

Combined Pharmacotherapy and Psychological Treatment for Depression

A Systematic Review

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Background: Adherence to antidepressant medication use is a problem in clinical practice. Some authors have posited that combined psychological treatment facilitates adherence to pharmacotherapy.

Objectives: To study the relationship between adherence to use of and efficacy of antidepressant drugs plus psychological treatment vs drug treatment alone in depressive disorders.

Data Sources: MEDLINE, Current Contents, PsychInfo, Cochrane Library, and reference lists were searched, from January 1980 to November 2002.

Study Selection: Randomized clinical trials comparing antidepressant treatment alone with antidepressant treatment in combination with a psychological intervention in depressive disorders were considered. The decision to include studies in the meta-analysis was performed by 2 reviewers.

Data Extraction: Three independent reviewers extracted the data, using a precoded form. Methodological quality of the studies was evaluated in terms of allocation concealment and independence of evaluators.

Data Synthesis: Sixteen trials met the inclusion criteria, with 932 patients randomized to pharmacotherapy alone and 910 to combined treatment. Overall, patients receiving combined treatment improved significantly compared with those receiving drug treatment alone (odds ratio [OR], 1.86; 95% confidence interval [CI], 1.38-2.52), but dropouts and nonresponders did not differ in distribution between the 2 treatment modalities (OR, 0.86; 95% CI, 0.60-1.24). Studies longer than 12 weeks showed a significant advantage of combined treatment over drug treatment alone (OR, 2.21; 95% CI, 1.22-4.03), with a significant reduction in dropouts compared with nonresponders (OR, 0.59; 95% CI, 0.39-0.88). These estimates were not affected by study quality.

Conclusions: Psychological treatment combined with antidepressant therapy is associated with a higher improvement rate than drug treatment alone. In longer therapies, the addition of psychotherapy helps to keep patients in treatment. Further studies are needed to investigate whether the improvement in response attributable to the combination of drug treatment and psychotherapy can be achieved by a combination of pharmacotherapy and a compliance-enhancing intervention.

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ADHERENCE TO TREATMENT with antidepressant drugs is an issue of clinical relevance. A review of controlled therapeutic studies suggests a dropout rate of up to 33% irrespective of drug class.¹ In clinical practice, higher rates are observed.² The main factors affecting adherence to treatment pertain to the length of psychiatric history, latency and safety profile of the drug, and quality of the patient-physician relationship.³ However, this knowledge has not been integrated into pharmacological research: 92% of antidepressant trials consider assessment of depression as the only outcome measure, and 87% of them present results without application of the

intention-to-treat approach.⁴ Inadequate attention to adherence is evident in the choice of a solely therapeutic intervention, in the lack of additional outcome measures to complement efficacy such as patient satisfaction, and in the removal of dropouts from the analysis. A review of the few controlled studies in which treatment adherence was the main end point does not provide clear evidence on how to affect adherence, as they often adopt composite interventions and, in many cases, cannot relate efficacy to adherence because they do not systematically measure clinical outcome.²

Psychological treatment is the most common nonpharmacological intervention added to pharmacotherapy, with the

objective to enhance efficacy, improve patients' social functioning and quality of life, and prevent or delay recurrence. Some authors have suggested that psychological treatment may also affect adherence to pharmacotherapy.^{5,6} So far, systematic reviews of combined treatment vs pharmacotherapy alone have only focused on efficacy data.⁷⁻⁹ However, evidence on adherence-enhancing effects of psychological interventions could be obtained as a by-product of studies in which pharmacotherapy is common to all arms and at least 1 of the arms being compared is pharmacotherapy alone. Although treatment adherence includes several behaviors, we focused in this study on its ultimate expression, the premature interruption of treatment (ie, dropout). To investigate the relationship between completion of treatment and efficacy, we reviewed all randomized clinical trials (RCTs) contrasting antidepressant pharmacotherapy vs combined psychological treatment, to determine whether combined treatment is more efficacious than pharmacotherapy alone and whether combined intervention affects nonresponse to and dropping out of drug treatment.

