by using 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 Comprehensive Meta-Analysis, version 2.2.021).

RESULTS

Characteristics of the Included Studies

All inclusion criteria were met by 25 studies,[6–11,20–38] with a total of 2,036 patients (1,018 in the pharmacotherapy conditions and another 1,018 in the combined treatments). The mean number of patients per study was 81 (ranging from 20 to 453), with 15 studies having fewer than 50 patients, 5 having 50 to 100 patients, and 5 having 100 or more patients. Selected characteristics of the included studies are presented in Table 1.

Sixteen studies were aimed at adults in general, while 9 were aimed at more specific target groups (3 on older adults and 1 each on older adults who lost their spouse, adult women, patients with comorbid borderline personality disorder, patients with chronic depression, patients with coronary artery disease, and women with postpartum depression). Patients were recruited through clinical referrals (18 studies), from the community (5 studies), or through a combination of both (2 studies). Fifteen studies were aimed at patients with a major depressive disorder and 5 at patients with dysthymia, while the remaining 5 studies were aimed at patients with other definitions of depressive disorders (major depression and/or dysthymia, other). In 17 studies, the Hamilton Depression Rating Scale (HDRS) score at pretest was presented (range, 16.7–27.4), while 10 studies reported the pretest Beck Depression Inventory (BDI) score (range, 13.7–36.9).

Eight studies examined cognitive-behavioral therapy, another 8 examined interpersonal psychotherapy, and 9 examined other psychological treatments, such as psychodynamic therapy or problem-solving treatment. Individual psychotherapies were examined in 21 studies, while 4 studies used group therapies (1 used a combined individual and group format). Selective serotonin reuptake inhibitors (SSRIs) were examined in 9 studies, and tricyclic antidepressants (TCAs) were also examined in 9 studies (other medications or a protocol was used in 7 studies).

The quality of the included studies varied. Eight of the 25 studies reported that allocation to conditions was conducted by an independent party. Blinding of assessors was reported in 18 studies. Intention-to-treat analyses were conducted in 16 studies (the other studies were limited to completers-only analyses). Five studies met all 3 quality criteria.

Differences Between Pharmacologic and Combined Treatments: Overall Effect Sizes

The mean effect size indicating the difference between pharmacotherapy and combined therapy was $d = 0.31$ (95% CI, 0.20 ~ 0.43; Table 2) for the 25 included studies, indicating a small effect in favor of the combined treatment, which was highly significant ($Z = 5.17$, $P < .001$). This effect size corresponds with a number needed to treat (NNT) of 5.75. Heterogeneity was low to moderate ($Q = 34.33$, $P < .1$; $I^2 = 30.08$). The effect sizes and 95% confidence intervals of the individual contrast groups are plotted in Figure 1.

When we limited the analyses to the effect sizes with the HDRS, comparable results were found ($d = 0.32$; 95% CI, 0.19 ~ 0.44; $P < .001$; $Q = 27.16$, not significant [NS]; $I^2 = 26.37$; NNT = 5.56). The same was true when we limited the analyses to the effect sizes found with the BDI ($d = 0.28$; 95% CI, 0.10 ~ 0.46; $P < .01$; $Q = 5.32$, NS; $I^2 = 0$; NNT = 6.41).

Visual inspection of the funnel plot suggested that the study by Macaskill and Macaskill[7] could be an outlier. The resulting effect size was comparable with the effect size of all comparisons ($d = 0.30$; 95% CI, 0.19 ~ 0.42; $Z = 5.22$, $P < .001$) and heterogeneity was somewhat lower ($Q = 30.29$, NS; $I^2 = 24.07$).

Several of the included studies differed on essential characteristics from the other studies. For example, 1 study[7] examined rational-emotive therapy, another[30] examined dialectic behavior therapy, and yet another study[36] did not report any details about the pharmacotherapy used. It is possible that 1 or more of such atypical studies had a negative effect on the overall mean effect size. Therefore, we conducted a series of meta-analyses in which we removed the study with the largest impact on the overall effect size. We first removed the study with the largest impact and examined the extent to which the effect size was increased or decreased and repeated this procedure several times. In this way we could examine whether removal of 1 or more studies resulted in important changes to the outcomes.

