Review

Efficacy of Pharmacotherapy and Psychotherapy for Adult Psychiatric Disorders
A Systematic Overview of Meta-analyses

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IMPORTANCE There is debate about the effectiveness of psychiatric treatments and whether pharmacotherapy or psychotherapy should be primarily used.

OBJECTIVES To perform a systematic overview on the efficacy of pharmacotherapies and psychotherapies for major psychiatric disorders and to compare the quality of pharmacotherapy and psychotherapy trials.

EVIDENCE REVIEW We searched MEDLINE, EMBASE, PsycINFO, and the Cochrane Library (April 2012, with no time or language limit) for systematic reviews on pharmacotherapy or psychotherapy vs placebo, pharmacotherapy vs psychotherapy, and their combination vs either modality alone. Two reviewers independently selected the meta-analyses and extracted efficacy effect sizes. We assessed the quality of the individual trials included in the pharmacotherapy and psychotherapy meta-analyses with the Cochrane risk of bias tool.

FINDINGS The search yielded 45 233 results. We included 61 meta-analyses on 21 psychiatric disorders, which contained 852 individual trials and 137 126 participants. The mean effect size of the meta-analyses was medium (mean, 0.50; 95% CI, 0.41-0.59). Effect sizes of psychotherapies vs placebo tended to be higher than those of medication, but direct comparisons, albeit usually based on few trials, did not reveal consistent differences. Individual pharmacotherapy trials were more likely to have large sample sizes, blinding, control groups, and intention-to-treat analyses. In contrast, psychotherapy trials had lower dropout rates and provided follow-up data. In psychotherapy studies, wait-list designs showed larger effects than did comparisons with placebo.

CONCLUSIONS AND RELEVANCE Many pharmacotherapies and psychotherapies are effective, but there is a lot of room for improvement. Because of the multiple differences in the methods used in pharmacotherapy and psychotherapy trials, indirect comparisons of their effect sizes compared with placebo or no treatment are problematic. Well-designed direct comparisons, which are scarce, need public funding. Because patients often benefit from both forms of therapy, research should also focus on how both modalities can be best combined to maximize synergy rather than debate the use of one treatment over the other.

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Much controversy surrounds psychiatry, including a debate about the effectiveness of its treatments. For example, the efficacy of antipsychotics,[1] cholinesterase inhibitors,[2] and lithium prophylaxis[3] has been questioned, and Kirsch et al[4] concluded that antidepressants should be used only in severely ill patients. Leucht et al[5] showed that psychiatric drugs have the same range of efficacy as frequently used drugs from other medical specialties. Nevertheless, the criticism has expanded to psychotherapy, in particular psychoanalysis,[6] but also to cognitive behavioral therapy (CBT).[7] Moreover, whether psychotherapy or medication should be used to treat psychiatric conditions is strongly disputed. This ongoing criticism of psychiatry and the debate about the appropriate treatment make it necessary to examine the situation and present a broad appraisal. Such an attempt has been made possible by meta-analyses, which provide standardized quantitative measures of their efficacy by the calculation of effect sizes.[8] We therefore conducted a systematic overview of meta-analyses on the efficacy of drug therapy and psychotherapy for major psychiatric disorders, which we classified in 3 comparisons: psychotherapy or pharmacotherapy compared with placebo or no treatment, head-to-head comparisons of pharmacotherapies and psychotherapies, and the combination of both treatments. Moreover, we compared the methodologic quality of the individual drug and psychotherapy trials included in these meta-analyses. We had 3 objectives. First, we aimed to present an overview of what benefits psychiatry as a field can provide for patients, examining the contributions of pharmacotherapy and psychotherapy. Second, we wanted to determine the understudied areas, which can be roughly derived from the numbers of studies and participants included in the meta-analyses. Finally, we examined whether pharmacotherapy and psychotherapy trials have general methodologic differences that would be important for the interpretation of their meta-analyses. We emphasize that, because of obvious limitations, our overview is not a guideline of which treatments should be used and which should not be used for a disorder. Nevertheless, the systematic approach should lead to results with important implications for psychiatry.

Methods

Identification of Diseases and Search Strategy

We drafted a protocol and made it freely available on our institutional website (http://tinyurl.com/d6b277p; Supplement [eAppendix 1]).[9] Two authors (M.H. and S.L.) selected major psychiatric disorders by reviewing the *DSM-IV* and *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) (Supplement [eAppendix 1]). We did not examine child psychiatric disorders (*ICD-10* categories F80-F98 and *DSM-IV* categories 307-319).

