A Review of Combined Psychotherapy and Pharmacotherapy in the Treatment of Depression

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The effectiveness of combined psychotherapy and pharmacotherapy for depression is a clinical issue of increasing importance. Using a box score approach, the authors review the 17 available studies in the literature, provide a methodological critique, summarize results, and suggest directions for further research and for clinical practice. Overall, given methodological limitations in the existing literature, it appears that combined treatment is no less effective than psychotherapy or pharmacotherapy alone and may have specific advantages for subpopulations of depressed patients.

First begin with prayer and then use physick; not one without the other but both together.
—Robert Burton, Treatise on Melancholia

When psychotherapy and antidepressant medication are administered individually, each is effective in only 60–80% of patients. Many patients who respond to treatment do not experience full remission of symptoms, nor are they necessarily protected from recurrence of depressive episodes. Furthermore, the onset of therapeutic effect of medication or psychotherapy may take weeks or months. Hence, it is not surprising that combined treatment with psychotherapy and medication has become prevalent among clinicians hoping to achieve a faster, fuller, and broader spectrum response than might result from either treatment alone. Mirroring the interest among practitioners, researchers in the last decade have focused increasingly on clinical trials that compare combined therapy with single-modality treatment of depression.

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Numerous reviews of this research have also been conducted over the years. Initial optimism among early reviewers about the superiority of combined therapy has waned in more recent commentaries. Earlier reviews concluded that combined therapy was superior to either mode of treatment alone, and they discerned separate and specific effects of medication and psychotherapy. This implied a synergy of the two.\textsuperscript{1,2} More contemporary reviews drew more tempered conclusions: that combined therapy showed a modest superiority over either single component in some studies, and that combined treatment might benefit selected patient populations, such as those with severe depression or a history of poor response to single-modality therapy.\textsuperscript{3-4}

Our review of the literature on combined treatment of depression encompasses 17 studies that targeted nonpsychotic major depression. To our knowledge, it is the most comprehensive that has been performed to date. In reviewing the literature, we asked the following questions: 1) How does combined therapy compare in efficacy with medication or psychotherapy alone in various outcome domains, e.g., vegetative symptoms, cognitive distortions, interpersonal functioning, temporal course of response, and selective benefits for depressive subgroups? 2) If combined therapy is more efficacious than a single approach, is this due to an enhanced or broader spectrum of effect, and are specific combinations of therapies indicated or contraindicated? 3) How trustworthy are the conclusions reached by existing studies; that is, how methodologically sound are they? In this article we describe our methodology and the results of the review; we then suggest practical guidelines for prescribing combined psychopharmacotherapy based upon current knowledge and our own clinical experience.

\textbf{M}ethods

The 17 studies were compiled by MEDLINE search covering the years 1969 through 1989, and through communication with investigators in this subject area. The data comprise all English-language studies that contrast the combination of an antidepressant drug plus any specified form of psychotherapy with comparison conditions that included a single component of the combination, where the two conditions were randomly assigned in treating patients with unipolar, nonpsychotic depression. Two studies were excluded because they did not adequately describe the treatments delivered. In one report,\textsuperscript{7} depressed patients were treated by general practitioners, usually with medication, and randomized to cognitive therapy versus no additional treatment; however, the treatment received was inadequately defined. In the second study,\textsuperscript{8} which compared combined group cognitive therapy and alprazolam to each treatment alone, cell assignment was nonrandom. We did not require inclusion of placebo controls.

We used the box score method of summarizing studies. This categorizes for each study whether the effect of combined therapy was more or less effective than or equal to comparison treatments. Totals across studies for each of the three possible outcomes were then tallied. A major limitation of this approach is that it requires subjective judgments on study results that are frequently open to alternative interpretations. For example, combined therapy might outperform the comparison condition on one important outcome variable yet prove inferior in other, less important areas. Box score assessment is more quantitative than the narrative method most popular in previous reviews of this literature. However, it is far less precise than meta-analysis, which considers relative differences in methodological soundness of studies and utilizes the effect size, a statistic that transforms raw data from various studies into a common metric. Our literature review did not use meta-analysis because the raw data reported in the studies under review proved insufficient, often lacking standard deviations or results of direct cell comparisons.
Future investigators should avoid this deficiency in data reporting; if the psychiatric literature is to become amenable to conve-
nient aggregation, it is crucial that reports describe adequate raw data and suitable between-group comparisons.