METHODS

DATA SOURCES

To identify RCTs contrasting antidepressant pharmacotherapy with combined treatment (pharmacotherapy and psychological treatment), we searched MEDLINE, Current Contents, and PsychInfo, from January 1980 to November 2002. The search strategy included all key words ordered by MEDLINE under the following medical subject headings: patient compliance, depressive disorder, antidepressive agents, psychotherapy, mental health services, and RCTs. The Cochrane Library was similarly searched. Numerous review articles, textbooks of treatment of depression, and treatment guidelines for depression were also screened to identify potential studies. Two of us (B.K. and P.B.) read each abstract and retained RCTs that contrasted pharmacotherapy alone vs pharmacotherapy combined with psychological treatment. To classify the latter, we followed the system of Rush and Thase,⁸ who consider problem-solving, interpersonal, cognitive, behavioral, marital, and psychodynamic therapies. Although these therapies have different conceptual backgrounds, the rationale of considering them together is that they aim at the reduction in symptoms of depression and prevention of recurrence.

STUDY SELECTION

Copies of articles regarding RCTs were obtained, and their reference lists were screened to identify additional studies of interest. We excluded articles that had additional nonpharmacological intervention besides psychotherapy in the combined treatment arm. We also excluded articles that were a subsequent publication regarding an original trial, that concerned a subset of patients of the original trial, or that presented long-term follow-up results of the original trial. When data could not be extracted from the article, we contacted the authors by e-mail to clarify aspects of the study design or to obtain outcome data in a form suitable for the meta-analysis.

DATA EXTRACTION

An ad hoc form was designed for data extraction, including diagnosis, sex (percentage female), and mean age of the study sample; antidepressant drug administered; type of combined interven-

tion; and duration of the study. For each treatment arm, we extracted the number of patients randomized and the clinical outcome according to 3 categories: (1) the number with full response (according to the most stringent criteria if more than 1 categorization was used), (2) the number with partial or no response, and (3) the number who dropped out of the study treatment for any reason. The mean daily doses of antidepressants were converted to milligram equivalents of imipramine hydrochloride, according to conversion factors available in the literature.^{10,11} We assessed the methodological quality of the studies in terms of treatment allocation concealment (adequate vs inadequate) and independence of evaluators from those providing the interventions (yes vs no).¹² Data were extracted by 3 of us (P.B., G.T., and S.P.) and controversies resolved in a meeting.

QUANTITATIVE DATA SYNTHESIS

In this meta-analysis, we estimated the effect of psychotherapy as an addition to pharmacotherapy of depression to increase the response rate, and we investigated how it affected dropout and nonresponse rates. For descriptive purposes, and to guide the interpretation of other results, a random-effects estimate¹³ (and corresponding 95% confidence interval [CI]) of the rate difference (combined treatment minus pharmacotherapy alone) of each of the 3 categories listed in the "Data Extraction" subsection was computed. (The estimated pooled rate differences of responders, dropouts, and nonresponders would sum to zero only if the same weights were used to pool the estimates from each of 16 trials. Herein, each pooled estimate is generated by a separate weighted analysis, using a different set of weights. Therefore, the estimated rate differences of the categories do not sum to zero.) However, these quantities being interdependent and sensitive to the absolute rate observed in the drug-alone arm, they are not directly amenable to an unbiased analysis. We therefore followed the perspective used for partitioning the χ^2 test.¹⁴ (For a 2-row \times J-column table, the χ^2 statistic can be divided into J-1 independent components: in the present context, J=3 identifies the 3 possible outcomes [responder, dropout, and nonresponder] of each of the 2 treatments being compared. We first considered the series of 2×2 tables [1 for each of the 16 studies], in which the first column corresponded to responders and the second column combined dropouts and nonresponders. The distribution of dropouts and nonresponders, conditional on response, was then studied, restricting the analysis to the series of 2×2 tables in which the first column corresponded to dropouts and the second to nonresponders.)