Removal of the study by Browne and colleagues[10] resulted in the largest increase of the effect size (the resulting effect size was $d = 0.37$; $I^2 = 3.53$). After the removal of this study, we repeated this procedure and examined which study should be removed in order to realize the next largest increase of the effect size. This study was the one by Bellack and colleagues,[9] and the meta-analysis resulted in an effect size of $d = 0.39$ ($I^2 = 0$). Repeating this procedure a third time (which removed the study by Lesperance and colleagues[28]) resulted in a mean effect size of $d = 0.41$ ($I^2 = 0$). A comparable procedure to examine whether individual studies resulted in a decrease of the effect size indicated that removal of the study by Keller and colleagues[27] resulted in the largest decrease (effect size: $d = 0.29$; $I^2 = 23.00$), followed by the

Table 1. Selected Characteristics of Studies Comparing Combined Psychological and Pharmacologic Treatment With Pharmacotherapy Alone in Adults With Depressive Disorders

Study	Population	Recruitment Method	Definition of Depression	Combined Treatment
Bellack et al[9] (1981)	Adult women	Community/clinic	DD (Feighner criteria)	Social skills training + pharmacotherapy
Bellino et al[6] (2006)	Adults with BPD	Clinic	MDD (SCID)	Interpersonal psychotherapy + pharmacotherapy
Blackburn et al[8] (1981)	Adults	Clinic	MDD (RDC) + BDI score ≥ 14	Cognitive-behavioral therapy + pharmacotherapy
Blom et al[20] (2007)	Adults	Clinic	MDD (SCID) + HDRS score ≥ 14	Interpersonal psychotherapy + pharmacotherapy
Browne et al[10] (2002)	Adults	Community	Dysthymia (*DSM-IV*/UM-CIDI)	Interpersonal psychotherapy + pharmacotherapy
Burnand et al[21] (2002)	Adults	Clinic	MDD (SCID)	Psychodynamic psychotherapy + pharmacotherapy
de Jonghe et al[22] (2001)	Adults	Clinic	MDD (*DSM-IV*) + HRSD score 12–24	Psychodynamic psychotherapy + pharmacotherapy
De Mello et al[23] (2001)	Adults	Clinic	Dysthymia (ICD-10 symptom checklist)	Interpersonal psychotherapy + pharmacotherapy
Hautzinger et al[24] (1996)	Adults	Clinic	MDD/Dysthymia + HDRS score ≥ 20 + BDI score > 20	Cognitive-behavioral therapy + pharmacotherapy
Hellerstein et al[25] (2001)	Adults	Clinic	Dysthymia (*DSM-III-R*; SCID) + HDRS score ≥ 14	CIGP + pharmacotherapy
Hollon et al[26] (1992)	Adults	Clinic	MDD (RDC) + BDI score ≥ 20 + HDRS score ≥ 14	Cognitive-behavioral therapy + pharmacotherapy
Keller et al[27] (2000)	Adults with chronic depression	Clinic	MDD + dysthymia or recurrent MDD (*DSM-IV*/SCID) + HDRS score ≥ 20	CBASP + pharmacotherapy
Lespérance et al[28] (2007)	Adults with coronary artery disease	Community/clinic	MDD + HDRS score ≥ 20	Interpersonal psychotherapy + pharmacotherapy
Lopez et al[29] (2004)	Adults	Clinic	DD (*DSM-IV*), not further specified	Bellak's psychotherapy + pharmacotherapy
Lynch et al[30] (2003)	Older adults	Clinic	MDD (DDES) + HDRS score ≥ 18 or BDI score ≥ 19	Dialectical behavior therapy + pharmacotherapy
Macaskill and Macaskill[7] (1996)	Adults	Clinic	MDD (*DSM-III-R*) + BDI score ≥ 20 + HDRS score ≥ 14 + DAS score ≥ 155	Rational-emotive therapy[a]
Markowitz et al[11] (2005)	Adults	Community	Dysthymia (SCID)	Interpersonal psychotherapy + pharmacotherapy
Misri et al[31] (2004)	Women with PPD	Clinic	HDRS score ≥ 18 + EPDS score ≥ 20 + DD (*DSM-IV*)	Cognitive-behavioral therapy + pharmacotherapy
Murphy et al[32] (1984)	Adults	Clinic	MDD (Feighner criteria) + BDI score ≥ 20 + HDRS score ≥ 14	Cognitive-behavioral therapy + pharmacotherapy
Mynors-Wallis et al[33] (2000)	Adults	Clinic	MDD + HDRS score ≥ 13	Problem-solving therapy + pharmacotherapy
Ravindran et al[34] (1999)	Adults	Community	Dysthymia (*DSM*/MINI)	Cognitive-behavioral therapy + pharmacotherapy
Reynolds et al[35] (1999)	Older adults who lost their spouse	Community	MDD (SADS/RDC)	Interpersonal psychotherapy + pharmacotherapy
Sirey et al[36] (2005)	Older adults	Clinic	MDD (*DSM*/SCID)	Treatment Initiation Program + pharmacotherapy
Thompson et al[37] (2001)	Older adults	Community	MDD (SADS/RDC) + HDRS score ≥ 14 + BDI score ≥ 16	Cognitive-behavioral therapy + pharmacotherapy
Weissman et al[38] (1979)	Adults	Clinic	MDD (SADS/RDC) + RDS score ≥ 7	Interpersonal psychotherapy + pharmacotherapy