**TABLE 1. Summary of study characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Range</th>
<th># Studies Reporting (of 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>91</td>
<td>18-250</td>
<td>17</td>
</tr>
<tr>
<td>n per cell</td>
<td>26</td>
<td>6-55(^a)</td>
<td>14</td>
</tr>
<tr>
<td><strong>Sample demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, % female</td>
<td>76</td>
<td>44-100</td>
<td>17</td>
</tr>
<tr>
<td>Age</td>
<td>49(^b)</td>
<td>17-81</td>
<td>15</td>
</tr>
<tr>
<td>Education, years</td>
<td>12</td>
<td>11-16</td>
<td>12</td>
</tr>
<tr>
<td>% Married</td>
<td>50</td>
<td>10-74</td>
<td>12</td>
</tr>
<tr>
<td>% Employed</td>
<td>58</td>
<td>39-81</td>
<td>8</td>
</tr>
<tr>
<td>Race, % white</td>
<td>88</td>
<td>77-100</td>
<td>9</td>
</tr>
<tr>
<td><strong>Profile of depressive symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of episode, months</td>
<td>—</td>
<td>3-50</td>
<td>8</td>
</tr>
<tr>
<td>% RDC probable or definite endogenous</td>
<td>57</td>
<td>52-91</td>
<td>5</td>
</tr>
<tr>
<td>% situational</td>
<td>53</td>
<td>27-76</td>
<td>4</td>
</tr>
<tr>
<td>% with previous episode</td>
<td>56</td>
<td>22-76</td>
<td>8</td>
</tr>
<tr>
<td>HRSD</td>
<td>—</td>
<td>18-25</td>
<td>12</td>
</tr>
<tr>
<td>BDI</td>
<td>—</td>
<td>24-30</td>
<td>10</td>
</tr>
<tr>
<td><strong>Study parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase of treatment studied:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>13</td>
<td>7-20</td>
<td>16</td>
</tr>
<tr>
<td>Continuation</td>
<td>24</td>
<td>6-156</td>
<td>16</td>
</tr>
<tr>
<td>Maintenance</td>
<td>47</td>
<td>6-164</td>
<td>16</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3.5</td>
<td>2-6</td>
<td>17</td>
</tr>
<tr>
<td>Length of treatment, weeks</td>
<td>16</td>
<td>7-30</td>
<td>15</td>
</tr>
<tr>
<td>Acute phase</td>
<td>14</td>
<td>6-20</td>
<td>17</td>
</tr>
<tr>
<td>Total treatment phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment and follow-up</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Treatment cells</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Therapy sessions, acute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant medications</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclics (TCA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCA dosage, mg/day</td>
<td>179</td>
<td>100-300</td>
<td>10</td>
</tr>
<tr>
<td>Other: MAOI, lithium, benzodiazepine, with or without TCA</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of pharmacotherapy, weeks, acute phase</td>
<td>14</td>
<td>6-20</td>
<td>17</td>
</tr>
</tbody>
</table>

**Note:** RDC = Research Diagnostic Criteria; HRSD = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; MAOI = monoamine oxidase inhibitor.

\(^a\)Only 2 studies had > 50 patients/cell.
\(^b\)Mean age excluding geriatric studies = 37.

**RESULTS**

Before 1974, the only controlled study on the combined treatment of depression to appear in the literature employed psychodynamic psychotherapy. Since then, reports have been published at an accelerating rate. Between 1974 and 1980 two studies used interpersonal therapy (IPT), whereas one employed psychodynamic and one marital therapy. Since 1980 there have been 12 comparison trials; cognitive behavior therapy (CBT) has been used most frequently, appearing in 6 reports compared with 4 behavioral and 2 IPT studies. There were no comparative studies of psychodynamic or marital therapy in the 1980s. Thus, overall, CBT has been the most frequently investigated therapy (n = 6), followed by IPT and behavior therapy (n = 4 apiece), with only 2 psychodynamic studies and 1 marital therapy study. This frequency distribution does not reflect general clinical practice, in which psychodynamic treatments continue to predominate, because until recently these have been more difficult to study systematically. Most studies combined medication with individual treatment rather than with group or marital therapy.