We searched PubMed, EMBASE, and PsycINFO (last search on April 22, 2012; no time or language limit) and individual records of the Cochrane Library for systematic reviews and meta-analyses of randomized clinical trials (RCTs) on the following comparisons: (1) pharmacotherapy or psychotherapy vs placebo, (2) head-to-head pharmacotherapy vs psychotherapy, and (3) combinations of pharmacotherapy and psychotherapy vs monotherapy with each intervention. Search terms were *meta-analy** or *metaanaly** or *systematic review** combined with the thesaurus of the individual databases concerning each disorder (Supplement [eAppendix 2]). Titles, abstracts, and, subsequently, full articles were examined by one author (M.H.), and another (M.T.) independently examined a random sample of 20% of the retrieved publications. Disagreements were resolved by discussion with a third author (S.L.). Only between-group effect sizes were extracted; within-treatment effect sizes were not used because they generally inflate effects. We included only standard treatments (eg, antipsychotics for schizophrenia [not lithium]) and aimed to include one meta-analysis for each disorder. We applied the following a priori–defined criteria to operationalize the selection: (1) all patients rather than special populations (eg, only first-episode patients); (2) classes of drugs rather than single drugs (eg, any antipsychotic rather than only haloperidol); (3) CBT and psychodynamic approaches (the former are usually recommended by guidelines; we checked the National Institute for Health and Clinical Excellence[10] and noted that psychodynamic therapy is considered a counterpart to CBT) unless other treatments are the standard (eg, cognitive training for dementia); when reviews on these specific psychotherapies were not available, we used meta-analyses on all psychotherapies; (4) the most up-to-date findings; and (5) full reporting of the results. In case of doubt, Cochrane reviews were preferred.

Parameters Extracted From the Meta-analyses

Two authors (M.H. and M.T.) independently extracted results on the primary efficacy outcomes, which generally were the mean (change) scores of overall symptoms at the end point (eg, Hamilton Scale for Depression) and study-defined responder rates (for acute treatment) or relapse rates (for maintenance treatment). We also recorded the number of studies and participants included in the meta-analyses and the mean study duration and number of psychotherapy sessions.

Dichotomous Outcomes

We extracted the percentage of responders (or relapsers) in drug and placebo groups, the response ratio or relative risk reduction (both abbreviated as RR), the absolute response or risk difference (ARD), and the number needed to treat (NNT), all with their 95% CIs. The Supplement (eAppendix 3) presents a detailed explanation.

Continuous Outcomes

For mean values of rating scales, we recorded between-group mean differences (MDs) (ie, the difference between the raw scores) and standardized MDs (SMDs) (effect size, Hedges g[8] value if available), which express MD in standard deviation (SD) units. We followed the original authors' decisions concerning fixed- vs random-effects models (the general use of a random-effects model did not change the overall results [Supplement; eAppendix 4 and eTable 4]).

Missing Parameters

If necessary, we transformed the data to our 5 parameters (MD/SMD/ARD/RR/NNT) or recalculated meta-analyses by entering single-trial results into meta-analytic software programs.[11,12] When only effect sizes for dichotomous outcomes (ARD, RR) were available, SMDs were estimated with Comprehensive Meta-analysis, version 2.[12] The purpose was to present all results in a single unit (SMD) in the figures.

Extraction of Quality Indicators From Individual Studies

One author (M.H., C.L., M.S., or M.D.) retrieved all studies included in the meta-analyses (only the acute phase to enhance comparabil-

ity) and assessed their quality with the Cochrane risk of bias tool,[13] which is based on scientific evidence of associations between overestimates of effect and methodologic shortcomings in the following domains:

1. appropriate randomization (eg, computer-generated randomization sequence),
2. allocation concealment (eg, voice mail system),
3. blinding (because blinding of therapists is impossible in psychotherapy trials, we compared blind outcome assessment with no blinding), and
4. missing outcomes (whether patients who withdrew from the study and their reasons for withdrawal were reported, an intention-to-treat analysis was performed, and we also reported the size of the overall dropout rate).

We did not examine the tool's domain *selective reporting* but added an item to the control groups that we classified as any *contemporaneous treatment* (placebo, treatment as usual, or ineffective therapy) vs wait list or no treatment. All items were rated as low, unclear, and high risk of bias, with items rated as unclear (eg, indicated as randomized without further explanation) combined with those having a high risk of bias in the statistical analysis. Moreover, we analyzed how often follow-up data after the trial end point were collected.

Statistical Analysis

Statistical analysis was conducted in 4 steps.

1. We compared the sample sizes of psychotherapy and pharmacotherapy meta-analyses and their quality as measured by A Measurement Tool to Assess Systematic Reviews (AMSTAR) score.[14]
2. We compared the sample sizes and the methodologic quality of the individual acute-phase studies included in the psychotherapy and pharmacotherapy meta-analyses with the Cochrane risk of bias tool.[13] The same analysis was performed on the single disorders (Supplement [eAppendix 4, eFigures 1-7]).
3. We examined whether the meta-analyses conducted subgroup comparisons on the risk of bias tool domains (eg, between studies using waiting lists or placebo), whether effects had remained constant in follow-up assessments, and how often indications of publication bias were found.
4. We compared the mean baseline severity in pharmacotherapy and psychotherapy trials on major depressive disorder (MDD) included in evaluations by Turner et al[15] and Cuijpers et al.[16] Because such an analysis requires a sufficient number of studies for both treatment modalities, it was not possible for other disorders.