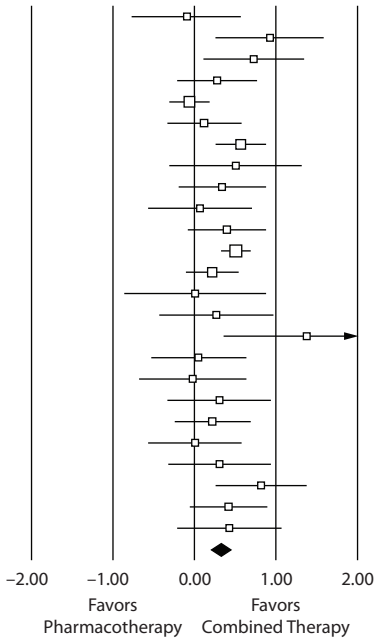
Abbreviations: BDI = Beck Depression Inventory, BDI-II = Beck Depression Inventory II, BPD = borderline personality disorders, CBASP = cognitive behavioral-analysis system of psychotherapy, CDRS = Cornell Dysthymia Rating Scale, CES-D = Center for Epidemiological Studies-Depression Scale, CIGP = cognitive-interpersonal group psychotherapy for chronic depression, DAS = Dysfunctional Attitude Scale, DD = depressive disorder, DDES = Duke Depression Evaluation Schedule, EPDS = Edinburgh Postnatal Depression Scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, MINI = Mini-International Neuropsychiatric Interview,

No. of Subjects in Combined Treatment	No. of Sessions	Format	Pharmacotherapy	No. of Subjects in the Pharmacotherapy	Measure	Country
12	12	Individual	Amitriptyline	8	HDRS, BDI	United States
20	24	Individual	Fluoxetine	19	HDRS	Italy
22	15	Group	Drug of choice	20	BDI, HDRS	United Kingdom
49	12	Individual	Nefazodone	47	HDRS, MADRS	The Netherlands
122	10	Individual	Sertraline	117	MADRS, CES-D, VAS	Canada
35	10	Individual	Clomipramine	39	HDRS	Sweden
83	16	Individual	Protocol	84	HDRS, SCL-90-D	The Netherlands
16	16	Individual	Moclobemide	19	HDRS, MADRS	Brazil
68	24	Individual	Amitriptyline	45	HDRS, BDI	Germany
20	16	Group	Fluoxetine	20	HDRS, BDI, CDRS	United States
16	20	Individual	Imipramine	32	HDRS, BDI, RDS, MMPI-d	United States
227	18	Individual	Nefazodone	226	HDRS	United States
67	12	Individual	Citalopram	75	HDRS, BDI-II	Canada
10	NR	Individual	Fluoxetine	10	HDRS	Mexico
17	56	Group/individual	Physician's choice	17	HDRS, BDI	United States
10	30	Individual	Lofepramine	10	HDRS, BDI	United Kingdom
21	17	Individual	Sertraline	24	HDRS, BDI, CDRS	United States
19	12	Individual	Paroxetine	16	HDRS, EPDS	Canada
22	20	Individual	Nortriptyline	24	HDRS, BDI	United States
35	6	Individual	Fluvoxamine or paroxetine	36	HDRS, BDI	United Kingdom
25	12	Group	Sertraline	22	HDRS, MADRS, CDRS	Canada
16	16	Individual	Nortriptyline	25	HDRS	United States
26	5	Individual	No details reported	26	HDRS	United States
36	18	Individual	Desipramine	33	BDI, HDRS	United States
24	16	Individual	Amitriptyline	24	RDS	United States