The treatment cells contrasted with combined therapy have varied considerably across studies. Hollon and DeRubeis have outlined the eight possible comparison conditions: 1) psychotherapy alone, or 2) in combination with placebo; 3) medication alone or 4) coupled with sham psychotherapy; 5) placebo or 6) sham therapy alone or 7) together; and 8) no treatment. The most frequent comparison has been between combined therapy and psychotherapy (n = 12), or psychotherapy and placebo (n = 12, out of 41 comparisons). Combined therapy was com-

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pared with medication alone or drug/attention control only half as often (11 of 41). These choices presumably mirror particular interests of the investigators.

None of the studies was conducted by investigators primarily interested in psychopharmacology. Amitriptyline (n = 6) and imipramine (n = 5) have been the most commonly used medications. It is noteworthy that only 7 studies provided a placebo condition for comparison with combined treatments. Thus it is difficult to prove that any superiority of the combined conditions does not simply reflect an augmented placebo effect.

<table>
<thead>
<tr>
<th>First Author</th>
<th>N (% Female)</th>
<th>Cells</th>
<th>Treatments</th>
<th>Weeks</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daneman</td>
<td>195 (69)</td>
<td>C, Pd</td>
<td>Dynamic; IMI 50-200 mg/d</td>
<td>9-12</td>
<td>C &gt; Pd</td>
</tr>
<tr>
<td>Coví</td>
<td>149 (100)</td>
<td>C, Dp, Pd</td>
<td>Dynamic; D1: IMI 100-200mg/d; D2: diazepam 10-20mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friedman</td>
<td>196 (79)</td>
<td>C, Dp, Pd, cpd</td>
<td>Marital; AMI 100-200mg/d</td>
<td>12</td>
<td>C = D = Pd = cpd</td>
</tr>
<tr>
<td>DeMascio</td>
<td>96 (86)</td>
<td>C, D, P, p</td>
<td>IPT; AMI 100-200mg/d</td>
<td>16</td>
<td>Completers: all = End point: C = all others</td>
</tr>
<tr>
<td>Rush</td>
<td>44 (86)</td>
<td>C1, P1, P2</td>
<td>P1: indiv. CBT; P2: group CBT; AMI, doxepin 150mg/d; phenelzine 60-90mg/d; lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blackburn</td>
<td>24 (80)</td>
<td>C, D, P</td>
<td>CBT; AMI, CMI ≥ 150 mg/d</td>
<td>20</td>
<td>GP: C &gt; P &gt; D</td>
</tr>
<tr>
<td>Geriatric patients</td>
<td>40 (75)</td>
<td>C, D, P</td>
<td>CBT; AMI, CMI ≥ 150 mg/d</td>
<td>20</td>
<td>GP: C &gt; P &gt; D</td>
</tr>
<tr>
<td>Bellack</td>
<td>125 (100)</td>
<td>C1, P1, Pd, cpd</td>
<td>P1: social skills; P2: dynamic; AMI 50-300mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hersen</td>
<td>18 (72)</td>
<td>C1, C2, Pd</td>
<td>IPT; IMI; alprazolam</td>
<td>6</td>
<td>Compliance, response comparable to younger patients</td>
</tr>
<tr>
<td>Wilson</td>
<td>64 (66)</td>
<td>C, Dp, Pd, cpd</td>
<td>Task assignment; relaxation; AMI 150 mg/d/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roth</td>
<td>26 (66)</td>
<td>C, P</td>
<td>Self-control gp; DMI 150-200mg/d</td>
<td>12</td>
<td>C = P</td>
</tr>
<tr>
<td>Murphy</td>
<td>80 (77)</td>
<td>C, Pd, D, P</td>
<td>CBT; NOR</td>
<td>12</td>
<td>C = D = Pd acute; C = P = Pd &gt; D maintenance</td>
</tr>
<tr>
<td>Beck</td>
<td>33 (72)</td>
<td>C, P</td>
<td>CBT; AMI 75-200 mg/d</td>
<td>12</td>
<td>C = P</td>
</tr>
<tr>
<td>Coví</td>
<td>70 (60)</td>
<td>P1, C1, P1, P2</td>
<td>P1: CBT gp; P2: IPT/dynamic gp; IMI 50-300 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becker</td>
<td>39 (48)</td>
<td>C1, C2, P1d, P2d</td>
<td>P1: social skills; P2: crisis support; NOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hollon</td>
<td>106</td>
<td>C, D, P</td>
<td>CBT; IMI 200-300mg/d</td>
<td>12</td>
<td>C &gt; D, C ≥ P, D = P</td>
</tr>
</tbody>
</table>

**Note:** C = combined; Dp = drug/attention control; Pd = therapy/placebo; D = drug alone; P = therapy alone; d = placebo alone; p = attention control; cpd = attention control/placebo; CBT = cognitive-behavioral therapy; IPT = interpersonal therapy; AMI = amitriptyline; CMI = clomipramine; DMI = desipramine; IMI = imipramine; NOR = nortriptiline adjusted to blood level.