Nonparametric tests were used throughout our study. Group means were compared with Mann-Whitney tests and dichotomous data with χ^2 tests; the α level was set at $P < .05$. Because all analyses were considered exploratory rather than confirmatory, adjustments for multiple testing were not made.

Results

The search retrieved 45 233 responses; 20 703 remained after elimination of duplicates. Detailed PRISMA flowcharts on the selection process are provided in the Supplement (eAppendix 5).[9] We included 61 meta-analyses (mean AMSTAR score, 8.4 [95% CI, 7.8-9.0]) on 21 disorders (852 individual trials and 137 126 participants). Thirty-three (54.1%) meta-analyses examined pharmacotherapy[15,17-48]; 17 (27.9%), psychotherapy[16,19,49-63] (most focused on CBT or specific treatments; very few examined psychodynamic approaches[50,59]); 7 (11.5%), direct comparisons[49,59,64-68]; and 12, combination therapies (19.7%)[49,57,59,65,68-75] (several meta-analyses included >1 comparison).

Figure 1, **Figure 2**, and **Figure 3** present the effect sizes in SMD units. Because of the limitations of effect size estimates, we strongly recommend that readers review *the detailed narrative description of the underlying meta-analyses*, including the drug classes analyzed, responder rates, RRs, ARDs, NNTs, and SMDs in the Supplement (eAppendix 6, with eTable 5). The sequence we used for our report always follows the order of the disorders in the *ICD-10*.

Pharmacotherapy and Psychotherapy Compared With Placebo or No Treatment

There were eligible reviews for at least one treatment modality for all a priori–selected disorders except personality disorders other than borderline personality disorder, impulse control disorders other than trichotillomania, and substance-related disorders other than alcohol and opiate dependence (Figure 1). Most meta-analyses examined acute treatment; only 5 examined maintenance treatment. All but 5 reviews demonstrated statistical significance compared with placebo, which could be expected because only treatments recommended by guidelines were chosen. However, the mean SMD of all meta-analyses (0.50 [95% CI, 0.41-0.59]) suggests medium efficacy of psychiatric treatments according to Cohen,[8] and few treatments had large effect sizes (mean SMD, ≥0.80).[19,21,23,26,33,52-54,63] Acute-phase psychotherapy effect sizes for the same disorder tended to be larger than those of pharmacotherapy (mean SMD, 0.40 [95% CI, 0.28-0.52] vs 0.58 [0.40-0.76]). However, Figure 1 also shows that the number of patients included in the acute-phase psychotherapy meta-analyses (median and mean sample sizes, 270 and 595, respectively) was generally smaller than in the pharmacotherapy studies (2507 and 3623) ($U = 650.00$; $P < .001$). The lower sample sizes resulted in broader CIs and, thus, more uncertainty about the true SMD. Finally, maintenance treatment with psychotropic drugs was associated with consistently larger effect sizes than was acute treatment.

Head-to-Head Pharmacotherapy and Psychotherapy

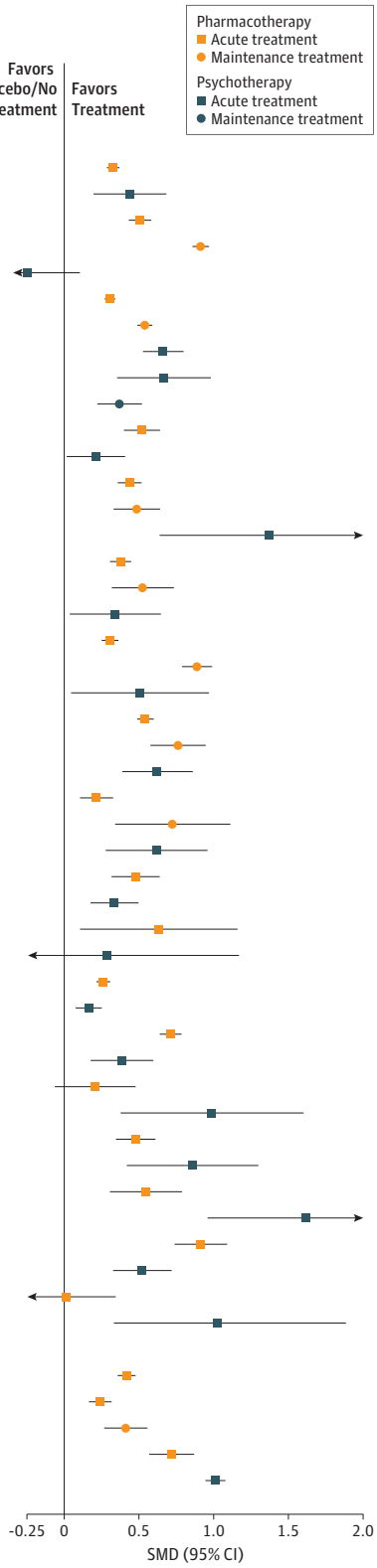
Seven meta-analyses, often with small sample sizes (range, 92-1662; median 375), on schizophrenia,[59] MDD,[64,67] dysthymic disorder,[49] panic disorder,[68] generalized anxiety disorder,[66] social phobia,[68] and bulimia[65] compared pharmacotherapy and psychotherapy head-to-head. Although there was a trend in favor of psychotherapy, this trend was significant only for relapse prevention in depression[64] and for bulimia[65]; pharmacotherapy was more effective for dysthymic disorder[49] and schizophrenia (compared with psychodynamic therapy)[59] (Figure 2).