Considering all patients in each study, we first analyzed the odds ratio (OR) of response in the combined arm relative to the pharmacotherapy-only arm. This comparison was intended to investigate whether the combined treatment induced an increase in responders. We then restricted our analysis to patients who dropped out or failed to respond and analyzed the OR of dropping out in the combined arm relative to the pharmacotherapy-only arm. This comparison was intended to investigate whether, irrespective of the level of response achieved in each arm, the relative distribution of dropouts and nonresponders was the same in the 2 arms. A test for publication bias¹⁵ was performed for the analysis of the OR of response. The χ^2 test for heterogeneity of ORs (on the natural logarithm scale) was applied, using as weights the inverse of the variance from the fixed-effects model.¹⁶ Random-effects¹³ pooled estimates of ORs (on the natural logarithm scale) were computed, with their 95% CIs (back-transformed using the inverse logarithm transformation for presentation purposes). We conducted a sensitivity analysis of overall study quality, separating trials with appropriate allocation concealment and independent evaluators from the other trials. The effect of each study on the overall estimates was also assessed, computing the pooled estimates

Table 1. Characteristics of the Studies Included in the Analysis*

| Source | Arm | Response | Dropout | Nonresponse | Odds Ratio (95% Confidence Interval)† |
|-----------------------------------------|-------------------------------------------------------|----------|---------|-------------|------------------------------------------|
| Bellack et al, ³¹ 1981 | Social skills training and drug | 4 | 5 | 8 | 1.08 (0.22-5.22) |
| | Drug alone | 4 | 10 | 4 | 0.25 (0.05-1.25) |
| Miller et al, ^{32,33} 1989 | Cognitive-behavioral therapy and drug | 14 | 7 | 8 | 3.03 (0.80-11.54) |
| | Drug alone | 4 | 7 | 6 | 0.75 (0.17-3.33) |
| Ravindran et al, ³⁴ 1999 | Group cognitive therapy and drug | 17 | 1 | 7 | 1.77 (0.54-5.81) |
| | Drug alone | 12 | 0 | 10 | 4.20 (0.15-117.92) |
| Blackburn and Moore, ³⁵ 1997 | Cognitive therapy and drug | 4 | 5 | 13 | 0.93 (0.22-4.01) |
| | Drug alone | 5 | 5 | 16 | 1.23 (0.29-5.19) |
| Scott et al, ³⁶ 1997 | Brief cognitive therapy and drug | 15 | 6 | 3 | 3.33 (1.02-10.90) |
| | Drug alone | 8 | 8 | 8 | 2.00 (0.37-10.92) |
| Murphy et al, ³⁷ 1984 | Cognitive therapy and drug | 12 | 6 | 4 | 2.00 (0.62-6.49) |
| | Drug alone | 9 | 8 | 7 | 1.31 (0.26-6.64) |
| Weissman et al, ³⁸ 1979 | Interpersonal psychotherapy and drug | 13 | 8 | 3 | 4.49 (1.26-16.01) |
| Herceg-Baron et al, ³⁹ 1979 | Drug alone | 5 | 16 | 3 | 0.50 (0.08-3.06) |
| Blackburn et al, ⁴⁰ 1981 | Cognitive therapy and drug | 18 | 8 | 4 | 2.32 (0.81-6.64) |
| | Drug alone | 11 | 8 | 9 | 2.25 (0.49-10.41) |
| Mynors-Wallis et al, ⁴¹ 2000 | Problem-solving treatment and drug | 21 | 6 | 8 | 0.75 (0.28-1.98) |
| | Drug alone | 24 | 6 | 6 | 0.75 (0.16-3.53) |
| Hollon et al, ⁴² 1992 | Cognitive therapy and drug | 12 | 9 | 4 | 2.17 (0.82-5.72) |
| | Drug alone | 17 | 25 | 15 | 1.35 (0.35-5.16) |
| Friedman, ⁴³ 1975 | Marital therapy and drug | 10 | 7 | 32 | 1.08 (0.40-2.96) |
| | Drug alone | 9 | 8 | 30 | 0.82 (0.26-2.54) |
| Keller et al, ⁴⁴ 2000 | Cognitive-behavioral therapy and drug | 75 | 48 | 104 | 2.60 (1.66-4.09) |
| | Drug alone | 36 | 59 | 131 | 1.02 (0.65-1.62) |
| Burnand et al, ⁴⁵ 2002 | Psychodynamic psychotherapy and drug | 30 | 9 | 3 | 1.48 (0.60-3.69) |
| | Drug alone | 27 | 5 | 11 | 6.60 (1.23-35.43) |
| Browne et al, ⁴⁶ 2002 | Interpersonal psychotherapy and drug | 122 | 24 | 90 | 1.09 (0.76-1.56) |
| | Drug alone | 117 | 40 | 79 | 0.53 (0.29-0.95) |
| de Jonghe et al, ⁴⁷ 2001 | Short psychodynamic supportive psychotherapy and drug | 26 | 24 | 33 | 5.02 (2.04-12.7) |
| | Drug alone | 7 | 51 | 26 | 0.37 (0.18-0.75) |
| Hellerstein et al, ⁴⁸ 2001 | Group cognitive-interpersonal therapy and drug | 16 | 2 | 2 | 2.15 (0.52-9.00) |
| | Drug alone | 13 | 3 | 4 | 1.33 (0.11-15.70) |