* Dosage not available.
Table 1 summarizes characteristics of study design.

Numbers of subjects enrolled varied greatly. Even when many patients enrolled in a study, the large number of cells in study designs resulted in a mean of only 26 patients per treatment cell. Only two studies had more than 30 patients per cell, yet this is the likely minimum required to achieve adequate statistical power to detect the small but potentially significant advantage of combined treatments over already-effective single-modality antidepressant regimens.14

Most studies (88%, 15 of 17) focused on the acute phase of antidepressant treatment (see Table 2). Seven of the 17 studies included a follow-up (see Table 3), whereas only 4 looked at continuation or maintenance treatment (see Table 4). The emphasis on acute depression treatment effects ignores the issue of durability of treatment effect for combined versus individual therapy in what is often a relapsing and recurrent illness.

Twelve of 17 studies used the Hamilton Rating Scale for Depression (HRSD)15 and 10 used the Beck Depression Inventory (BDI).16 Additional instruments reflect the theoretical predilections of the psychotherapy researchers: CBT studies measured changes in depressive cognitions, whereas IPT studies emphasized alterations in social and role functioning. Unfortunately, the HRSD and BDI provided almost the only overlap of instruments across studies, making comparison of outcomes difficult beyond the measure of depressive symptomatology.

Lack of Negative Interactions

Perhaps the most striking finding is that no study found combined therapy less effective than its component treatments. Only two studies described possible interference of drug therapy and psychotherapy, and these were equivocal. In one,17 data analysis on the first 72 of an eventual 120 patients sampled indicated that social-skills training (SST) plus placebo resulted in a greater percentage of treatment responders than did SST plus amitriptyline, amitriptyline alone, or dynamic psychotherapy plus placebo. Analysis of the full patient sample, however, negated this. In the second trial,18 patients receiving SST plus nortriptyline fared significantly less well than patients in all other conditions in only 1 out of 13 symptom measures at midtreatment. Although the data suggesting negative inter-
actions are to date unconvincing, it is noteworthy that both of these studies employed SST as psychotherapy.

The most robust finding to report, then, is that combined therapy is not less effective than medication or psychotherapy alone. Psychotherapists once commonly believed that medication might interfere with psychotherapy, and some psychopharmacologists have conversely believed that psychotherapy might compromise drug efficacy. Evidently this is not so.

Table 5 shows that the number of psychotherapy studies is small. It is thus impossible to comment on differential efficacy of combined treatment as a function of which of the five specific psychotherapies was employed. Further accumulation of studies may point to felicitous marriages of specific medications and psychotherapies.

Evidence for Positive Interaction

Summing all studies, irrespective of type of therapy, the combined approach outperformed medication alone (i.e., drug alone and drug/attention-control conditions) in 4 of 10 instances, or 40% of the time. Combined therapy was found superior to psychotherapy (i.e., psychotherapy alone or with placebo) in 7 of 18 instances, or 39% of the time.

These findings do not indicate that combined therapy is necessary for all unipolar depressed outpatients, but they do suggest its overall superiority in comparison with individual treatments delivered alone. The intimation of some advantage, but lack of overwhelming superiority, for combined over single-modality therapy suggests that combined treatment may benefit some but not all patients. Questions that need further study are, which patients? And in what specific areas does combined therapy confer an advantage over pharmacotherapy or psychotherapy alone in their treatment?

The Problem of Attrition

Attrition significantly affects overall outcome and differs across groups. Because reported subject attrition rates range from 25% to 50%, subjects who complete a protocol are
not necessarily representative of the original sample variables such as demographic factors, severity of illness, and prognosis. Differential cell dropout may also bias outcome findings. Analysis of attrition patterns may reveal biases in patient-treatment selection, which may themselves reflect differential suitability of treatment approaches for patients with particular characteristics.

Most authors discuss subject dropout patterns. Of the 11 authors who reported attrition rates, 9 found no difference between study completers and noncompleters with respect to pre-treatment variables. Blackburn et al. found completers to be less depressed and less educated than noncompleters. Findings of Hersen's group were somewhat different: completers in their study were more intelligent, more highly educated, and better socially adjusted than noncompleters.