Combinations of Pharmacotherapy and Psychotherapy

Twelve meta-analyses, also with small sample sizes (range, 23-2131; median, 256) on schizophrenia,[59,74] MDD,[70,71] dysthymic disorder,[49] bipolar disorder,[57] panic disorder,[72,75] social phobia,[68] posttraumatic stress disorder,[73] opiate addiction,[69] and bulimia[65] examined the effects of combining pharmacotherapy with psychotherapy. All analyses, except those on posttraumatic stress

Figure 1. Comparison of Effect Sizes in Meta-analyses of Acute and Maintenance Treatment in Pharmacotherapy and Psychotherapy

	SMD (95% CI)
Therapy	
Dementia drug (n = 8069)[18,28,35]	0.33 (0.29 to 0.37)
Dementia PT (n = 270)[60]	0.44 (0.20 to 0.69)
Schizophrenia acute drug (n = 5568)[30]	0.51 (0.44 to 0.58)
Schizophrenia relapse drug (n = 6493)[31]	*0.92 (0.86 to 0.97)*
Schizophrenia psychodynamic therapy (n = 164)[59]	-0.25 (-0.59 to 0.11)
MDD acute drug (n = 12 564)[15]	0.31 (0.27 to 0.80)
MDD relapse drug (n = 9268)[25]	*0.54 (0.49 to 0.59)*
MDD acute PT (n = 3465)[16,a]	0.67 (0.53 to 0.80)
Depression psychodynamic therapy, acute (n = 196)[50,b]	0.69 (0.30 to 1.08)
MDD relapse PT (n = 881)[57]	*0.37 (0.23 to 0.52)*
Dysthymia drug (n = 1454)[32]	*0.52 (0.40 to 0.64)*
Dysthymia PT (n = 275)[49]	0.21 (0.02 to 0.41)
OCD acute drug (n = 3097)[43]	0.44 (0.36 to 0.52)
OCD relapse drug (n = 951)[23]	*0.48 (0.32 to 0.64)*
OCD PT (n = 240)[54]	1.37 (0.64 to 2.24)
Panic acute drug (n = 7725)[37]	0.38 (0.31 to 0.45)
Panic relapse drug (n = 796)[23]	*0.53 (0.32 to 0.74)*
Panic PT (n = 328)[54]	0.35 (0.04 to 0.65)
GAD acute drug (n = 11 427)[38]	0.31 (0.26 to 0.36)
GAD relapse drug (n = 1342)[23]	*0.89 (0.79 to 0.99)*
GAD PT (n = 95)[54]	0.51 (0.05 to 0.97)
Social phobia acute drug (n = 7619)[27]	0.55 (0.49 to 0.60)
Social phobia relapse drug (n = 760)[23]	*0.76 (0.58 to 0.95)*
Social phobia PT (n = 377)[54]	0.62 (0.39 to 0.86)
PTSD acute drug (n = 2507)[44]	0.22 (0.11 to 0.33)
PTSD relapse drug (n = 272)[23]	*0.73 (0.34 to 1.11)*
PTSD PT (n = 266)[54]	0.62 (0.28 to 0.96)
Somatoform disorder drug (n = 832)[24]	0.48 (0.32 to 0.64)
Somatoform disorder PT (n = 1647)[56]	0.35 (0.18 to 0.50)
Borderline personality disorder drug (n = 1151)[47]	*0.63 (0.11 to 1.16)*
Borderline personality disorder DBT (n = 20)[61,c]	0.29 (-0.59 to 1.17)
Alcohol drug (n = 10 605)[40,41]	*0.26 (0.22 to 0.31)*
Alcohol PT (n = 2338)[58,62]	0.17 (0.08 to 0.26)
Opiates drug (n = 4001)[33,34]	*0.71 (0.64 to 0.79)*
Opiates PT (n = 545)[51]	0.39 (0.18 to 0.60)
Anorexia drug (n = 211)[22,29]	0.21 (-0.06 to 0.48)
Anorexia PT (n = 77)[52]	0.99 (0.38 to 1.60)
Binge-eating drug (n = 1254)[39]	*0.48 (0.35 to 0.61)*
Binge-eating PT (n = 90)[53]	0.86 (0.42 to 1.30)
Bulimia drug (n = 824)[17]	*0.55 (0.31 to 0.79)*
Bulimia PT (n = 204)[53]	*1.61 (0.96 to 2.29)*
Primary insomnia drug (n = 566)[26]	0.90 (0.74 to 1.09)
Primary insomnia PT (NI)[55]	0.52 (0.33 to 0.72)
Trichotillomania drug (n = 72)[19]	0.02 (-0.32 to 0.35)
Trichotillomania PT (n = 59)[19]	1.14 (0.38 to 1.89)
Disorders for which only meta-analyses on 1 modality were available	
Bipolar mania acute drug (n = 11 092)[48]	0.42 (0.36 to 0.48)
Bipolar depression acute drug (n = 3770)[42,45]	*0.24 (0.17 to 0.32)*
Bipolar disorder relapse drug (n = 2829)[46]	*0.41 (0.27 to 0.56)*
Adult ADHD drug (n = 1045)[21]	0.73 (0.57 to 0.87)
Specific phobia PT (n = 1217)[63]	1.03 (0.91 to 1.16)