*Data are given as number of patients unless otherwise indicated.

†Estimates of the odds ratios of response (first line) and of dropouts (second line) are given for each study. See the "Methods" section for further details.

after removing each study in turn. Meta-regression analysis on the random-effects estimates was performed using overall study quality and study duration (≤ 12 weeks vs > 12 weeks) as covariates. All statistical analyses were performed with the computer package Stata.¹⁷

RESULTS

The abstracts of 1123 articles retrieved by the search were screened, and the full publications of 94 articles were examined for pertinence to our meta-analysis. Of these, we retained 29 trials of antidepressant use combined with psychological treatment vs antidepressant use alone. We excluded 13 articles from the final analysis for the following reasons: treatment was not assigned randomly,^{18,19} an additional nonpharmacological intervention or medication affecting outcome and adherence was administered in one of the study arms,²⁰⁻²² results were not reported by treatment arm,²³ outcome data could not be extracted,²⁴⁻²⁸ and drug treatment was not prescribed to all patients.^{29,30} Sixteen original studies (reported in 18 articles) were therefore available for analysis.³¹⁻⁴⁸ The main characteristics of the studies are listed in **Table 1**.

Across all study arms considered, 932 patients were randomized to receive pharmacotherapy alone and 910 to

combined treatment. The diagnosis was major depression in 10 studies, dysthymic disorder in 3, and unipolar depression in 2, while mixed diagnoses were considered in 1. The mean age was 40 years or younger in 7 of 13 studies that reported the information and older than 40 in 6 studies. The percentage of female patients varied from 50% to 100% (median, 65%). Study length varied from 4 to 24 weeks (median, 12 weeks). The dose equivalent of imipramine varied from 100 to 269 mg daily for the 13 studies in which drug data could be extracted. In all but 1 such studies, the dose used in the pharmacotherapy-alone arm was identical to the dose used in the combined treatment arm. The psychological interventions included the following: cognitive therapy (7 studies), interpersonal psychotherapy (2 studies), psychodynamic therapy (2 studies), and marital therapy, social skills training, problem-solving therapy, a combination of cognitive and behavioral psychotherapy, and a combination of cognitive and interpersonal psychotherapy (1 study each). Most studies described pharmacotherapy (in the pharmacotherapy-only and the combined treatment arms) as given within the context of the usual care provided by the participating institutions.

In 11 of 16 studies, the randomization procedure was described and appropriate, and in 12 the evaluators

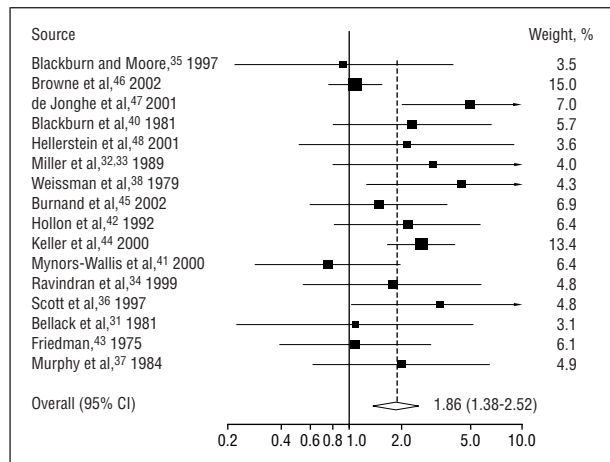


Figure 1. Odds ratios of response and corresponding 95% confidence intervals (CIs). Odds ratios greater than 1.00 indicate a higher response rate in the combined treatment.

were independent from those providing treatment. Nine studies met both quality criteria.