Regarding the effect of treatment condition on the dropout rate, only one study found that attrition differed between single and combined treatment conditions. Another study suggested that combined therapy retains patients better than single-modality treatments: Murphy discovered that, although there was no differential attrition by cell, collapsing cells into single versus combined treatment revealed a lower dropout rate for the latter. The last study found that endogenously depressed patients dropped out less frequently when taking amitriptyline alone than did nonendogenous patients. Furthermore, when the two cells with active drug components (SST plus amitriptyline and amitriptyline alone) were combined and compared with the remaining cells (SST plus placebo and short-term therapy plus placebo), melancholic patients had a higher completion rate in treatments that included an active medication component.

Subjects' satisfaction with the treatment they receive may offer a clue to the motivation behind attrition. Weissman found a higher rate of treatment refusal among patients randomized to psychotherapy than to pharmacotherapy, and Hollon also noted this as a trend. Hollon inferred a possible advantage for combined therapy over single-modality treatment: patients can in effect avoid the full impact of randomization by refusing half of the therapy package and yet remaining in treatment. Roth noted that several combined-therapy patients said that they would have discontinued medication had it not been for the psychotherapy component. Hersen ascertained that severity of depression, and especially melancholia, correlated with dissatisfaction at lack of early improvement in psychotherapy, whereas patients who were less depressed were also less tolerant of medication side effects. Wilson reported that over half of dropouts cited medication side effects as their reason for ending treatment, although another study found side effects not to be a prominent reason given for attrition. Medication dosage did not appear markedly different in these two reports.

Although most investigators found no significant differences in attrition across treatment conditions, the small size of treatment cells may obscure subtle self-selection in the course of treatment trials. Subjects more suited to their assigned treatment, i.e., pleased with their randomized assignment, may be more likely to complete trials; those who are less well suited may drop out. Thus, outcome measures favoring combined therapy may largely reflect subjects' satisfaction in receiving desired treatment. This would render comparison conditions spuriously equivalent. Regardless of why patients fail to complete treatment in these trials, a large group does fall through the cracks. Combined therapy may improve treatment compliance but by no means solves the problem.

Diagnostic Subtypes

Depression can be described along several dimensions: acute, chronic, or intermittent; mild or severe; endogenous or not; situational or not; by age of onset, etc. How do individual and combined treatments over-
lap in effectiveness along these dimensions, or how do they target differential benefits for depressive subtypes? The literature unfortunately yields few data on differential response according to depressive subtype. Five (29%) of the 17 studies addressed this issue. Three failed to find endogenous features predictive of differential treatment response. However, Weissman correlated endogeneity with superior efficacy of combined therapy relative to interpersonal therapy alone. Further distinguishing endogenous patients as situational or nonsituational, she found that the latter group showed even stronger differential treatment response. Weissman concluded that combined therapy may best suit the endogenously depressed patient, whereas single-modality therapy may be sufficient for nonendogenous patients.

Hollon's group explored a number of depressive dimensions. They found that patients who were less depressed fared better than more severely depressed patients in the drug-alone conditions, which consisted of imipramine 200–300 mg daily for 12 weeks and mean serum levels of 180 ng/dl. More severe depression responded better to combined therapy than to medication alone. Mildly and moderately depressed patients did well in all therapy conditions. Family history of depression augured better for response to combined treatment than cognitive therapy alone. Family history of mania correlated with better response to combined therapy than to medication alone. Medication responders were more likely to be nonsuppressors than suppressors on the dexamethasone suppression test; however, this did not predict response to cognitive therapy. Degree of cognitive dysfunction also did not predict differential treatment response.

Timing and Duration of Effects

The distress and morbidity of depressive suffering makes desirable a rapid therapeutic response. An assumption behind clinical use of combined therapy is that two treatments may work faster than one. The subset of studies (n = 6) that examined this issue tended to support this thinking. Two authors found that combined therapy produced earlier symptom relief than medication or psychotherapy alone. Three others found that medication worked faster than psychotherapy, suggesting that the addition of drug to psychotherapy reduces latency of therapeutic effect. Only Hollon et al. reported no difference in temporal effect among treatments. Yet Hollon did find another advantage for combined therapy: all active treatments significantly reduced symptoms in the initial 6 weeks of therapy, but only combined treatment showed continued significant symptom reduction in weeks 6 through 12. Thus, addition of medication to psychotherapy may speed symptomatic relief, and combined therapy may also extend the duration of therapeutic gains. Evidence for this is not, however, conclusive.