Abbreviations continued: MMPI-d = Minnesota Multiphasic Personality Inventory-depression scale, NR = not reported, PPD = postpartum depression, RDC = research diagnostic criteria, RDS = Raskin Depression Scale, SADS = Schedule for Affective Disorders and Schizophrenia, SCID = Structured Clinical Interview for *DSM-III-R*, SCL-90-D = Symptom Checklist-90-Depression subscale, UM-CIDI = University of Michigan Composite International Diagnostic Interview, VAS = Visual Analogue Scale.

Figure 1. Standardized Effect Sizes Indicating Differences Between the Effects of Pharmacologic and Combined Treatment of Depression at Posttest

Study	Standard Difference in Means	Lower Limit	Upper Limit	*Z* Value	*P* Value
Bellack et al[9] (1981)	−0.10	−0.78	0.58	−0.29	0.77
Bellino et al[6] (2006)	0.92	0.26	1.58	2.73	0.01
Blackburn et al[8] (1981)	0.72	0.10	1.34	2.26	0.02
Blom et al[20] (2007)	0.27	−0.23	0.77	1.07	0.29
Browne et al[10] (2002)	−0.07	−0.32	0.18	−0.54	0.59
Burnand et al[21] (2002)	0.11	−0.35	0.57	0.47	0.64
de Jonghe et al[22] (2001)	0.56	0.25	0.87	3.55	0.00
deMello et al[23] (2001)	0.50	−0.32	1.32	1.20	0.23
Hautzinger et al[24] (1996)	0.33	−0.21	0.87	1.20	0.23
Hellerstein et al[25] (2001)	0.06	−0.58	0.70	0.18	0.86
Hollon et al[26] (1992)	0.39	−0.08	0.86	1.61	0.11
Keller et al[27] (2000)	0.50	0.31	0.69	5.20	0.00
Lesperance et al[28] (2007)	0.21	−0.12	0.54	1.25	0.21
Lopez et al[29] (2004)	0.00	−0.88	0.88	0.00	1.00
Lynch et al[30] (2003)	0.26	−0.45	0.97	0.72	0.47
Macaskill and Macaskill[7] (1996)	1.37	0.34	2.40	2.62	0.01
Markowitz et al[11] (2005)	0.04	−0.55	0.63	0.13	0.89
Misri et al[31] (2004)	−0.03	−0.70	0.64	−0.09	0.93
Murphy et al[32] (1984)	0.30	−0.34	0.94	0.92	0.36
Mynors-Wallis et al[33] (2000)	0.21	−0.26	0.68	0.88	0.38
Ravindran et al[34] (1999)	0.00	−0.57	0.57	0.00	1.00
Reynolds et al[35] (1999)	0.30	−0.33	0.93	0.93	0.35
Sirey et al[36] (2005)	0.81	0.24	1.38	2.81	0.00
Thompson et al[37] (2001)	0.41	−0.07	0.89	1.68	0.09
Weissman et al[38] (1979)	0.42	−0.23	1.07	1.27	0.20
	0.31	0.20	0.43	5.17	0.00



study by de Jonghe[22] (effect size: $d = 0.26$; $I^2 = 15.52$) and the study by Sirey et al[36] (effect size: $d = 0.22$; $I^2 = 4.04$). These analyses suggest that removal of studies did not result in major changes in the effect sizes.

Neither the funnel plot nor Duval and Tweedie's trim-and-fill procedure pointed to a significant publication bias. The effect size indicating the difference in reduction of depressive symptomatology between combined (including psychological) and pharmacologic treatments did not change significantly after adjustment for possible publication bias (the observed and adjusted effect size did not differ from each other).