For all disorders, we present the standardized mean difference (SMD) of pharmacotherapy (orange) and psychotherapy (blue) in acute (squares) and maintenance (circles) treatment vs placebo. We always chose the efficacy outcome with the most participants as reported in the Supplement (eTable 5). If there was more than 1 treatment for 1 disorder (eg, dementia [acetylcholinesterase inhibitors and memantine], bipolar depression [antidepressants, antipsychotics, and mood stabilizers], or opiate addiction [buprenorphine and methadone]), we presented their mean effect size. Italicized SMDs were estimated from odds ratios. ADHD indicates attention-deficit/hyperactivity disorder; DBT, dialective-behavioral therapy; GAD, generalized anxiety disorder; MDD, major depressive disorder; NI, not indicated; OCD, obsessive-compulsive disorder; PT, psychotherapy; and PTSD, posttraumatic stress disorder.

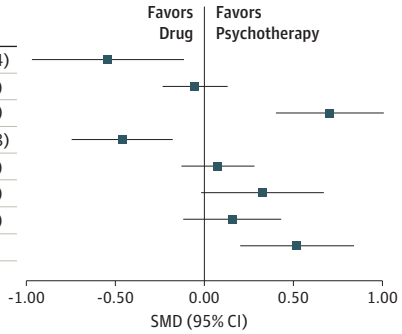
[a]We included only studies examining MDD.

[b]Mixed depressive disorder was available.

[c]Only 1 study was available.

Figure 2. Comparison of Effect Sizes in Meta-analyses of Direct Comparisons of Pharmacotherapy and Psychotherapy

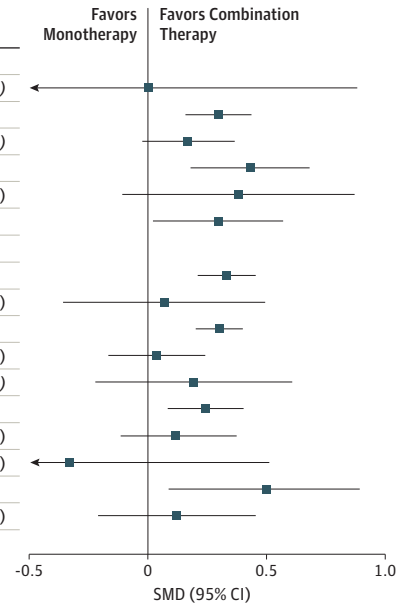
Diagnosis	SMD (95% CI)
Schizophrenia (n = 92)[59,a]	-0.56 (-0.98 to -0.14)
Major depressive disorder, acute (n = 1662)[67]	-0.05 (-0.24 to 0.13)
Major depressive disorder, relapse (n = 231)[64]	*-0.71 (-0.40 to 1.01)*
Dysthymic disorder (n = 874)[49]	-0.47 (-0.75 to -0.18)
Panic disorder (n = 375)[68]	0.08 (-0.13 to 0.28)
Generalized anxiety disorder (NI)[66]	0.33 (-0.02 to 0.67)
Social phobia (n = 208)[68]	0.15 (-0.12 to 0.43)
Bulimia (n = 237)[65]	*0.52 (0.20 to 0.84)*



The outcome in all studies was reduction of overall symptoms except for relapse prevention in depression. Italicized standardized mean differences (SMDs) were estimated from odds ratios. NI indicates not indicated.
[a]Drug vs psychodynamic psychotherapy.

