Psychotherapy and Medication in the Treatment of Adult and Geriatric Depression: Which Monotherapy or Combined Treatment?

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Objective: The authors reviewed the literature with respect to the relative efficacy of medications and psychotherapy alone and in combination in the treatment of depression.

Data Sources and Study Selection: Findings from empirical studies comparing medications and psychotherapy alone and in combination were synthesized and prognostic and prescriptive indices identified. We searched both MEDLINE and PsychINFO for items published from January 1980 to October 2004 using the following terms: *treatment of depression, psychotherapy and depression*, and *pharmacotherapy and depression*. Studies were selected that randomly assigned depressed patients to combined treatment versus monotherapy.

Data Synthesis: Medication typically has a rapid and robust effect and can prevent symptom return so long as it is continued or maintained, but does little to reduce risk once its use is terminated. Both interpersonal psychotherapy (IPT) and cognitive-behavioral therapy (CBT) can be as effective as medications in the acute treatment of depressed outpatients. Interpersonal psychotherapy may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk following treatment termination. Ongoing treatment with either IPT or CBT appears to further reduce risk. Treatment with the combination of medication and IPT or CBT retains the specific benefits of each and may enhance the probability of response over either monotherapy, especially in chronic depressions.

Conclusion: Both medication and certain targeted psychotherapies appear to be effective in the treatment of depression. Although several prognostic indices have been identified that predict need for longer or more intensive treatment, few prescriptive indices have yet been established to select among the different treatments. Combined treatment can improve response with selected patients and enhance its breadth (IPT) or stability (CBT).

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Both medication and psychotherapy are used widely in the treatment of depression. Antidepressant medications have been shown to be efficacious in literally hundreds of placebo-controlled trials and represent the current standard of treatment.[1] Psychotherapy is widely practiced but has been less intensively studied than pharmacotherapy. Nonetheless, several of the newer psychotherapeutic approaches tailored specifically to the treatment of depression have fared well in direct comparisons with medications.[2]

This article focuses on when to choose medications, psychotherapy, or the combination. Given the apparent efficacy of each monotherapy, it is not surprising that the 2 are sometimes combined. Early trials rarely documented a clear advantage for the combination over either monotherapy in terms of acute symptom reduction, but these studies uniformly lacked sufficient power to detect clinically or statistically meaningful differences. Given the largely inadequate empirical evidence, recommendations on when to use combined treatment relied largely on clinical consensus. Thus, the practice guideline published by the Agency for Health Care Policy and Research (AHCPR)[3] suggested that combined treatment was particularly likely to be indicated for patients with more complex or chronic disorders. Combined treatment was also recommended for those patients with a clinically unsatisfactory response to either monotherapy (e.g., lack

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of symptom remission or continuing psychosocial dysfunction). Similar conclusions were drawn by the American Psychiatric Association (APA) in the recent revision of its practice guideline for depression.[4] We searched both MEDLINE and PsychINFO for items published from January 1980 to October 2004 using the following terms: *treatment of depression*, *psychotherapy and depression*, and *pharmacotherapy and depression*.

REASONS FOR PROVIDING COMBINED TREATMENT

These recommendations are sensible but may not go far enough. Combined treatment can prove advantageous in any of several respects. First, combined treatment can enhance the magnitude of response for the average patient; that is, each patient obtains more complete benefit in terms of symptom reduction or improved daily function from the combination than from either single modality.[5] Second, combined treatment can enhance the probability of response. If different patients respond to different treatments, then combining modalities should increase the proportion of patients who obtain clinically meaningful benefits.[6]

Third, combined treatment may enhance the breadth of response. Medications work faster than some types of psychotherapy, whereas certain types of psychotherapy may have broader or more enduring effects than medications.[5] For example, interpersonal psychotherapy (IPT) appears to have a delayed effect on the quality of interpersonal relationships not found for medications, and cognitive-behavioral therapy (CBT) appears to have an enduring effect that reduces risk for subsequent symptom return even after treatment is over.[1] Combined treatment typically retains the specific advantages associated with each monotherapy. Finally, combined treatment may enhance the acceptability of treatment relative to each single modality. Adding medication can make some patients more tractable and receptive to psychotherapy, whereas adding psychotherapy can make some patients more willing to accept medications or tolerate their side effects.[6]

PROGNOSTIC VERSUS PRESCRIPTIVE DESIGNS AND INFORMATION

Given that different kinds of depressions may respond to different interventions or combinations, a key question becomes how to select the best treatment for a particular patient. There are 2 kinds of information relevant to the prediction of outcome, and each is based on a different type of design. Prognostic indications typically predict which patients most improve under a given set of conditions. These indications are based on designs that hold treatment constant (or ignore differences) and allow patient characteristics to vary. Prognostic designs can determine which kinds of patients are most likely to respond to a given intervention. These designs also can provide useful information about what a given patient can expect as a consequence of treatment. However, they are not well suited to determine which treatment is best for a given patient.[7]

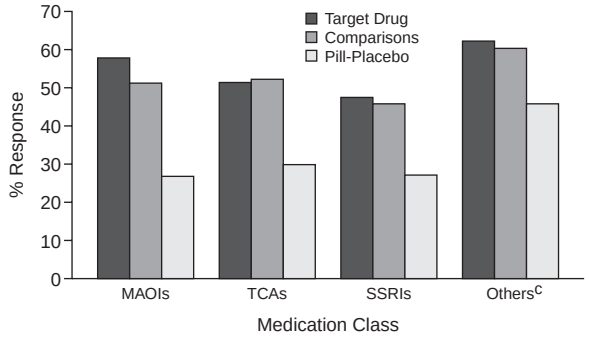
On the other hand, prescriptive indications predict to which of 2 or more treatments a given patient is more likely to respond. These indications are derived from designs that systematically vary treatment conditions while taking individual differences into account. Since each patient has fixed characteristics at treatment initiation (e.g., age, gender, prior history of illness), prescriptive information is needed to select the best option for a given patient from among the range of possible treatments. More studies are needed that provide this type of information, since prescriptive indications provide the best guide for clinical practice.