Subgroup Analyses

Because there was some heterogeneity, we decided to conduct a series of subgroup analyses. The results of these are presented in Table 2. As can be seen, we found no indication of a significant difference between studies aimed at adults in general and studies aimed at more specific target groups, nor did we find a significant association between effect size and type of psychotherapy, between studies in which individual therapies were used and those in which group therapies were used, between studies in which intention-to-treat analyses were conducted and studies in which completers-only analyses were conducted, or between studies that met all quality criteria and those that did not. We also grouped the studies into those that did or did not include a separate psychotherapy alone condition (although these psychotherapy-only conditions are not examined in this meta-analysis). However, this subgroup analysis did not indicate that the effect sizes in these groups differed significantly from each other.

However, we did find that studies aimed at patients with dysthymia resulted in significantly lower effect sizes ($d = 0.00$) compared to studies aimed at patients with major depressive disorder ($d = 0.40$). We also found that studies in which SSRIs were used resulted in significantly lower effect sizes than studies in which TCAs or other pharmacotherapies were used ($P = .004$). The studies in which SSRIs were used did not indicate that combined treatment was more effective than treatment with pharmacotherapy alone ($d = 0.10$). Furthermore, studies in which patients were recruited from clinical samples resulted in higher effect sizes than studies in which patients were recruited in other ways ($P < .001$).

Because we found that studies in patients with dysthymia resulted in smaller effect sizes than studies in patients with major depression, we conducted some additional subgroup analyses. In these analyses, we removed the studies with dysthymic patients and included only the studies of patients with major depressive disorder. Then we examined whether we still found a difference between studies with TCAs and studies with SSRIs. As can be seen in Table 2, in these analyses, we found that psychotherapy had an additional effect for both TCAs and SSRIs. The difference between the additional

Table 2. Meta-Analyses of Studies Comparing the Effects of Pharmacologic Treatments on Depression Compared to Combined Treatments at Posttest

Study	No. of Comparisons	*d*	95% CI	*Z*	I^2 (%)[a]	*P*[b]	NNT
Overall effects							
All studies	25	0.31	0.20 ~ 0.43	5.17***	30.08†		5.75
HDRS only	21	0.32	0.19 ~ 0.44	4.83***	26.37		5.56
BDI only	10	0.28	0.10 ~ 0.46	3.00**	0		6.41
One possible outlier removed[c]	24	0.30	0.19 ~ 0.42	5.22***	24.07		5.95
Subgroup analyses[d]							
Target group							
Adults	17	0.30	0.16 ~ 0.45	4.06***	36.34†	.751	5.95
Specific groups	8	0.35	0.12 ~ 0.57	3.00**	23.67		5.10
Recruitment							
Clinical	18	0.44	0.33 ~ 0.55	7.79***	0	.000	4.10
Other	7	0.08	−0.08 ~ 0.24	1.02	0		21.74
Diagnosis							
MDD	20	0.40	0.30 ~ 0.51	7.52***	2.92	.000	4.50
Dysthymia	5	0.00	−0.20 ~ 0.20	−0.03	0		…
Psychological treatment							
CBT	7	0.32	0.11 ~ 0.53	2.96**	0	.548	5.56
IPT	8	0.23	0.02 ~ 0.44	2.13*	31.10		7.69
Other	10	0.38	0.20 ~ 0.57	3.98***	34.17		4.72
Format							
Individual	21	0.32	0.19 ~ 0.45	4.86***	35.22†	.693	5.56
Group	4	0.25	−0.08 ~ 0.58	1.50	7.39		7.14
Analyses							
Intention to treat	16	0.36	0.26 ~ 0.47	6.79***	0	.906	5.00
Completers only	9	0.38	0.07 ~ 0.70	2.39*	56.11*		4.72
Design of study[e]							
Psychotherapy possible	12	0.29	0.14 ~ 0.45	3.64***	33.69	.695	6.17
All received medication	13	0.34	0.15 ~ 0.53	3.49***	31.54		5.26
Study quality							
High quality studies	5	0.36	0.19 ~ 0.52	4.25***	9.85	.761	5.00
Other studies	20	0.32	0.17 ~ 0.47	4.15***	34.47†		5.56
Medication category							
TCAs	10	0.35	0.17 ~ 0.54	3.79***	0	.004	5.10
SSRIs	9	0.10	−0.06 ~ 0.27	1.24	7.55		17.86
Other medication	3	0.47	0.30 ~ 0.65	5.37***	0		3.85
Protocol/other	3	0.57	0.32 ~ 0.83	4.42***	0		3.18
Subgroup analyses limited to patients with MDD							
Recruitment							
Clinical	16	0.44	0.33 ~ 0.56	7.41***	3.05	.117	4.10
Other	4	0.23	−0.00 ~ 0.47	1.95†	0		7.69
Medication category							
Tricyclics	10	0.35	0.17 ~ 0.54	3.79***	0	.201	5.10
SSRIs	5	0.26	−0.01 ~ 0.53	1.89†	20.53		6.85
Protocol/other	5	0.50	0.36 ~ 0.65	6.83***	0		3.62
Severity							
HDRS score[f]							
≤ 20	5	0.52	0.32 ~ 0.72	5.00***	0	.113	3.50
> 20	10	0.29	0.11 ~ 0.48	3.07**	0		6.17
BDI score[g]							
≤ 18	3	0.11	−0.26 ~ 0.48	0.57	0	.243	16.13
19–29	7	0.37	0.13 ~ 0.62	2.97**	16.97		4.85