An important criterion of the efficacy of antidepressant treatment is its durability. Because depression frequently is recurrent or chronic, continuation and maintenance benefits are important. The question of whether combining medication and psychotherapy protects against depressive relapse and recurrence better than using either alone is confounded by vagueness in the literature in discriminating between relapse and recurrence; this in turn obscures the differing impacts that various treatments may have upon these states.

Our review found reports of 28 acute, 6 continuation, 12 follow-up, and no maintenance-treatment comparisons. Most combined-therapy studies focus more on the acute phase, with less attention paid to follow-up. The paucity of continuation and maintenance-phase trials leaves unclear the relative value of extended combined versus extended single-modality treatment either in promoting eventual complete recovery in acute-phase partial responders or in protecting against relapse and recurrence. Findings suggest that the advantage of acute combined
therapy over either component treatment alone appears not to endure thereafter: specifically, psychotherapy appears eventually to outdistance pharmacotherapy with chronic treatment. Although Blackburn et al.\textsuperscript{19} found all treatment conditions equivalent in mean symptom reduction at 6-month follow-up, a greater percentage of subjects who received cognitive therapy with or without medication remained in remission than of those who received medication alone. Weissman et al.\textsuperscript{5} noted improved social functioning at 1-year follow-up in patients who received interpersonal therapy, regardless of medication status. Murphy et al.\textsuperscript{21} found no overall difference in relapse rate by treatment cell; but when they applied strict criteria for remission (BDI<4), the relapse rate was significantly lower for patients receiving cognitive therapy. Two other investigators\textsuperscript{25,27} found no advantage for combined medication and psychotherapy over the latter alone at 1-year follow-up. An important limitation to these conclusions is that most studies (8 of 14, or 57%) employed a 12-week acute medication trial, with cessation of pharmacotherapy after that period—a 3-month antidepressant treatment probably inconsistent with clinical practice. The only study to use pharmacotherapy for as long as a year found it equivalent to short-term psychotherapy in preventing "symptomatic failure," or relapse.\textsuperscript{30}

**Specific Domains of Treatment Effect**

Pharmacotherapy and psychotherapy differ so fundamentally in nature and delivery that they might be expected to treat different symptom domains and to produce complementary, synergistic effects when combined. Klerman et al.\textsuperscript{10} found that interpersonal therapy preferentially enhanced work and social functioning late in treatment. Friedman\textsuperscript{12} found that marital therapy addressed family-role functioning more effectively than amitriptyline, whereas the tricyclic antidepressant was superior in reducing depressive symptoms. Weissman's group\textsuperscript{5} corroborated Friedman's observations comparing interpersonal therapy and amitriptyline. Hersen et al.\textsuperscript{24} found that SST enhanced interpersonal skills better than did medication. Covi and Lipman\textsuperscript{31} noted greater reduction of phobic anxiety and somatization by combined therapy than psychotherapy alone. However, three other authors who considered differential treatment effects on symptom domain failed to distinguish among active therapies. Medication and psychotherapy generally appear to overlap in their effects on depressive symptomatology. Patients who respond tend to improve globally, regardless of treatment modality.

In summary, some studies do suggest that when there are differential effects among therapies, psychotherapy particularly benefits social and role functioning, whereas pharmacotherapy preferentially targets somatic symptoms of depression.

**Discussion**

Numerous methodological problems complicate the literature on combined therapy, making it a particularly difficult area for research and for the interpretation of findings. Several studies took place at centers known for their allegiance to a particular psychotherapeutic approach, thereby introducing potential for bias in both investigators and subjects. Subject selection poses another problem: the need for a demographically and symptomatically homogeneous population may well result in including so small a percentage of patients initially screened as to severely limit generalizability to the population at large.

The shortcoming most hampering interpretation of the available literature is the relatively small number of subjects completing protocols. Attrition limits the statistical power available to protect against Type II errors (finding no difference when one indeed exists). That limitation becomes a special concern in this research because combined treatment must compete with
treatments already demonstrated to have efficacy when delivered alone. With little "room at the top" to show additional benefits, larger sample sizes and the use of a wider array of outcome measures are required in order to find variance. Absent larger samples, chronically depressed and medication-resistant patient populations may be particularly suitable for studies of combined treatment because they are less likely to respond to either modality alone, so that their outcomes for single versus combined therapy may have greater potential to show variance than those of treatment responders.