Figure 3. Comparison of Effect Sizes in Meta-analyses of Alone vs Combined Pharmacotherapy or Psychotherapy

Diagnosis	SMD (95% CI)
Pharmacotherapy added to psychotherapy	
Schizophrenia PDT (n = 24)[59]	*0.00 (-0.86 to 0.86)*
Major depressive disorder (n = 903)[71]	*0.28 (0.13 to 0.43)*
Panic disorder (n = 532)[72,75,a]	*0.17 (-0.03 to 0.36)*
Social phobia (n = 267)[68]	0.42 (0.18 to 0.68)
Posttraumatic stress disorder (n = 65)[73]	0.38 (-0.11 to 0.87)
Bulimia (n = 257)[65]	0.29 (0.02 to 0.86)
Psychotherapy added to pharmacotherapy	
Schizophrenia CBT (n = 2131)[74]	0.33 (0.21 to 0.45)
Schizophrenia PDT (n = 90)[59]	0.07 (-0.34 to 0.49)
Depressive disorder (n = 2036)[70]	0.31 (0.20 to 0.40)
Dysthymic disorder (n = 541)[49]	0.04 (-0.17 to 0.24)
Bipolar disorder (n = 487)[57]	*0.19 (-0.21 to 0.60)*
Panic disorder (n = 746)[72,75]	*0.24 (0.08 to 0.40)*
Social phobia (n = 256)[68]	0.12 (-0.13 to 0.36)
Posttraumatic stress disorder (n = 23)[73]	-0.33 (-1.17 to 0.51)
Bulimia (n = 141)[65]	0.49 (0.09 to 0.89)
Opioid dependence (n = 232)[69]	0.12 (0.45 to -0.21)



The outcome in all studies was reduction of overall symptoms. Italicized standardized mean differences (SMDs) were estimated from odds ratios. CBT indicates cognitive-behavioral therapy; PDT, psychodynamic therapy.
[a]For panic disorder, the effect size is the mean of 2 meta-analyses.[72,75]

disorder[73] and psychodynamic therapy for schizophrenia,[59] showed a trend in favor of combination therapy, which was statistically significant in 7 studies. The combination was better when psychotherapy was added to drug therapy and vice versa (Figure 3).

Comparison of the Quality of Research

Quality of Pharmacotherapy and Psychotherapy Meta-analyses

No significant difference exists in the overall quality of pharmacotherapy and psychotherapy meta-analyses based on AMSTAR total scores (mean, 8.7 [95% CI, 7.9-9.4] vs 8.2 [7.1-9.3]; Mann-Whitney test, $U = 277.500$; $P = .38$) or subscores apart from conflict of interest, which was reported by all pharmacotherapy meta-analyses but only by 63% of psychotherapy meta-analyses ($\chi^2_1 = 12.55$; $P < .001$) (Supplement [eAppendix 4, eTable 3]).

Quality of the Individual Included Trials

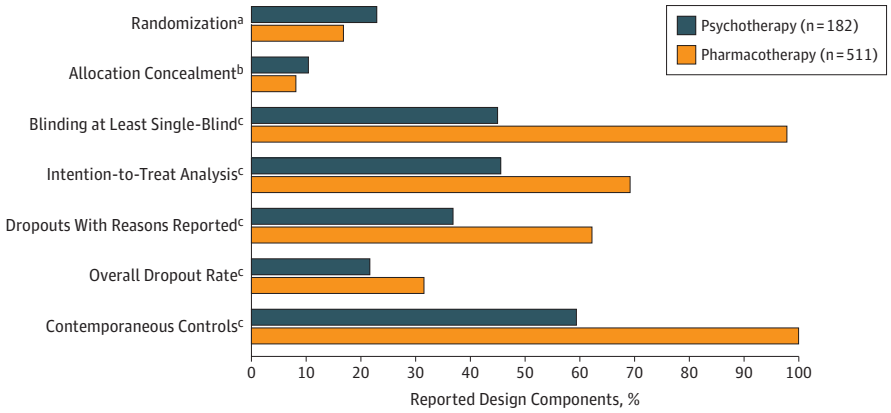
Only acute-phase studies with overall 113 833 participants were included to enhance comparability. The median and mean sizes of the 182 individual psychotherapy trials were significantly lower (62 and 89) than those of the 511 individual pharmacotherapy trials (117 and 191) ($U = 63\,036$; $P < .001$).

More individual pharmacotherapy vs psychotherapy trials used at least blind outcome assessment (97.7% vs 44.5%; $\chi^2_1 = 281.92$; $P < .001$), used placebo controls rather than wait lists (99.2% vs 59.3%; $\chi^2_1 = 213.66$; $P < .001$), used intention-to-treat data (68.7% vs 45.1%; $\chi^2_1 = 31.98$; $P < .001$), and reported withdrawal rates with their reasons (62.2% vs 36.3%; $\chi^2_1 = 38.64$; $P < .001$).[13] In contrast, psychotherapy trials had overall lower withdrawal rates (31.0% vs 21.3%; $U = 48\,217$; $P < .001$).

Most trials of both modalities were described as *randomized* without any description of the methods (appropriate randomization in psychotherapy vs pharmacotherapy, 22.5% vs 16.8%; $\chi^2_1 = 2.91$; $P = .08$; appropriate allocation concealment, 10.4% vs 8.2%; $\chi^2_1 = 0.82$; $P = .36$) (**Figure 4**).