DISORDER AND PATIENT CHARACTERISTICS

Several characteristics of the patient or disorder have been linked to differential response, both within (prognostic) and between (prescriptive) treatments. Depressive symptom severity, the best-studied characteristic, has some prognostic value. Less severe depressions are more likely to exhibit spontaneous remission and respond to nonspecific factors, whereas more severe depressions are more likely to require some form of active treatment.[8] Whether severity is prescriptive with respect to type of treatment remains unclear. Medications or somatic treatments are said by some to be necessary for those patients with more severe depressions,[4] but that is largely because other interventions have been so rarely tested in inpatient populations.[1] Similarly, it is widely believed that depressions with more prominent vegetative symptom patterns or certain biological abnormalities may be less responsive to psychotherapy than they are to medications, although empirical support is limited.[2]

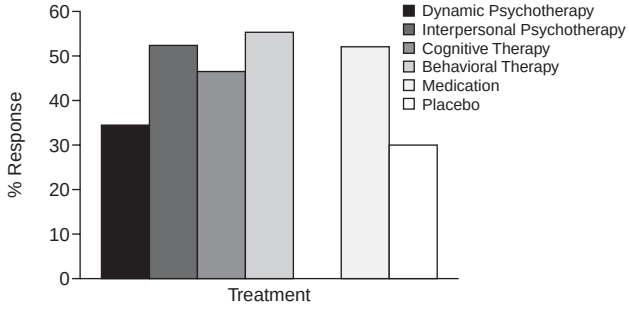
Depressions superimposed on underlying personality disorders appear to be less responsive to treatment than those depressions without personality disorders,[9] although that has not always been the case.[10] Patients with chronic depressions may or may not be less responsive to treatment than patients with less chronic depressions, but they clearly are less likely to remit spontaneously without treatment. Thus, each of these disorder features can be said to be prognostic with respect to probability of response and indicative of the need for more treatment of greater intensity and duration, regardless of modality or whether used singly or in combination. However, it remains unclear whether either index can be said to be prescriptive with respect to choosing from among different active treatment options (as described later).

Figure 1. Response to Different Medication Classes and Placebo Controls[a,b]



[a]Reprinted with permission from Hollon et al.[1]
[b]Each target drug is compared with a number of different alternative medications (Comparisons) and placebo (Pill-Placebo). The figure is based on a meta-analysis conducted in outpatients for the Agency for Health Care Policy and Research.[3]
[c]Others = other miscellaneous and typically newer medications (listed as "heterocyclics" in the original report).
Abbreviations: MAOIs = monoamine oxidase inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

Figure 2. Response to Psychotherapy vs. Medications and Placebo in the Treatment of Unipolar Depression[a,b]



[a]Adapted with permission from Hollon et al.[1]
[b]The estimates for the 4 kinds of psychotherapies are based on a meta-analysis conducted in outpatients for the Agency for Health Care Policy and Research[3]; the estimates for medications and placebo are drawn from a subsequent update of that review.[18]

The foregoing indications are clearly prognostic with respect to spontaneous remission. For that reason, they are informative with respect to need for treatment (such patients are unlikely to get better on their own). Nonetheless, it remains unclear whether any of these indications are truly prescriptive with respect to different interventions. That is, there is little evidence that patients with these different kinds of depressions necessarily do better in one type of treatment than another.

RESPONSE TO MEDICATION TREATMENT

There is little question that medication is efficacious in the treatment of depression in both adult and geriatric populations. As shown in Figure 1, about half of all outpatient depressions will respond to any single class of medications, and each medication class is generally superior to placebo.[1] Inpatient samples show a similar pattern of response with comparability across different classes of medications and superiority of each to placebo controls, although absolute rates of response to medication or placebo are often lower than they are for outpatients. The same pattern of response also seems to hold for geriatric patients, although side effects are a greater problem in the frail elderly. In general, there is little difference in efficacy between the different classes of medications (as shown by the comparison with other medications in Figure 1). Most clinicians choose first-line agents with more benign side effect profiles such as the selective serotonin reuptake inhibitors (SSRIs).[11]

Nonetheless, there are lingering concerns that the SSRIs may be less efficacious than more noradrenergic or dual-action agents such as the tricyclic antidepressants (TCAs) or venlafaxine in the treatment of more severe inpatient populations.[12,13] Moreover, some types of depression appear to be more responsive to some selected agents than to others.[14] For example, patients with atypical depression appear to respond best to the older monoamine oxidase inhibitors (MAOIs) compared with the TCAs or the SSRIs.[15] Similarly, among patients with chronic depression, women are somewhat more likely to respond to SSRIs (at least until menopause), whereas men are more likely to respond to TCAs.[16]

Clearly, different depressions respond to different medications or combinations, based on the evidence that response often can be achieved when initial treatments fail by switching to or augmenting with a different medication.[17] Practice guidelines typically recommend providing an adequate dose of a given medication for 6 to 8 weeks before deciding whether to switch medications (in the case of nonresponse) or augment with a second medication (in the case of partial response).[3,4]

RESPONSE TO PSYCHOTHERAPY

As shown in Figure 2, response to treatment differs as a function of type of psychotherapy. Response rates for the different psychotherapies are drawn from the original AHCPR review,[3] whereas estimates for medication treatment and their placebo controls are drawn from a subsequent update of newer agents.[18] As can be seen, IPT and the cognitive and behavioral therapies (CT and BT, respectively; sometimes referred to collectively as *CBT*) compare favorably with medications in studies with depressed outpatients, whereas the more traditional dynamic psychotherapies have not fared so well.[1] Such findings have led some to conclude that both IPT and CBT are efficacious in the treatment of all but the most severe depressions and that the efficacy of other types of psycho-

therapy for depression remains in question.[4] As described below, some of these conclusions are based on more and better studies than others, but, on the whole, they provide a reasonably succinct synopsis of the available literature.[19,20]

