Combining Drug Therapy and Psychotherapy for Depression

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It was just over a generation ago that the routine combination of psychotherapy and drug therapy seemed impossible. Especially in America, psychiatry was polarized by ideologic and political struggles between psychoanalysis and biologic psychiatry. American psychoanalysts tended to regard psychopharmacology as an inferior treatment that covered over problems rather than addressing them. They assumed that symptoms suppressed by drugs would eventually be replaced by others equally disabling. In turn, proponents of biologic psychiatry often viewed psychoanalysis as a form of quackery that was, at best, a costly waste of time, and, at worst, heightened distress that the psychopharmacologist was trying to ameliorate.

Benefits of combined treatment
In the 1970s, a number of influential studies cut through ideologic assumptions and began to reshape the way we viewed the practice of combining therapy and medications. Klerman and coworkers tested the assumption that psychotherapy and psychopharmacology were essentially in conflict, each undermining the work of the other. There was no evidence that psychopharmacologic treatment led to therapy discontinuation or to symptom substitution or that psychotherapy exacerbated patients' distress. Then, Luborsky and colleagues, in a meta-analysis comparing the effectiveness of different psychodynamic psychotherapies, made an interesting discovery. All therapies were equally effective, with one notable exception: combined treatment with psychotherapy and medication was found to be notably superior to either treatment alone.

Since then, numerous studies have shown combined treatment for depression to have many benefits over single-modality treatment (Table 1). This applies not only to psychodynamic therapy, but also to interpersonal therapy (IPT), a manualized descendent of psychodynamic psychotherapy. The evidence was less clear for cognitive-behavioral therapies (CBT), with several early studies showing only nonsignificant trends toward a benefit of combined treatment. It appears, however, that this may reflect limitations in study design typical of that period. Other studies showed a benefit to combining CBT and pharmacotherapy.

### TABLE 1
Empirically validated benefits of combined treatment

<table>
<thead>
<tr>
<th>Finding</th>
<th>Supporting evidence</th>
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<tbody>
<tr>
<td>Improved short-term recovery rates</td>
<td>Multiple studies</td>
</tr>
<tr>
<td>Faster responses</td>
<td>Bowers, 1990</td>
</tr>
<tr>
<td>Improved long-term recovery rates</td>
<td>Fava et al, 1998</td>
</tr>
<tr>
<td>Decreased rate of relapse</td>
<td>Paykel et al, 1999, Teasdale et al, 2000</td>
</tr>
<tr>
<td>Improved long-term recovery rates</td>
<td>Klerman et al, 1974</td>
</tr>
</tbody>
</table>
social functioning

- Greater patient satisfaction: Seligman, 1995; de Jonghe et al, 2001
- Lower long-term health and social service costs: Browne et al, 2002; Goldman et al, 1998

Does this mean that all patients presenting with depression should be offered treatment with a combination of psychotherapy and medications? In an ideal world with unlimited resources, this might be the case. However, there is the cost/benefit ratio to consider. Though combined treatment is more effective than single-modality treatment, the effect sizes are generally modest. Differences that are statistically significant may not be clinically significant. Given the added strain of providing combined treatment on limited mental health services, it would be far better selectively to provide combined treatment to those patients most likely to show a significant benefit. **Types of patients likely to respond to combined treatment**

Although the evidence base is still rather small, there is some guidance about which patients with depression would most likely have a substantial benefit from combined treatment. Patients with more severe depression, endogenous depression, chronic depression, and dysfunctional cognitions all show more robust and clinically significant responses to combined treatment (Table 2).

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Patients demonstrating a clinically significant response to combined treatments</th>
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<tr>
<td>Patients with severe depression</td>
<td>Bowers, 1990; Miller et al, 1989; Thase et al, 1997</td>
</tr>
<tr>
<td>Patients with endogenous (nonsituational) depression</td>
<td>Prusoff et al, 1980</td>
</tr>
<tr>
<td>Patients with chronic depression</td>
<td>Keller et al, 2000; Hellerstein et al, 2001</td>
</tr>
<tr>
<td>Patients with dysfunctional cognitions</td>
<td>Miller et al, 1990</td>
</tr>
<tr>
<td>Incomplete responders to pharmacotherapy alone</td>
<td>Fava et al, 1994</td>
</tr>
</tbody>
</table>
Incomplete responders to psychotherapy alone

Thase et al, 1997

Inadequate response to single-modality treatment is another reason to consider combined treatment. Patients whose depression has not responded well to antidepressant therapy alone show an increased rate of response when that treatment is paired with psychotherapy. Similarly, nonresponders to psychotherapy receive added benefit when antidepressants are added. It is worth noting that these categories of patients are the ones that typically are receiving treatment from psychiatrists. With the majority of antidepressants prescribed by nonpsychiatrists, psychiatrists typically see patients with more severe, chronic, and treatment-resistant conditions and those patients whose treatments are complicated by dysfunctional attitudes and maladaptive personality styles. Consequently, most patients receiving referral for specialized psychiatric treatment would be appropriately treated with combined treatment with psychotherapy and medications.