Only 4.9% of pharmacotherapy trials provided follow-up data compared with 54.9% of psychotherapy trials ($\chi^2_1 = 227.42$; $P < .001$).

Figure 4. Methodologic Characteristics of Individual Studies in Psychotherapy and Pharmacotherapy Meta-analyses on Acute Treatment According to the Cochrane Risk of Bias Tool



Percentage of individual studies within the meta-analyses with appropriate components of design. The randomization and allocation methods were not described in 60% and 87% of psychotherapy trials and 86% and 94% of pharmacotherapy trials, respectively; therefore, they were coded as *unclear*, which was grouped with studies that were not randomized. Contemporaneous controls included patients receiving placebo, treatment as usual, or ineffective therapy in contrast to wait list or no treatment. Statistical significance was examined with χ^2 tests for all parameters except overall dropout rates, which were compared with the Mann-Whitney test.

[a] $P = .08$.

[b] $P = .36$.

[c] $P < .001$.

These patterns were similar in most sensitivity analyses of the single disorders (Supplement [eAppendix 4, eFigures 1-7]).

Subgroup Analyses of Methodologic Quality

In psychotherapy meta-analyses, subgroups with contemporaneous controls (placebo, treatment as usual, and ineffective therapy) had effect sizes that were, on average, only half of those with wait lists (8 meta-analyses; mean wait list, 0.86; mean active treatment, 0.46; $U = 5.00$; $P = .003$).[16,37,56,58,63,66,76,77] Too few systematic reviews presented subgroup analyses for the other Cochrane risk of bias tool domains to make a statistical analysis meaningful. One review[78] found significantly lower effect sizes in studies with appropriate vs unclear randomization methods, whereas 3 others[31,69,74] found no significant difference. One[78] of 3 meta-analyses[31,74,78] found significantly lower effect sizes in studies with appropriate allocation concealment. All 3 meta-analyses that addressed blinding found significantly lower effect sizes in blinded trials.[31,74,78] The use of intention-to-treat-data led to significantly lower effect sizes in 3 reviews[54,74,78] of 9 in total.*

Publication Bias, Follow-up Assessments, and Baseline Severity in MDD Trials

Eighteen percent of psychotherapy meta-analyses and 38% of pharmacotherapy meta-analyses found indications for publication bias ($\chi^2_1 = 1.18$; $P = .28$). In the few psychotherapy meta-analyses reporting follow-up results, the effect sizes had remained stable compared with the end point (4 meta-analyses, mean end point SMD, 0.29; mean follow-up SMD, 0.34; $U = 7.00$; $P = .89$). The mean (SD) baseline severity in psychotherapy depression trials was 3.6 (0.7) Hamilton Scale for Depression score points lower than in antidepressant trials (77 trials, Mann-Whitney test, $U = 1005.00$; $P < .001$) (Supplement [eAppendix 4, eTable 2]).

*References 37, 38, 54, 56, 70, 72, 74, 78, 79

Discussion

This systematic overview showed that effective medication and psychotherapy are available for most of the psychiatric disorders examined, but medium effect sizes suggest that there is also a lot of room for improvement. Direct comparisons of drug therapy and psychotherapy did not show consistent differences, but their combination was often superior. Finally, we found fundamental differences in the methods of psychotherapy and drug trials, which are important for the interpretation of our findings.

Effectiveness of Psychiatric Treatments

The mean SMD of all meta-analyses suggests medium efficacy of psychiatric treatments according to Cohen,[8(p26)] who described an SMD of 0.50 as a clear difference, large enough to be "visible to the naked eye, for example, the difference between 14-year-old and 18-year-old girls (about 1 inch)." Some readers may wonder why it was not larger. That all patients improve with treatment and no patient improves with placebo is a common misconception. However, many patients improve without therapy because of the natural course of the disease, for example, manic episodes remit spontaneously. In addition, important placebo effects can account for up to 40% of patients who experience improvement in antidepressant drug trials.[80] Notably, the effect sizes found were overall *similar to those of many common general medicine drugs*, with a mean of 0.45,[5] providing an important perspective.

Methodologic Differences Between Psychotherapy and Pharmacotherapy Trials

Fundamental methodologic differences of individual trials included in pharmacotherapy and psychotherapy meta-analyses may explain in part why psychotherapies sometimes had larger

effect sizes vs control conditions compared with medication (eg, MDD, obsessive-compulsive disorder, posttraumatic stress disorder, and bulimia; the opposite also exists, eg, methadone for opiate addiction).[16,33,53,54] However, direct comparisons produced no consistent differences (eg, SMD for psychotherapy vs placebo or no treatment for MDD, 0.67; antidepressants vs placebo, 0.31; but antidepressants vs psychotherapy, 0.05).