Several issues relevant to the selection and structuring of treatment conditions also limit the interpretation of results. Most striking is the lack of comparison between active-treatment and placebo and/or attention-control conditions. Antidepressant pharmacotherapy has not clearly established superiority to placebo in alleviating the mild to moderate range of depression often treated in these studies. Approximately half the subjects suffered from nonendogeneous and/or situational depression, yet active medication was compared with placebo alone or with a placebo/attention-control condition in only 5 studies. The absence of attention-control or attention-control/placebo conditions in 12 studies leaves in question whether psychotherapy contributes specific or non-specific factors in augmenting pharmacotherapy.

Another issue is whether dosage and duration of either psychotherapy or drug have been adequate. For example, the typical research format of a 12-week trial of antidepressant medication followed by abrupt withdrawal of medication is neither adequate nor representative of good clinical practice. Clinical wisdom dictates a longer acute medication trial followed by a maintenance dose achieved by gradual taper, which can be modified should signs of relapse occur.

Another problem is whether investigators are capturing all relevant aspects of therapeutic change attributable to the various treatment modalities. The most frequent outcome measures, the BDI and the HRSD (used in 10 and 12 of the 17 studies, respectively), may lack the necessary specificity to detect important areas of therapeutic effect, especially in milder depressions and dysthymia. High and often unbalanced subject attrition further compromises the interpretation of study results.

The major methodological limitations of our literature review reflect the broad variability of the available studies. Very different psychotherapies have been employed, both singly and in combination with medication. Too few studies currently exist for any single psychotherapeutic approach to permit conclusions about differential efficacy. There was less variability among medications used: 14 of 17 of the studies employed a tricyclic antidepressant only, and 2 of the remaining 3 included a TCA among 2 or more antidepressants used.

Comparison of study results would also have been facilitated by greater uniformity in types and numbers of treatment cells. For example, the attention-control conditions differed significantly across studies. The range embraced "nonscheduled treatment," which consisted of telephone contact with a therapist whenever the subject felt the need, and half-hour "structured sessions" for 7 out of 12 weeks. Subject characteristics also varied widely. Sample sizes ranged from 18 to 230; severe depression, although defined almost uniformly by a score of 14 on the 17-item HRSD and a BDI score of greater than 20, ranged from primarily "neurotic" to predominantly severe. Duration of symptoms varied as well, from patients with acute depression of 6 months or less to dysthymic patients averaging 50 months of symptoms.

There was also considerable variation in the methodological soundness of studies. These problems in aggregating the literature, added to the inability to use a meta-analytic approach, should encourage caution in interpreting results and should stimulate further work in this important area.
Whether combined antidepressant treatment has benefits greater than either psychotherapy or pharmacotherapy alone is a crucial question. Depression has considerable mortality and morbidity, and significant numbers of patients respond inadequately to a single treatment approach. It would be useful to know whether, and for which patients, the combined approach might increase compliance, reduce dropout, or increase speed, spectrum, or impact of therapeutic effect.

This question has proved especially difficult to study, not only because answering it requires a sophisticated research design, but also because it is cumbersome to conduct research of sufficient power. Large sample sizes are essential for two reasons: 1) there is little “room at the top” to show additional benefits because combined treatment is competing with already-effective treatments; and 2) multiple treatment cells are needed to provide useful comparisons.

A design feature that should inform future studies is selection of patients who have already failed to respond to one treatment alone. Sequential trials of psychotherapy, pharmacotherapy, and the two combined for patients with a history of inadequate treatment response would increase the variance in improvement and address the patient population arguably of greatest clinical importance in the use of combined treatment.

The most obvious conclusion to be drawn from the available literature is that combined treatment appears to be at least as effective as psychotherapy or pharmacotherapy delivered alone. This is important in contradicting historical beliefs that psychotherapy hinders medication, or vice versa. Yet even this conclusion requires qualification. Combined treatment costs more and may have more side effects than a single-modality approach. Research must still take account of these potential liabilities along with the greater likelihood of success with combined therapy.