The pooled estimates of the rate differences (combined treatment minus pharmacotherapy alone) of response, dropout, and nonresponse were 12.6% (95% CI, 6.9% to 18.2%), -6.5% (95% CI, -12.1% to -1.0%), and -5.0% (95% CI, -10.8% to 0.8%), respectively. Although this analysis was biased, it suggests that the increase in response attributable to the combined treatment is associated with a reduction in dropouts and nonresponders with respect to pharmacotherapy alone.

ANALYSIS OF ALL PATIENTS

Results of the test for publication bias were not significant ($P = .32$). The borderline significant findings of the test for heterogeneity ($P = .06$) led us to choose the random-effects model, which was applied to all analyses for consistency. The overall random-effects estimate of the OR of response was 1.86 (95% CI, 1.38-2.52), indicating a significant advantage of combined treatment over pharmacotherapy alone (**Figure 1**). No individual study showed a particular effect on this result: when pooled estimates were obtained by removing each of the studies in turn, they were always within the CI of the overall estimate (data not shown). A sensitivity analysis was performed, stratifying the results according to study quality, which showed no effect (data not shown). Examining the effect of study duration on response, we found no appreciable difference between studies of up to 12 weeks vs those that were longer. A formal test of the role of study quality and duration was performed by means of meta-regression analysis, which confirmed the results, with the P value for the coefficients for study quality and study duration being $P = .79$ and $P = .58$, respectively, when both factors were modeled simultaneously. For further reference, we computed the pooled estimates of response rate differences for shorter and longer studies, which were 12.2% (95% CI, 6.0%-18.4%) and 15.1% (95% CI, 4.6%-25.6%), respectively.

Table 2. Pooled Estimates of Odds Ratios (ORs) of Combined Treatment vs Pharmacotherapy Only for All Studies and According to Study Duration*

| Analysis | All Patients OR of Response | Dropouts and Nonresponders OR of Dropout |
|---------------------------------|--------------------------------|------------------------------------------------|
| All 16 studies | 1.86 (1.38-2.52) | 0.86 (0.60-1.24) |
| According to study duration, wk | | |
| ≤12 (9 studies) | 1.87 (1.37-2.53) | 1.11 (0.71-1.74) |
| >12 (7 studies) | 2.21 (1.22-4.03) | 0.59 (0.39-0.88) |

*Data are given as OR (95% confidence interval).

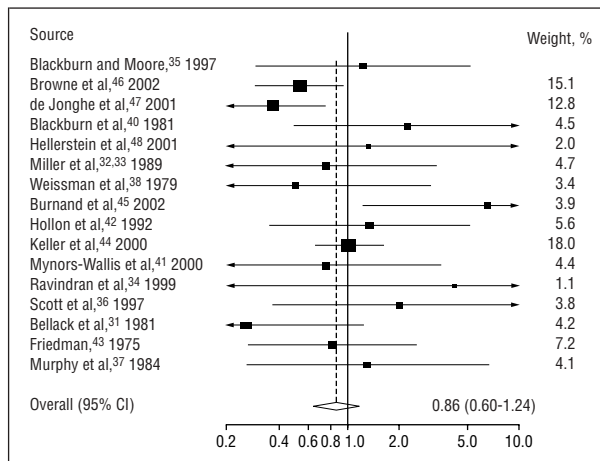


Figure 2. Odds ratios of dropout and corresponding 95% confidence intervals (CIs). Odds ratios greater than 1.00 indicate a higher dropout rate in the combined treatment.