Dynamic Psychotherapy

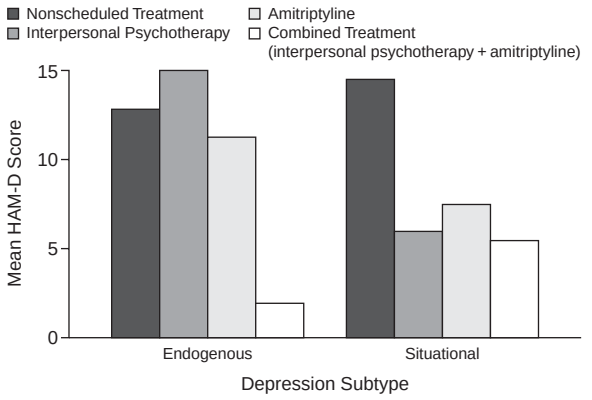
Although dynamic psychotherapy has not fared well in controlled trials of major depression, questions remain as to whether it has been tested in a fair and reasonable manner. For example, only one of the studies with nongeriatric adults cited in the AHCPR review was conducted by an investigator invested in the approach.[21] The investigators who conducted the remaining studies in that review had allegiances to other approaches. In those studies, dynamic psychotherapy typically was viewed as a comparison condition for a more valued intervention. Thus, it is possible that the dynamic interventions in those trials may not have been adequately implemented.[22–25] Recent studies conducted by advocates of that approach have been more promising, with combined treatment involving dynamic psychotherapy typically proving superior to medications alone.[26–28] Moreover, 2 studies in the geriatric literature failed to find any advantage for CBT over brief dynamic psychotherapy.[29,30] Dynamic psychotherapy was supervised in these studies by an acknowledged expert in the approach, suggesting that adequacy of implementation may affect outcome. However, since neither study included a minimal treatment control, it remains unclear how far to go in interpreting what were essentially null findings, especially since sample sizes were modest. A placebo-controlled comparison with medications is currently under way at the Center for Psychotherapy Research at the University of Pennsylvania (Philadelphia, Pa.) to test the efficacy of brief dynamic psychotherapy for depression in a study overseen by advocates of that approach.

Interpersonal Psychotherapy

In contrast to dynamic psychotherapy, IPT has fared well in comparisons with medication in a number of trials, including acute as well as continuation and maintenance phase studies. Although few in number, these studies have been fairly robust in documenting an effect for IPT across different stages of treatment. Moreover, there were indications in some early trials that IPT may have a broader effect than medications in terms of improving the quality of social adjustment. If true, this would have important clinical implications and deserves to be pursued.

Acute phase trials with IPT. In an early study of acute phase treatment, both IPT alone and medication alone were superior to a "treatment on demand" control.[31] Combined treatment was numerically but not statistically superior to either monotherapy. Although IPT was as efficacious as medications, it took somewhat longer to produce an effect.[32] As shown in Figure 3, patients with endogenous depressions were more likely to respond to combined treatment than they were to either monotherapy, whereas patients with situational depressions did no better with combined treatment than they did with either monotherapy.[33] This suggests that endogenous depression may be an indication for combined treatment with IPT. Moreover, IPT appeared to have a delayed effect on the quality of social adjustment; patients treated with IPT (either alone or with medications) reported improved social functioning relative to patients treated with medications alone that was first apparent about a year after the end of treatment.[34]

Figure 3. Differential Response to Drugs and Psychotherapy as a Function of Endogenous and Situational Subtypes as Measured by the HAM-D[a,b]



[a]Adapted with permission from Prusoff et al.[33]
[b]Lower scores on the HAM-D indicate greater response to treatment.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

IPT also compared favorably with medications in the National Institute of Mental Health Treatment of Depression Collaborative Research Program (NIMH TDCRP).[35] In that trial, patients with less severe depressions did comparably well in each of several conditions (including pill-placebo), but patients with more severe depressions did better with IPT alone or medication alone than with pill-placebo. Although IPT was as effective as medications (regardless of patient severity), it again took somewhat longer to produce that effect.[36] Social dysfunction predicted differential response, but in a curious fashion. Patients with high social dysfunction did worse in IPT than did patients with low social dysfunction (a somewhat counterintuitive prognostic indication). The only indication that approached prescriptive status was that IPT was superior to pill-placebo for patients with low social dysfunction.[37]

IPT was less efficacious than sertraline and did little to enhance medication efficacy when added in combination in a recent study with dysthymic patients.[38] It remains unclear whether this finding will replicate (it is the first time that IPT has been outperformed by medications), but if it does it could point to a patient character-

istic (dysthymia) that predicts better response to medication than to psychotherapy.

Continuation phase trials with IPT. In the earliest IPT study,[39] which focused on delaying subsequent symptom return, Klerman and colleagues found that IPT alone was no less effective than continuation medication in preventing relapse among patients first brought to remission on medications. Combined treatment did no more to delay relapse than medications alone. Combining IPT with pill-placebo (and thus leading patients to believe that they were still receiving medications when they were not) was associated with a higher relapse rate than IPT alone, although differences were not significant.[40] Regardless of whether or not patients were also taking medications, IPT had a delayed effect on the quality of interpersonal relations that emerged over the course of the 8-month continuation phase.[41] Combined with similar indications from the earlier acute phase trial by Weissman and colleagues,[34] this finding suggests that IPT may have a greater effect on social adjustment than medications and that this effect may be preserved even when IPT is combined with medications. These findings form the basis for the notion that IPT has a greater breadth of effect than do medications in terms of improved social adjustment with equivalent symptom reduction. Subsequent studies have not looked to see if this effect will replicate. This is unfortunate, since it would be important if true. Future studies should examine whether IPT does enhance relationship skills and improve social adjustment and whether this effect is preserved when combined with medications.

Maintenance phase trials with IPT. Frank and colleagues[42] found that maintenance phase IPT delayed the onset of recurrence among patients with multiple prior episodes as compared with placebo, but that IPT was less effective than medications alone in that regard. Interpersonal psychotherapy did little to enhance the preventive effect of medications when used in combination. The lower efficacy of IPT alone in this study as compared with medication alone may have been a "dosage" issue: IPT session frequency was reduced to once a month during the maintenance phase, whereas medications were maintained at full acute treatment doses. Also, this study had limited power to detect a moderate effect size if such a difference existed.

Reynolds and colleagues[43] conducted a similar study in a geriatric sample of patients over the age of 60. What they found was a clear ordering of recurrence rates over the next 3 years, with 90% recurrence rates for patients maintained on pill-placebo, 64% for patients maintained on IPT, 43% for patients maintained on medications alone, and only 20% for patients in combined treatment. Differences favoring each monotherapy were significant relative to pill-placebo, whereas differences favoring combined treatment were significant relative to IPT alone and showed a nonsignificant trend relative to medications alone. Age was a general prognostic factor; patients over the age of 70 were more likely to have a recurrence and to do so more rapidly than were younger geriatric patients regardless of treatment condition.