[a]The *P* values in this column indicate whether the *Q* statistic is significant (the I^2 statistic does not include a test of significance).
[b]The *P* values in this column indicate whether the difference between the effect sizes in the subgroups is significant.
[c]Macaskill et al.[7]
[d]All subgroup analyses were conducted with mixed-effects analyses.
[e]We also grouped the studies into those in which all patients received pharmacotherapy and those in which it was possible that they received psychotherapy alone (although these psychotherapy-only conditions are not examined in this meta-analysis).
[f]These analyses were limited to those studies that reported depression severity according to the HDRS at pretest.
[g]These analyses were limited to those studies that reported depression severity according to the BDI at pretest.
†$P < .10$.
*$P < .05$.
**$P < .01$.
***$P < .001$.
Abbreviations: BDI = Beck Depression Inventory, CBT = cognitive-behavioral therapy, DYST = dysthymia, HDRS = Hamilton Depression Rating Scale, IPT = interpersonal psychotherapy, MDD = major depressive disorder, NNT = number needed to treat, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 3. Results of Meta-Analyses Comparing the Dropout Rates of Pharmacologic and Combined Treatments for Depression: Odds Ratios

Variable	No. of Comparisons	OR	95% CI	*Z*	I^2 (%)[a]	*P*[b]
Overall results						
All studies	19	0.65	0.50 ~ 0.83	−3.44**	0.62	
Subgroup analyses[c]						
Target group						
Adults	12	0.53	0.36 ~ 0.77	−3.36**	7.90	.093
Specific groups	7	0.82	0.58 ~ 1.16	−1.11	0	
Recruitment						
Clinical	14	0.61	0.44 ~ 0.85	−2.97**	15.08	.342
Other	5	0.85	0.46 ~ 1.56	−0.52	0	
Diagnosis						
MDD	15	0.65	0.47 ~ 0.89	−2.72**	16.86	.914
Dysthymia	4	0.68	0.29 ~ 1.60	−0.89	0	
Psychological treatment						
CBT	6	0.74	0.41 ~ 1.33	−1.00	0	.944
IPT	7	0.66	0.41 ~ 1.05	−1.76†	0	
Other	6	0.66	0.35 ~ 1.22	−1.34	47.64†	
Format						
Individual	16	0.63	0.48 ~ 0.83	−3.23**	8.79	.379
Group	3	1.19	0.30 ~ 4.69	0.24	0	
Analyses						
Intention to treat	12	0.65	0.48 ~ 0.86	−2.97**	7.44	.962
Completers only	7	0.66	0.33 ~ 1.33	−1.17	3.66	
Design of study[d]						
Psychotherapy possible	8	0.71	0.53 ~ 0.96	−2.20*	0	.604
All received medication	11	0.61	0.36 ~ 1.02	−1.88†	13.71	
Medication category						
SSRIs	7	1.00	0.56 ~ 1.78	0.01	0	.521
TCAs	7	0.56	0.33 ~ 0.95	−2.16*	0	
Other medication	3	0.75	0.51 ~ 1.08	−1.55	0	
Protocol/other	2	0.53	0.08 ~ 3.42	−0.67	58.37	
Severity						
HDRS score[e]						
≤ 20	4	0.65	0.29 ~ 1.47	−1.04	58.00†	.918
> 20	8	0.68	0.41 ~ 1.12	−1.51	0	
BDI score[f]						
≤ 19	3	0.94	0.33 ~ 2.69	−0.12	0	.605
20–29	4	0.68	0.35 ~ 1.31	−1.16	0	