The literature suggests that combined therapy at times outperforms single-modality treatment, and that single modalities may have specific additive effects—medications preferentially improving somatic symptoms, psychotherapy improving cognitions or social maladjustment. There are hints that medication works faster but that the effects of brief psychotherapy endure longer than those of acute pharmacotherapy—an intuitively reasonable finding. More studies are needed to confirm greater benefits of combined treatment and specific targets or durations of effect of component therapies. The vicissitudes of the current literature justify further research in these areas, as well as into the current clinical practice of combining treatments for more severely depressed and nonresponsive patients.

The ratio of previous reviews of this literature and actual studies in it is 2:5, intimating both the interest this topic holds and the difficulty of performing and interpreting studies. Most reviews were narrative. One besides ours used a box score approach, and Conte et al. attempted a modified meta-analysis. The reviews agree in finding combined treatment at least equal to component treatments alone. More recent reviews, ours included, are less sanguine about the documentation of superiority for combined treatment, or of specific effects for component therapies. We hope that future reviews will have many additional studies to interpret, containing sufficient raw data to allow full-scale meta-analyses.

Based on our review of the literature and our own clinical experience, we offer some tentative, but we hope useful, clinical guidelines about indications for combined treatment. The variables most influencing our clinical decision to combine treatments for depression are the severity, urgency, and chronicity of the patient’s psychopathology, past treatment response, and patient preference.
There is a U-shaped relationship between our use of combined treatment and the severity of depression: we tend to withhold a combined approach from the least and most severely depressed patients and to reserve combined treatment most often for moderately severe cases. Our rationale is that many, if not most, milder depressions—particularly acute ones—resolve with psychotherapy alone, which obviates committing the patient to a long antidepressant medication trial with additional expense, inconvenience, and possible side effects. We indicate to such patients that their type of depression usually responds to specific psychotherapeutic techniques, and that medication will not be used in the first weeks or months of treatment and will be added later only if depressive symptoms persist or worsen. This approach saves many patients unnecessary medication trials and provides a sense of mastery in having learned to cope with depression. If medication proves necessary, it is important to continue psychotherapy, which may have an augmented effect when delivered adjunctively: a positive medication response often allows the patient to participate more fruitfully in psychotherapy. Psychotherapy may also help to prevent relapse when medication is eventually withdrawn and may prophylactically reduce risk of subsequent recurrences.

Patients presenting with the most severe depressions generally require somatic treatment and hospitalization. They are often unable to participate in psychotherapy that extends beyond general support, psychoeducation, and a physician’s caring attitude. Very severely depressed individuals may experience psychotherapy as unduly stressful; inability to participate may exacerbate their hopelessness and guilt. The treatment of choice for such patients is somatic: medication or electroconvulsive therapy. Psychotherapy should be added only when they have recovered sufficiently to engage in it.

Thus, for patients with milder depression we generally recommend beginning with psychotherapy alone and adding medication later, only if needed. For the most severely depressed patients we begin with somatic therapy alone and add psychotherapy only after they have responded. For patients between the extremes, combined treatment may be selected as an initial approach. These individuals have such severe suicidal ideation, somatic discomfort, and inability to function that it feels clinically unwise to employ psychotherapy alone, yet they are sufficiently engageable that the therapist feels combining psychotherapy with psychopharmacology is feasible. Combined therapy can usually be given on an outpatient basis, but it can also begin in the hospital for patients who are sufficiently suicidal, noncompliant, or physically ill to require admission.

In our experience, several other factors prognosticate benefits for combined treatment as an initial approach. The best predictor is the patient’s prior treatment response. If combined treatment has worked before, or if either psychotherapy or medication has been only partially successful in the past, it may be wise to combine treatments. The course of the patient’s disorder may also influence selection of combined treatment. We have found that chronic depressions are more likely to require combined treatment.

For many patients, a variety of alternative approaches, single and combined, may seem equally plausible. It is often useful to discuss these options with the patient, indicating the likely advantages and liabilities of each, and to involve the patient in choosing among them. Sharing with the patient the responsibility for treatment selection—truly informed consent—is likely to increase his or her cooperation and compliance.

These clinical guidelines are largely unsupported by research. Much research is needed to develop widely accepted, precise indications for combined treatment. In the meantime, it is fortunate that so many effective treatments for depression exist, that these frequently complement one another, and that we can attempt to match treatments to patients’ needs and preferences.
enough time and cooperation, one can nearly always succeed in finding a treatment or combination of treatments to alleviate and to protect against the great suffering and risk of depression.

References