Summary and conclusions for IPT. It would appear that acute phase IPT is about as effective as medications in the treatment of depressed outpatients (with the possible exception of dysthymia), although it seems to take several weeks longer to exert its effects. This effect appears to extend to outpatients with more severe depressions, although it may not hold for patients with dysthymia. In addition, IPT may have a delayed effect on social adjustment not shown by medications. This indication was evident in 2 early studies and has not been subsequently examined. Given its potential importance, this possibility is something that should be pursued. Extending treatment with IPT appears to prevent either relapse or recurrence, although perhaps to not the same extent as continuing or maintaining patients on medications. Combining IPT with antidepressant medication appears to enhance both the magnitude of acute response (especially among endogenous patients) and the prevention of recurrence (at least among geriatric patients). Combined treatment with IPT and medications also appears to retain the specific advantages associated with each monotherapy; it works faster than IPT alone and it may do more than medications alone to improve social adjustment.

CBT and Related Approaches

There are a number of different cognitive-behavioral interventions, some more cognitive in emphasis and others more behavioral. In this section, we discuss these various approaches, keeping them distinct from the more purely behavioral interventions. Despite their different names, all incorporate both cognitive and behavioral strategies; they are sometimes referred to collectively as *CBT*, a convention we adopt with some misgivings. The collective term *CBT* also is used to connote a larger class of interventions that includes the more purely behavioral interventions, as we do later in this article.

Acute phase studies with CBT. Cognitive therapy is one of the earliest and most frequently studied of the cognitive-behavioral approaches. Early studies suggested that acute phase CT might be superior to medication treatment in the reduction of depressive symptoms in both primary care[44] and psychiatric samples.[45] However, these trials did not implement medication treatment in an adequate fashion.[46] Subsequent trials that implemented medication treatment more adequately typically have found CT to be about as effective as medications.[47,48] However, those studies did not include pill-placebo controls. In the absence of such placebo controls it was not possible to be sure that either treatment was effective.[49]

The TDCRP was the first such study to include a placebo control.[35] As shown in Figure 4, CBT was less ef-

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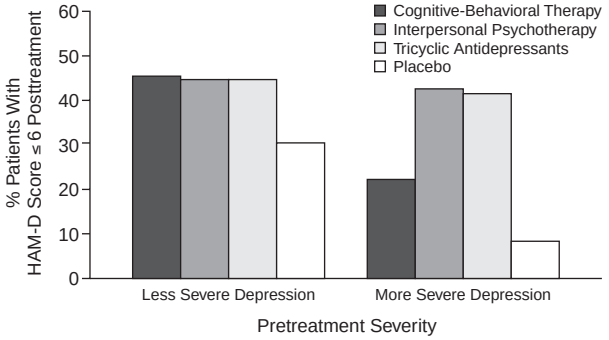
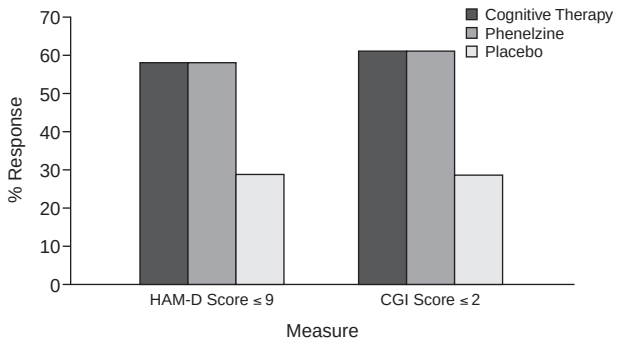
Figure 4. Response to Treatment as a Function of Pretreatment Severity of Depression: Patients in Full Remission at Posttreatment as Measured by the HAM-D (ITT)[a–c]



[a]Adapted with permission from Elkin et al.[35]
[b]Results from the National Institute of Mental Health Treatment of Depression Collaborative Research Program (NIMH TDCRP).
[c]Pretreatment scores on the HAM-D were used to categorize patients as having more severe or less severe depression, with a score of ≥ 20 indicating more severe depression.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, ITT = intent-to-treat.

Figure 5. Percent Response to Treatment of a Sample of Patients With Atypical Depression in a Placebo-Controlled Trial[a,b]



[a]Data from Jarrett et al.[55]
[b]Study conducted in outpatients.
Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression.

fective than either medications or IPT and no more effective than placebo in the treatment of more severely depressed patients.[50] This finding was interpreted by some to suggest that CBT is less effective than medications in the treatment of severe depression.[4] If replicated, this finding would suggest that severity is a negative prescriptive index with respect to CT.

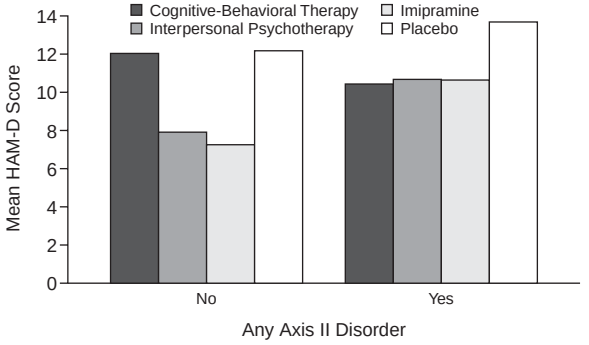
However, these findings were not robust even across sites within the TDCRP.[51] Patients treated with CT at 2 sites did no better than patients treated with pill-placebo, whereas those treated at the remaining site did as well as patients treated with medications.[52] Although patterns of response were not linked to specific sites in the TDCRP publications, it is clear from examining the sample sizes listed and other information available in the public domain that the site with the most experience with CT (Oklahoma) produced the best results for that modality. Similarly, the superiority of medications over CT reported in the TDCRP is not robust across other studies. DeRubeis and colleagues[53] conducted a mega-analysis of treatment response among more severely depressed patients in 4 of the outcome studies already cited (including the TDCRP) and found that patients treated with CT did as well as patients treated with medications. In those other studies, therapists were either more experienced with CT or received more intensive ongoing supervision than they did in the TDCRP.