ANALYSIS RESTRICTED TO DROPOUTS OR NONRESPONDENTS

Having established that the combined treatment is more efficacious than pharmacotherapy alone, we wanted to assess whether the different response rate corresponded to a different relative frequency of dropout and nonresponse between the 2 treatments. We therefore excluded responders and assessed the ORs of dropouts, considering only dropouts or nonresponders. Results of the test for heterogeneity of ORs were not significant ($P = .13$). The overall random-effects estimate of the risk ratio was 0.86 (95% CI, 0.60-1.24) (**Table 2**), indicating no significant difference in distribution of dropouts and nonresponders between combined treatment and pharmacotherapy alone (**Figure 2**). The analyses of effect and sensitivity (data not shown) provided results analogous to those described in the previous subsection. However, longer studies showed a significant reduction in dropouts in the combined treatment arm (OR, 0.59; 95% CI, 0.39-0.88). A meta-regression analysis confirmed the lack of effect of study quality ($P = .91$) and the significant role of study duration ($P = .02$). As an aid in the interpretation of the results, we also computed the pooled estimates of dropout and nonresponse rate differences for shorter and longer studies: for studies of up to 12 weeks, these were -1.9% (95% CI, -6.7% to 2.9%) and -8.3%

(95% CI, -15.9% to -0.8%), respectively, and for studies longer than 12 weeks, these were -12.9% (95% CI, -3.6% to -2.2%) and 0.4% (95% CI, -6.2% to 7.0%), respectively.

COMMENT

We showed that psychotherapy combined with antidepressant use is associated with a higher response rate than pharmacotherapy alone. We found borderline significant heterogeneity of the ORs, possibly due to differences in case mix, setting, and duration of treatment among studies. Subgroup analyses according to depression severity were not feasible because of unreported data. However, study entry and evaluation criteria were similar across studies. The distribution of dropouts and nonresponders was comparable in the 2 treatment modalities (OR, 0.86; 95% CI, 0.60-1.24). It is difficult to say whether the observed superiority of the combined treatment corresponds to an additive benefit of psychotherapy or to a nonadditive phenomenon. The results suggest, however, that the addition of psychotherapy reduces nonresponse and helps to keep patients in treatment.

The subgroup analysis according to study length provided more insight into this result. Study duration was an obvious effect modifier to be considered, because the number of patients in the dropout group can only increase, if it changes at all, with increasing duration of treatment. Our results indicate that in studies of up to 12 weeks the overall results of the meta-analysis are confirmed by the ORs; the rate differences can be considered consistent with this result based on the width of their corresponding CIs. In studies longer than 12 weeks, there is a significant reduction in the number of dropouts in the combined treatment arm, and the rate difference analysis indicates that there is no change in nonresponse rate (0.4%) but a strong and significant reduction in dropout rate (-12.9%). For shorter treatment, the combined modality may thus be effective in some patients who would not otherwise respond to pharmacotherapy alone, while for longer duration treatments, the addition of psychotherapy induces a stronger compliance with the combined treatment. The design of the trials reviewed did not allow us to determine whether in longer studies the improved response in the combined treatment arm corresponds to a joint therapeutic effect (additive or otherwise) of pharmacotherapy plus psychotherapy or to a prolonged exposure to medication in patients who remain on treatment. Nevertheless, one wonders what would be the effect of a compliance-enhancing intervention on the excess dropout rate in longer treatments among patients receiving pharmacotherapy only. The possible adherence-enhancing role of psychotherapy was suggested, although not supported by data, as early as 25 years ago by Klerman, as quoted by Paykel.⁵ Other authors have suggested that patients may be more satisfied with combined therapy than with single-modality treatments or that they would discontinue pharmacotherapy if it were not accompanied by psychotherapy.⁴⁹

By showing that dropout rates can be reduced by a combination of pharmacotherapy and psychological treatment, this study calls for the identification of simple but effective strategies to better respond to the needs of de-

pressed patients, thus keeping them in treatment. Research on adherence-enhancing interventions has not provided clear evidence in this respect, although a higher intensity of intervention² and multifaceted interventions^{50,51} appear promising. If the therapeutic effect of psychotherapy were only moderate compared with a strong compliance-enhancing effect, then more feasible and cheaper means of achieving the same goals could be explored. Only properly designed studies can help to disentangle the genuine therapeutic effect of psychotherapy from its compliance-enhancing effect, over and above the effect of drugs. However, psychological treatment may have a stronger effect than pharmacotherapy on patient satisfaction and social functioning or other dimensions of well-being that cannot be measured in terms of improvements in depression scores.⁵² The results of this study favor a broader approach to the management of depressed patients and the adoption of other axes of outcome evaluation besides the control of symptoms. Especially in longer treatment, research should aim at enhancing compliance and response rates, incorporating these principles.

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