Trikalinos et al[81] showed that systematic reviews in psychiatry with participant numbers below 1000 do not provide robust results. Small-study bias in individual psychotherapy trials and meta-analyses, which were an order of magnitude smaller than their pharmacotherapeutic counterparts, may have led to greater effect sizes.[82] For example, patients in small psychotherapy studies may be well selected because psychotherapy requires active participation. In contrast, participants in multicenter drug trials are often recruited by advertisements, attracting so-called "professional patients." Similarly, therapists in psychotherapy trials are often well-trained experts. *Researcher allegiance* means that the testing of a psychotherapy by its inventors might positively influence the effect size.[83] Fewer psychotherapy than pharmacotherapy meta-analyses indicated their authors' conflicts of interest, although conflicts are not restricted to financial ones. These factors may lead to higher generalizability in pharmacotherapy trials in exchange for more "statistical noise" and lower effect sizes. Obviously, the difference in sample size also results from imbalances in funding when powerful pharmaceutical companies sponsor drug trials. More public funding for psychotherapy research is needed.

Psychotherapists always know whether they deliver active or placebo treatment, and patients may realize whether they receive "real" psychotherapy or not. However, even blind outcome assessment was applied in only approximately 45% of psychotherapy trials in contrast to 98% in drug trials. The few meta-analyses that addressed blinding identified bias.[31,74,78] For example, blinded psychotherapy trials for depression had significantly lower effect sizes, and low-quality psychotherapy trials in general had a higher effect size (SMD = 0.74) than high-quality trials (SMD = 0.22) ($P < .001$).[78] In drug trials imperfect blinding can also be an issue if adverse effects allow one to guess the treatment group; unfortunately, this is rarely tested.[84]

Nearly all individual drug trials used pill-placebo control groups; 41% of psychotherapy trials used wait-list controls, which almost doubled effect sizes. Patients know they are waiting for therapy and do not expect improvement. There can even be a "nocebo effect" because being on a wait list can be a message of "you cannot improve now." In contrast, expectancy effects are considerable in patients receiving a placebo.

More than half of psychotherapy trials and a third of pharmacotherapy trials did not use an intention-to-treat-analysis. Per-protocol analysis breaks randomization in that characteristics of study completers in intervention and control groups can differ, for example, because participants in placebo groups may withdraw primarily because of inefficacy and patients in drug groups may withdraw more because of adverse effects.[85]

Effect sizes for relapse prevention were generally larger than for acute therapy with the same drugs that are given to a mixture of responders and nonresponders, lending strong support for continuation treatment, but long-term treatment might sensitize brain receptors, facilitating relapse after abrupt withdrawal.[86] Psychotherapy offers a more optimistic perspective because it could cure by inducing lasting cognitive and behavioral changes. Indeed, the few psychotherapy meta-analyses that examined follow-up after the study ended found that treatment effects persisted.

Evidence for publication bias was numerically more frequent in pharmacotherapy meta-analyses, where it is a well-known phenomenon,[15] although it also occurs in psychotherapy research.[16] Because the main driver for publication bias is trial failure and blind trials are more likely to fail, the infrequent use of blinding in psychotherapy trials is important. Finally, the mean baseline severity in psychotherapy trials on MDD was lower than that in antidepressant trials. This could mean that psychotherapy is particularly efficacious in milder forms of MDD in which antidepressants are less effective.[4]

Strengths and Limitations

In our study, the criteria of a systematic review were met, but obviously there are multiple limitations. Because the selection of the meta-analyses was most prone to bias, we described this process in detail (Supplement [eAppendix 5]). We always compared pharmacotherapy and psychotherapy for the same disorders, and we strongly discourage comparisons of treatments across disorders. Still, meta-analyses depend on the quality of the included studies. To be systematic, we chose the most recent meta-analyses because older ones, although sometimes methodologically better, would have been out of date. We analyzed classes of drugs rather than single agents, assuming that the original authors had made an appropriate decision to pool drugs. Therefore, our results are not specific, although, with few exceptions, no large efficacy differences exist within drug classes. We preferred psychotherapies under the umbrellas of CBT and psychodynamic therapy; occasionally, more efficacious psychotherapies may have been missed. We also did not examine effective interventions such as psychoeducation.[87,88] To examine adverse effects and balance them with efficacy was impossible, but this domain is a major advantage of psychotherapy. Although based on RCTs, meta-analysis itself is an observational method with many limitations (eg, "garbage in garbage out" and heterogeneity), and RCTs lack generalizability. Finally, the interpretation of effect size is controversial. Therefore, we emphasize the importance of *reading the actual numbers* in the Supplement (eAppendix 6).[89] However, meta-analysis served as a useful tool to systematically provide a rough overview of what benefit psychiatry can offer patients. Even if other authors made different choices, the chance of them reaching essentially different conclusions is unlikely.

Conclusions

Because of the multiple methodologic differences between pharmacotherapy and psychotherapy trials, indirect comparisons are problematic. Meta-analysts should consistently address quality indicators, such as control groups or degree of blinding. Head-to-head trials are scarce, and funding for them is urgently needed. Research should focus on how pharmacotherapy and psychotherapy can best be combined to obtain maximally synergistic effects rather than debate the use of one treatment over the other.

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