Finally, a recent placebo-controlled trial[54] found that CT was as effective as medications in the treatment of more severely depressed patients, although again there were indications that this effect might be moderated by therapist experience. In that trial, a site-by-treatment interaction indicated that CT was at least as effective as medications (and superior to pill-placebo) when implemented by more experienced therapists at the University of Pennsylvania and less effective than medications when implemented by therapists with less experience with that modality at the Vanderbilt University site (Nashville, Tenn.). Moreover, the less experienced therapists at Vanderbilt improved with additional practice and training, such that rates of response among their patients nearly matched those observed for the University of Pennsylvania over the second half of the trial. This suggests that the efficacy of CT may depend in part upon the quality of the therapy delivered, which in turn may be related to the experience of the therapists implementing the intervention. Combining these findings with those from the TDCRP[35] and the mega-analysis conducted by DeRubeis and colleagues,[53] it appears that the moderating effect of therapist experience may be most evident with more severely depressed or difficult patients.[5]

Jarrett and colleagues[55] conducted a second blinded randomized pill-placebo–controlled trial of acute phase CT that also involved experienced therapists. As shown in Figure 5, 10 weeks of CT was as effective as an MAOI (phenelzine), and each treatment was superior to pill-placebo in reducing the symptoms of depressed outpatients with atypical features. Once again, these positive findings did not replicate the null effects for CT in the TDCRP study. This set of results furthered the speculation that treatment adherence and therapist competence may partially mediate the antidepressant effect of CT.

However, there is a third placebo-controlled trial[56] that does suggest a lesser efficacy for CBT relative to medications. In this study, group CBT was no more efficacious than pill-placebo and less efficacious than medications in the treatment of patients with dysthymia. Moreover, CBT did little to enhance efficacy with respect to symptom reduction when added in combination with medications,

Figure 6. Personality Disorder Predicts Differential Response to Treatment as Measured by the HAM-D[a,b]



[a]Data from Shea et al.[68]
[b]Results from the National Institute of Mental Health Treatment of Depression Collaborative Research Program (NIMH TDCRP).
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

although there were indications that it did enhance level of functioning. Whether this poor showing for CBT with dysthymic patients reflects patient factors (which might then be prescriptive) or the method of treatment implementation (CBT was provided in a group format by therapists of unknown experience) remains unclear, but more studies with such patients are clearly indicated.

Prognostic and prescriptive indices for CBT. Other possible prescriptive indices have been proposed, but have yet to be established. Melancholic features have long been presumed to require more biological interventions and do predict lower rates of spontaneous remission and lack of response to pill-placebo.[57] However, CBT typically has fared as well as medications or other interventions with such patients.[37,44,47,48,58–60] Biological abnormalities like sleep or neuroendocrine dysregulation have predicted poor response to CBT in purely prognostic designs,[61–63] but have not predicted better response to medications in direct prescriptive comparisons.[64,65] There are indications that more severely depressed women may do better in IPT or medication treatment than in CBT,[66,67] especially when therapists are less experienced.[54] Although this has yet to be tested in a fully prescriptive randomized trial, investigators should be alert to a possible complex interaction between gender, severity, and therapist experience.

Several other suggested prescriptive indications require comment. The APA practice guideline[4] suggested that patients with underlying personality disorders respond better to CBT than they do to either IPT or medications. However, this statement was based largely on a misinterpretation of data from the TDCRP that indicated that presence of a personality disorder predicted response within the other conditions but not CBT and illustrates the risks of relying on secondary sources (the authors of the original article made no such claim).[68] As shown in Figure 6, the reason that personality disorder did not predict response within CBT was not because such patients did better in that modality than they did in the other treatments, but because patients without a personality disorder did less well in CBT than they did in the other modalities. Recent efforts to make CBT more efficacious for patients with personality disorders may or may not succeed,[69,70] but there is little in the existing empirical literature (and certainly nothing in the TDCRP) to suggest that any such advantage has already been accomplished.

The previous example illustrates how easy it is to misconstrue prognostic information. By way of contrast, a recent reanalysis of data from the NIMH TDCRP suggested that patients who engage in interpersonal avoidance do better in CBT than they do in IPT, whereas patients with a more obsessive style do better in IPT than in CBT.[71] This report is noteworthy in 2 respects: (1) it provides a compelling model for how to go about looking for prescriptive indices, and (2) it demonstrates that empirical findings are often counterintuitive. Although it was not what was predicted, patients did better in a kind of therapy that seemed poorly matched to their particular personality style.

These findings are reminiscent of the report cited earlier from the same TDCRP data set that found a counterintuitive relationship between level of social dysfunction and response to IPT.[37] That same report also found that patients with lower levels of cognitive distortion showed a greater differential response to CBT relative to placebo than did patients with higher levels of cognitive distortion. Similarly, Miller and colleagues[72] found that inpatients with higher levels of cognitive distortion responded better to combination treatment involving medications and either social skills training or CBT than to standard medication alone. Patients with lower levels of cognitive distortion showed no preferential response. Such findings have led some to suggest that patients are best matched to treatments that complement their strengths rather than to treatments intended to correct their deficits.[73]

Preventing relapse and recurrence with CBT. As was the case for both medications and IPT, extending the duration of CT beyond the point of initial response, that is, adding a continuation/maintenance phase, appears to reduce risk for subsequent relapse and possibly recurrence.[74] In a randomized controlled trial, Jarrett and colleagues[75] found that depressed outpatients who responded to acute phase CT were less likely to relapse during the 8-month study period if they stayed in monthly continuation treatment than if they discontinued shortly after initial response. As shown in Figure 7, patients with early onset of depressive illness or who showed residual symptoms (response without remission) were at greatest risk for relapse if CT was not continued.[75] In other words, patients with these risk factors needed continuation phase CT more than did patients without these risk factors. Similarly, Blackburn and Moore[76] found that maintenance