[a]The *P* values in this column indicate whether the *Q* statistic is significant (the I^2 statistics does not include a test of significance).
[b]The *P* values in this column indicate whether the difference between the odds ratios in the subgroups is significant.
[c]All subgroup analyses were conducted with mixed-effects analyses.
[d]We also grouped the studies into those in which all patients received pharmacotherapy and those in which it was possible that they received psychotherapy alone (although these psychotherapy-only conditions are not examined in this meta-analysis).
[e]These analyses were limited to those studies that reported depression severity according to the HDRS at pretest.
[f]These analyses were limited to those studies that reported depression severity according to the BDI at pretest.
†$P < .10$.
*$P < .05$.
**$P < .01$.
***$P < .001$.
Abbreviations: BDI = Beck Depression Inventory, CBT = cognitive-behavioral therapy, HDRS = Hamilton Depression Rating Scale, IPT = interpersonal psychotherapy, MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

effect of psychotherapy in TCAs and in SSRIs was very small and no longer significant. We also examined whether studies in which patients were recruited from clinical samples still resulted in higher effect sizes than studies in which patients were recruited in other ways, but this difference was also no longer significant.

Severity of Depression

We examined in several ways whether the severity of depression at baseline was associated with the effect sizes. First, we conducted a series of metaregression analyses. We selected the 15 studies in which the sample's mean HDRS (17-item version) score at baseline was presented and examined with a metaregression analysis whether the baseline HDRS was associated with the effect size. These analyses did not indicate that the baseline HDRS score was significantly associated with the effect size (point estimate of slope = −0.04; 95% CI, −0.10 ~ 0.01; $Z = -1.48$, $P = .14$). Because our subgroup analyses indicated a difference between studies on dysthymia, we repeated these analyses after removing the studies on dysthymia. Again, no significant association between effect size and baseline HDRS

was found. Then we divided the 15 studies that presented the baseline HDRS score into studies in which the HDRS score was 20 or lower and those in which it was higher than 20 (Table 2). A subgroup analysis did not indicate that the studies with lower baseline depression differed significantly from those with more severe depression.

We repeated this procedure on the 10 studies in which the baseline BDI was reported. In a metaregression analysis, we found no indication that the pretest BDI score was significantly associated with the effect size (point estimate of slope = 0.02; 95% CI, −0.01 ~ 0.05; $Z = 1.40$, $P = .16$). A subgroup analysis in which we divided the studies into those with mild to moderate depression (BDI score ≤ 18) or moderate to severe depression (BDI score 19–29) also did not find any indications for a significant difference between these groups (Table 2).

Effects on Dropout

We compared the dropout rates of pharmacologic and combined treatments in 19 studies and found that the dropout rate was significantly lower in the combined treatment compared to pharmacotherapy alone (OR = 0.65; 95% CI, 0.50 ~ 0.83; $Z = -3.44$, $P < .01$), with almost no heterogeneity ($Q = 18.11$, NS; $I^2 = 0.62$). We found no indications of significant publication bias when we examined the funnel plot and used Duvall and Tweedie's[19] trim-and-fill method. The adjusted OR was almost the same as the unadjusted OR (adjusted OR: 0.62; 95% CI, 0.49 ~ 0.80).

We conducted the same subgroup and metaregression analyses as we did with the effect sizes (Table 3). As can be seen in Table 3, none of the subgroup analyses indicated that there were significant differences between subgroups. There was a trend ($P < .1$), however, for the dropout rate to be lower in studies examining adults in general compared to studies in which more specific target groups were examined. Levels of heterogeneity were low or zero in most subgroups.