Combined treatment produces not only faster and greater short-term benefits, but greater long-term benefits as well. Patients receiving combined treatment with CBT have a lower relapse rate than do patients receiving medications alone. Patients who received IPT and drugs had better long-term social adjustment than patients on drugs alone. For patients older than 60 years, the combination of IPT and medication has been shown to reduce the rate of depressive relapse. In addition, compared with pharmacotherapy alone, combined medication and group therapy seems to reduce relapse after discontinuation of treatment.

What makes combined treatment better? We still do not know much about what accounts for the superiority of combined treatment. Some benefit may accrue simply from additive effects. Each treatment is effective in its own right; thus, adding the effectiveness of each provides a cumulative effect. Additive effects may result from the fact that therapy and medications converge on the problem of depression from 2 different angles, perhaps even literally. Functional neuroimaging of the differential effects of psychotherapy and antidepressant medications suggests that, while both treatments show considerable overlap in effects on cerebral metabolism, medication effects develop "bottom up," emanating from the brain stem upward, while psychotherapy effects emerge in a "top down" fashion, spreading downward from the frontal cortex. The 2 modalities may exert an additive effect by addressing different symptom domains. Therapy, for example, might address the hopelessness related to depression, while medications more directly address neurovegetative aspects of depression.

There may also be interactive effects that contribute to the increased efficacy of combined treatment. Pharmacotherapy may, for example, make some patients more available for therapy by easing treatment-interfering problems such as psychosis, disabling anxiety, or the amotivational syndrome of depression. Recent evidence suggests that there may also be some more directly biologic interactive effects. One of the neurobiologic effects of antidepressant use appears to be an increase in neural turnover, with increased sprouting and trimming of dendritic synapses. This intriguing research suggests that antidepressants may make for more plastic neural networks, which may, in turn, allow for more rapid learning, as in psychotherapy.

Psychotherapy may also enhance the effectiveness of medication. One way in which this may occur is through improved compliance. Several studies have demonstrated that patients receiving psychotherapy concurrently with medications have a lower rate of pharmacologic treatment discontinuation. Concurrent treatment may also improve the therapeutic alliance and enhance patient satisfaction with treatment. The therapeutic alliance, in turn, has a profound effect on antidepressant efficacy. Additionally, the psychosomatically preoccupied patient prone to negative medication reactions may benefit from attention to psychological origins of somatic reactions.

Combining and integrating treatments

How does one go about combining treatments? Some of the more robust findings in favor of combined treatment have been associated with structured and highly integrated forms of care, such as IPT or the cognitive behavioral analysis system of psychotherapy (CBASP). It seems likely that treatment integration is related to outcome. A treatment in which the psychopharmacologist and psychotherapist are openly skeptical of each other's work and are working at cross-purposes is not
likely to be successful. When there is a split treatment arrangement, with one person providing psychotherapy and another providing psychopharmacology, good communication between treaters and the sharing of overall treatment goals may enhance treatment. Treatments in which the pharmacologic work is seen to support the therapy and the therapy supports the drug treatment may be the most integrated, as with the model of psychodynamic psychopharmacology developed by Mintz and Belnap, which is tailored for work with treatment-resistant patients. In this model, pharmacologic treatment is aimed primarily at supporting the capacity of the patient to usefully engage in psychotherapy. The therapist then feels a direct connection to the medications and sees problems with medication (eg, noncompliance, fear of dependency, a tendency to develop side effects) as targets for therapeutic exploration. The psychotherapy then explicitly supports the patient’s healthy use of medication. The same kind of integrative approach could be undertaken with CBT and medication.

It is not clear at this point whether a single-provider model enhances treatment integration and outcome. To date, there are no published studies that address this issue. In the absence of evidence that single-provider treatments are superior, the economics of health care have tended to promote the delivery of split treatments under the assumption that it would be less costly to have psychotherapy provided by a lower-paid, nonmedical therapist than by the prescribing psychiatrist. In contrast to this assumption, 2 studies using different methodologies, have examined the question of which treatment (single-provider or split) was more costly. Both studies found single-provider combined treatment to be less costly than split treatments with a psychiatrist/pharmacologist and a nonmedical therapist. While it is not yet clear whether single-provider treatment is more clinically effective than split treatment, the evidence suggests that it is more cost-effective. While combined treatment has been shown to be generally more effective than single-modality treatments and substantially more effective for certain kinds of patients, there is still much work that needs to be done to establish whether there are other subpopulations of patients with depression who would benefit from combined treatment. There is also still much to learn about the specific factors (eg, treatment integration) that contribute to the greater treatment effectiveness of combined treatment.

Dr Mintz is director of residency training and continuing medical education at the Austen Riggs Center in Stockbridge, Mass. He reports no conflicts of interest concerning the subject matter of this article.

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