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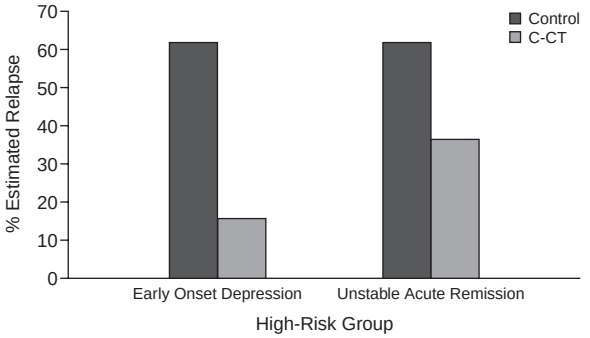
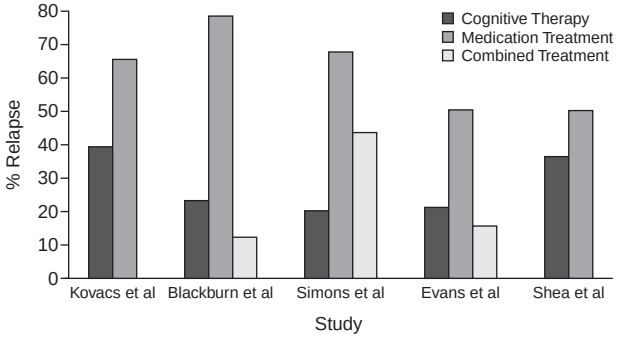
Figure 7. Relapse/Recurrence Following Successful Acute Phase Cognitive Therapy (CT): Continued CT (C-CT) Versus Discontinued CT (Control) in Highest-Risk Groups 24 Months Postrandomization[a]



[a]Data from Jarrett et al.[75]

Figure 8. Relapse Following Treatment Termination: Cognitive Therapy Versus Medication[a,b]

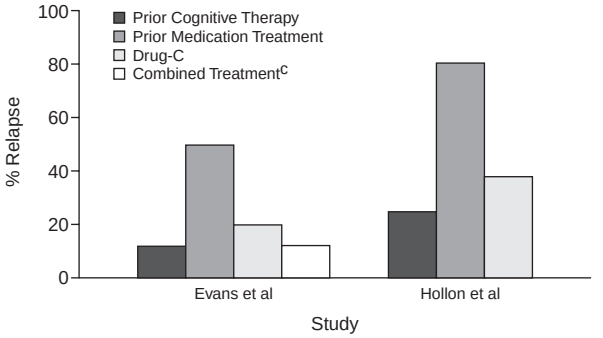


[a]Data from Kovacs et al.,[58] Blackburn et al.,[77] Simons et al.,[78] Evans et al.,[79] and Shea et al.[80]
[b]Patients first treated to remission, then withdrawn from treatment and followed over the subsequent year (18 months in the study by Shea and colleagues).

phase CT was no less effective than maintenance phase medications in a sample of patients with histories of recurrence. It is not possible to draw firm conclusions from the study by Blackburn and Moore, since it contained no minimal treatment control. One must be willing to accept the null hypothesis to conclude that the treatments did not differ. Nonetheless, it is noteworthy that maintenance phase CT did not do worse than maintenance phase medication, the current standard of treatment for the prevention of recurrence.

Moreover, acute phase CBT (including CT) also appears to have an enduring effect that lasts beyond the end of treatment.[1] Figure 8 depicts relapse rates following successful treatment with either CT or medications that is subsequently terminated. In most studies, patients who responded to CT were about half as likely to experience a relapse following treatment termination as patients who responded to medications.[58,77–79] The sole exception came

Figure 9. Relapse Following Successful Treatment: Prior Cognitive Therapy Versus Ongoing Medications[a,b]



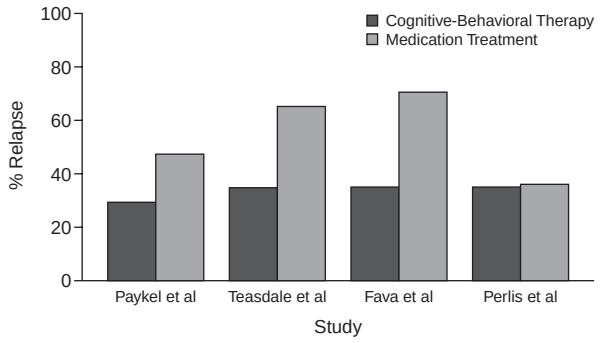
[a]Data from Evans et al.[79] and Hollon et al.[81]
[b]Patients first treated to remission, then withdrawn from treatment and followed over the subsequent year; patients in Drug-C group kept on continuation medications during that subsequent year.
[c]Combined treatment = prior treatment with drugs and cognitive therapy.
Abbreviation: Drug-C = continuation medication treatment.

from the TDCRP,[80] and even in that study, such differences as were apparent favored prior CT.

Although these studies speak to the existence of an enduring effect for CT, they provide little guidance to help clinicians select which patients should get what treatments. It is well established that patients who are treated with medications alone should be kept in continuation treatment for 6 to 12 months following remission to protect against relapse, the return of the treated episode.[4] However, even in the studies cited, roughly half of those switched to placebo do not relapse. If acute phase CT has an enduring effect that protects against subsequent relapse, it would need to approach the magnitude of the protection afforded by continuation medication to make it a reasonable clinical alternative (the same can be said for the preventive effect afforded by continuation CT). Figure 9 depicts risk for relapse in those 2 studies that have compared CT that is discontinued after initial response versus ongoing continuation medication. As can be seen, patients who responded to CT did as well following treatment termination as medication responders continued on medication throughout the period of risk for relapse.[79,81] This suggests that a brief course of CT may provide as much protection against subsequent relapse as a more extended course of medication treatment. In both studies, patients with residual symptoms at the end of treatment were particularly likely to relapse if taken off medications without the protection of prior exposure to CT.