We found no indication that severity of depression was associated with dropout in both the subgroup analyses (Table 3) and the metaregression analyses (HDRS: N = 14, point estimate of slope = −0.05, 95% CI, −0.13 ~ 0.22; $Z = 0.52$, NS; BDI: N = 7, point estimate of slope = −0.01, 95% CI, −0.10 ~ 0.07; $Z = -0.28$, NS).

We also examined whether adverse effects of medication differed in the pharmacotherapy and combined treatments. However, only 7 studies reported these data, and, because in most of the studies the number of adverse effects was very small (even zero in many cases), we did not find it informative to pool these outcomes into 1 effect size.

DISCUSSION

We found clear indications that a combined treatment including psychotherapy is more effective than pharmacotherapy alone. Although the effect size indicating the difference between pharmacotherapy and the combined therapy was small, it was highly statistically significant. This suggests that psychotherapy has an additional effect on depression apart from the effects of pharmacotherapy.

However, we also found that in studies aimed at patients with dysthymia, the combined treatment had no additional value compared to pharmacotherapy alone. Our subgroup analyses showed that the studies with dysthymia patients differed significantly from those with major depression patients. This is in agreement with the results of an earlier meta-analysis of studies in which psychotherapy and pharmacotherapy were directly compared to each other.[12] In the earlier meta-analysis, we found that psychotherapy alone was significantly less effective than pharmacotherapy alone in patients with dysthymia. It could be that current psychotherapies do not target a chronic disorder like dysthymia rapidly enough to keep up with pharmacotherapy. In that regard, it is of interest to note that one of the largest effect sizes found in the combinatorial literature was found when an approach developed specifically for use with chronic patients was applied to a sample with MDD.[27]

We also found that psychotherapy added less to pharmacotherapy in studies in which SSRIs were examined, compared to studies in which TCAs were used. However, this difference was not statistically significant in the sample studies examining patients with major depression, and is strongly influenced by the fact that most studies on dysthymic patients also examined SSRIs.

In addition, we found that the dropout rate was significantly lower in the combined treatment group compared to pharmacotherapy alone group. This finding is in agreement with our earlier research in which we found that dropout rates in psychotherapy are significantly lower than dropout rates in pharmacotherapy[12] and is in agreement with several other studies[39–41] that have shown that most patients prefer psychotherapy instead of pharmacotherapy.

We found no indication for an association between the effect size and severity of depression, which suggests that combined treatments are superior in both milder and more severe cases of depression. Because most studies examined patients with mild to moderate depression, this finding has to be interpreted with caution.

This study has several important limitations. First, the number of studies we could include was still relatively small, and the quality of several of the included studies was not optimal. Second, it was not possible in any of the included studies to blind patients with respect to treatment assignment. Patients know when they are assigned to the combined treatment because they receive psychotherapy. This may have distorted the results of these studies. Third, only a limited number of the studies conducted intention-to-treat analyses, and, because dropout rates differed significantly between pharmacotherapy and combined treatment, this may have introduced a bias in our outcomes. Fourth, we did not examine the long-term effects of both treatments. It may

well be possible that there are major differences between pharmacotherapy and combined treatments in the longer term. Because of these limitations, the results of this meta-analysis should be considered with caution.

From a clinical point of view, our results raise a number of questions and possibilities for future research. First, one interpretation of the results could be that certain patients only respond when given the additional push for change in psychotherapy. On the other hand, we do not know how the patients in the trials perceived the 2 treatments. Were both regarded as equally important? These questions could be addressed in more qualitative research. Second, how should clinicians handle the clinical situation with 2 active treatments, often not provided by the same clinician? It is known that follow-up visits in trials have a therapeutic effect,[42] and, potentially, this can cancel out some to the nonspecific effects of psychotherapy.

More research is also needed to further examine the effectiveness of psychotherapy in dysthymia, as well as the mechanisms through which psychological and pharmacologic treatment work, and characteristics of patients who respond better to pharmacologic or combined treatment. We can conclude that psychotherapy compared to pharmacotherapy alone seems to have an additional value in the treatment of depression.

Drug names: amitriptyline (Limbitrol and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac, Sarafem, and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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