Further, there are indications that acute phase CBT's enduring effect is robust regardless of whether it is applied alone or in combination with medications (Figure 8) or sequentially after medication treatment has been used to reduce acute distress.[5] As shown in Figure 10, adding CBT to ongoing continuation treatment appears to reduce

Figure 10. Relapse/Recurrence Following Cognitive-Behavioral Therapy for Residual Symptoms[a,b]



[a]Data from Paykel et al.,[82] Teasdale et al.,[83] Fava et al.,[84] and Perlis et al.[85]

[b]Patients first treated to at least partial remission with medications, then had cognitive-behavioral therapy added for residual symptoms before being followed over the subsequent year (3 years for the study by Fava and colleagues).

risk for subsequent symptom return regardless of whether medication treatment is continued[82] or withdrawn.[83,84] The sole exception involved a study in which CBT was no more efficacious in reducing risk than raising medication dosage with patients first brought to remission with fluoxetine.[85] It is possible that both clinical strategies used in that trial were efficacious (hence the tie score), and there are indications that CBT can be used to offset loss of response to medications.[86]

The study by Fava and colleagues[84] is particularly noteworthy in that medication treatment was continued long enough to bring patients to the point of recovery before it was withdrawn; subsequent differences suggested that CBT's enduring effect extends to the prevention of recurrence (i.e., the onset of wholly new episodes). In their study, Fava and colleagues expanded traditional CT to include a focus on positive adaptation (with a new approach called *well-being therapy*); whether that expansion contributed to the treatment's effect remains unclear, but it is an interesting procedural variation on traditional CT.

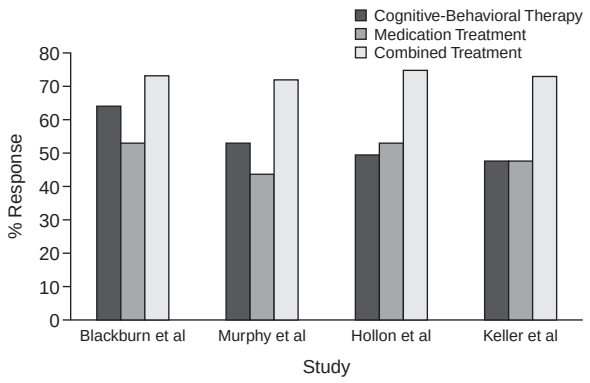
The larger question is how best to manage recurrent depression. As Fava and colleagues[87] describe, medication treatment is efficacious for many patients but does little to reduce subsequent risk once its use is discontinued. Patients with a history of chronic or recurrent depression (and the majority of those with neither) can opt for long-term pharmacotherapy, but they remain at elevated risk for symptom return at whatever point they stop. Patients can opt for lifelong pharmacotherapy, but high compliance is required and side effects are prolonged, and there is always the risk that the medications will lose their effect. Patients can opt for intermittent pharmacotherapy, but if they do, they expose themselves to discontinuation syndromes and a reduced potential for response when medication treatment is reinitiated. To the extent that CBT (or other psychosocial interventions like family therapy) can prevent the onset or return of symptoms, it could provide an alternative way to reduce risk that is relatively free of the problems and complications associated with long-term or intermittent medication treatment.[88]

Medication in combination with CBT. For the last 2 decades, conventional wisdom has held that combining medications and psychotherapy does little to enhance response over either single modality. Early studies typically found no significant advantage for combined treatment over either CBT or medications alone in terms of acute response.[44,47,48] However, few of those trials had sufficient power to detect anything less than large effects. In fact, early meta-analyses found that aggregating outcomes across studies suggested a modest advantage for combined treatment in outpatient samples.[89] More recently, Thase and colleagues[90] conducted a mega-analysis that aggregated data from individual patients across multiple studies involving IPT or CBT alone or in combination with medication. They found a clear advantage for combined treatment with more severely depressed patients. These findings are paralleled by earlier trials that found that adding CBT improved response over standard medication treatment among severely depressed inpatients[91,92] or outpatients referred from psychiatric clinics rather than general practice.[44]

Recent meta-analyses have confirmed the basic finding that combined treatment is associated with a modest increment in overall response and suggested that this increment may be greatest for more chronic and severe patients and may work in part by keeping them in medication treatment.[5,6] Whether these conclusions will extend to less severely depressed patients seen in primary care remains to be seen. One recent study found that adding medications did nothing to enhance the efficacy of a problem-solving approach,[93] whereas a second found that the addition of CBT enhanced the efficacy of "treatment as usual" that included medication.[94]

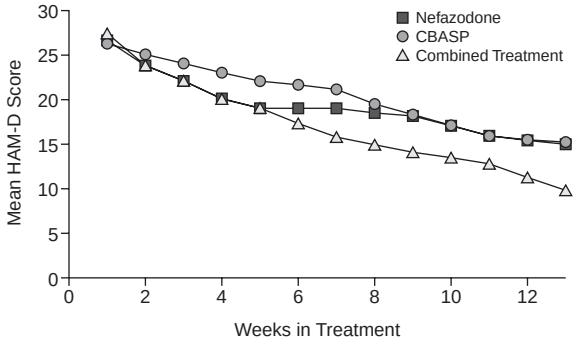
However, it was a recent study by Keller and colleagues[95] that caught the attention of the treatment community with respect to combined treatment. In that study, combined treatment with a novel cognitive-behavioral intervention was found to be considerably more effective than either monotherapy alone among patients with chronic depression with respect to both response and remission. The particular psychotherapy involved, called a *cognitive behavioral-analysis system of psychotherapy* (CBASP), represents an innovative blend of cognitive, behavioral, and interpersonal elements.[96] It remains unclear whether the magnitude of the advantage observed for combined treatment is specific to the kinds of chronic patients studied or the particular modalities involved, but the size of the advantage has sparked renewed interest in combined treatment. Moreover, it is not clear that the findings from the study by Keller and colleagues[95] are

Figure 11. Response to Combined Treatment With Cognitive-Behavioral Therapy and Medications in Adult Outpatients[a]



[a]Data from Blackburn et al.,[44] Murphy et al.,[47] Hollon et al.,[48] and Keller et al.[95]

Figure 12. HAM-D Scores During Combined Treatment of Chronic Depression With CBASP and Nefazodone[a,b]



[a]Reprinted with permission from Keller et al.[95]
[b]Higher HAM-D scores indicate more severe depression.
Abbreviations: CBASP = Cognitive Behavioral-Analysis System of Psychotherapy, HAM-D = Hamilton Rating Scale for Depression.

necessarily all that different from those observed in earlier trials. Figure 11 presents response rates across the relevant combined treatment trials involving CBT. Combined treatment typically improved response relative to either monotherapy. Although the study by Keller and colleagues produced the largest increments found in the literature, the major difference between that study and the earlier comparisons lay in the size of the samples (and hence statistical power to detect differences) rather than in the magnitude of the advantage for combined treatment.

As for IPT, there are indications that any advantage specific to either single modality is retained when the 2 are combined.[5] As previously described, any enduring effect observed for any of the cognitive-behavioral interventions was typically retained when combined with medications, either during acute treatment (Figure 8) or when added in sequence (Figure 10). This principle of complementary benefit also seems to extend to the pace of change; as shown in Figure 12, Keller and colleagues[95] found that patients treated with combined treatment showed both the rapid early response produced by medications and the somewhat delayed response produced by CBASP over the second half of treatment.

This need not always be the case. Barlow and colleagues[97] found that patients treated for panic disorder are more likely to derive an enduring effect from CBT that reduces risk for subsequent relapse if exposed to that modality alone rather than in combination with medications. To date, there is little evidence that the same is true for depression (Figure 8), but it is something about which the field should be vigilant.

Summary and conclusions for CBT. On the whole, it appears that CBT is about as effective as medications (although questions still remain about the most severely depressed patients) and quite possibly more enduring following treatment termination. Furthermore, increasing the duration of CT (by adding a continuation/maintenance phase after acute phase CT or medication) may reduce relapse and recurrence, especially in "high-risk" patients. This enduring effect appears to be robust regardless of whether CBT is provided alone or in combination with medications or whether that combination is applied in a simultaneous or sequential fashion. As was the case for IPT, combined treatment with CBT appears to enhance the probability of response (especially for patients with severe or chronic depressions and most clearly but perhaps not exclusively for CBASP). Moreover, it appears to retain the specific advantages associated with each monotherapy, including the more rapid response associated with medications and the more enduring response produced by CBT.

Behavior Therapy

More purely behavioral interventions have also fared well in direct comparisons with medications, although the studies have been few and typically not placebo-controlled.[24,25] Nonetheless, interest in more behavioral interventions had languished somewhat until the publication of a recent component analysis that suggested that behavioral activation alone accounted for the bulk of the response in a more inclusive cognitive-behavioral intervention.[98] This study gave rise to renewed interest in more purely behavioral interventions that coalesced around a contextual approach to behavioral activation.[99]

Unfortunately, Neil Jacobson, the driving force in this approach, died unexpectedly shortly after initiating a major placebo-controlled trial, and the manual describing his approach (called *behavioral activation* or *BA*) did not appear until after his death.[100] His colleagues have worked to bring the trial he initiated to completion. Although not yet published, the findings indicate that BA holds up well in comparison with both CT and medications.[101] In brief,

what they show is that (1) BA is no less efficacious than either medications or CT (and possibly better than CT for more severely depressed patients), (2) active treatments are superior to pill-placebo but only among more severely depressed patients, and (3) both BA and CT have an enduring effect that is no less effective than keeping patients on medications. It would be premature to make too much of a single as-yet-unpublished study. However, these findings, combined with those from earlier studies described above, suggest that more purely behavioral interventions may produce a range of effects similar in nature and magnitude to those produced by CT and related cognitive-behavioral interventions. To the extent that this is true, it provides additional justification for using the term *CBT* to refer to these approaches in the collective.

The combination of depression and marital discord may provide a prescriptive indication. Marital discord represents a significant risk factor for depression.[102] An early study by McLean and colleagues[103] showed that conjoint behavior therapy reduced depressive symptoms and improved relationship functioning more than a nonspecific treatment, which involved medication, group or individual psychotherapy, or their combination. O'Leary and Beach[104] found that behavioral marital therapy improved the dyadic adjustment of depressed women with marital distress, while CT did not. Jacobson and colleagues[105] studied a sample of depressed women with and without marital distress. For the women with no marital distress, CT reduced depression more than behavioral marital therapy. In the women with marital distress, the 2 treatments produced comparable effects on depression. However, only behavioral marital therapy improved relationship satisfaction in the distressed couples. Since marital distress can increase risk for relapse in depression,[106] the findings that only behavioral marital therapy improved dyadic adjustment have implications not only for acute phase treatment selection, but also for what longer-range effects might be expected. A reasonable hypothesis at this point is that when both relationship distress and depression exist, it may be particularly important to include the spouse or significant other in treatment to produce optimal results. Behavioral marital therapy has yet to be compared or combined with medications.[107]

Traditional Marital and Family Therapy

Although marital and family problems are common and may play a precipitating role in some instances, traditional marital and family therapies have been little studied in the treatment of depression. Friedman[108] found that medications produced greater symptom relief, whereas marital therapy did more to improve the quality of the marital relationship; combined treatment retained the benefits of each. Psychoeducational approaches have shown promise in the treatment of bipolar disorders, but have been little studied in unipolar depression.[109] Clarkin and colleagues[110] found that adding psychoeducational family therapy enhanced response to standard inpatient treatment (including medication) among female patients, but those gains were maintained only by female patients with bipolar disorders, who also showed gains in social functioning. Male patients, particularly those with unipolar disorders, actually did worse in the combined treatment condition than they did in standard treatment. Whether this finding will replicate remains to be seen, but researchers in this area should be alert to the possibility that women with bipolar illness respond better than do men to these psychoeducational treatment programs.

CONCLUSIONS

Both medications and certain time-limited psychotherapies targeted at depression appear to be effective in the treatment of nonpsychotic outpatients. Medication is rapid and robust but does little to reduce risk once it is discontinued. Interpersonal psychotherapy appears to work as well as medications in the reduction of acute distress (albeit somewhat more slowly) and may have a greater breadth of effect on interpersonal skills and social adjustment (although further studies are needed). Cognitive-behavioral therapy also is about as effective as medications in the reduction of acute distress (although questions remain about more severely depressed patients), and it appears to have an enduring effect that reduces subsequent risk even after treatment termination among high-risk patients. As such, it can be used to help patients discontinue medications without increasing risk for subsequent relapse or recurrence. All 3 of these efficacious treatments further reduce risk so long as they are continued or maintained. Combined treatment typically provides at least a modest increment in response (and more for selected populations like patients with severe or chronic depression) and appears to retain any specific advantages associated with each of its constituents. Although few clear prescriptive indices have yet to be identified, clinicians are well advised not to stay too long with an ineffective treatment.

Drug names: fluoxetine (Prozac and others), imipramine (Tofranil and others), phenelzine (Nardil), venlafaxine (Effexor).

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