

Integrating Psychotherapy and Pharmacotherapy to Improve Outcomes Among Patients With Mood Disorders

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A number of studies have demonstrated comparable benefits of psychosocial interventions and pharmacologic treatments in subgroups of patients with mood disorders. The two treatment modalities are often combined in clinical practice. However, concerns about the costs of health care are paramount. For the optimum but judicious use of resources, it is valuable for mental health professionals to know the indications for and evidence pertaining to the efficacy of combined treatment. The authors demonstrate that a reexamination of existing research data in light of the recent advances in understanding of the design of clinical trials reveals a systematic underestimation of the benefits of combined treatment for certain subgroups of patients. Existing studies of combined treatments need to be reexamined in light of information about design sensitivity, ceiling effects, and nonspecific placebo effects. The authors summarize by arguing for a new generation of adequately powered investigations of efficacy, which they believe is necessary before the issue of cost-effectiveness can be properly addressed. (*Psychiatric Services* 54:1484–1490, 2003)

During the past three decades, treatment standards and practices for mood disorders have undergone enormous changes. As a result of rapid increases in the quality and quantity of empirical data, newer forms of treatment have come into use while others have fallen out of favor. A number of studies have demonstrated comparable benefits for psychosocial interventions and pharmacologic treatments in subgroups of patients. However, with only a few exceptions, these “horse races” did not have the statistical power to detect modest—but still clinically meaningful—differences between treatments, and relatively few studies have examined the treat-

ments factorially—that is, singly and in combination.

In our quest to provide the best possible symptom relief to our patients in the quickest possible time, it makes intuitive sense to combine both treatment modalities. Moreover, combined treatments generally receive high marks from consumers (1) and have been recommended by expert consensus panels that reviewed therapeutics for depression (2,3). However, at the beginning of the 21st century, concerns about the costs of health care are paramount, and routinely providing combined treatment to everyone seeking care would likely overwhelm the capacities of existing health services. Therefore, for the op-

timum but judicious use of resources, it is valuable for mental health professionals to know the indications for and evidence pertaining to the efficacy of combined treatment.

A philosophic switch to evidence-based medicine conveys the need to look for convincing evidence that combined treatment is superior before that approach can be recommended. In some areas, the current weight of empirical evidence does not clearly establish the superiority of combination treatments. Before it can be assumed that these studies have established a lack of additive value of combined treatments—as opposed to trials that resulted in false-negative results—there is a need to evaluate the research methods used in these studies. As we demonstrate in this article, a reexamination of research in light of the recent advances in understanding of clinical trial design reveals a systematic underestimation of the benefits of combined treatment for certain subgroups of patients. We summarize by arguing for a new generation of adequately powered investigations of efficacy, which is necessary before the issue of cost-effectiveness can be properly addressed.

The rationale for combined psychotherapy and pharmacotherapy

Although combined treatment approaches have found acceptance from a large proportion of mental health professionals, concerns persist that alleviation of symptoms with medication in the absence of the necessary lifestyle changes is a “bandage” rather than a sustainable “cure” (4–6). How-

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ever, with time, pharmacotherapy began to be viewed more favorably as a way of hastening recovery and helping patients make better use of psychotherapy (5). Clinical trials of combined treatments were not showing any evidence of a negative effect of combining treatment modalities as had been feared by some (7). Moreover, awareness was increasing of the limitations of psychotherapy as the only treatment. For example, it was becoming clear that psychotherapy alone would be ineffective for mania and depression with psychotic features. The paradigm shift was also aided by the availability of better tolerated medications.

Evidence simultaneously accumulated to show that pharmacotherapy alone was insufficient in many cases. Despite effective treatment with medication, patients continued to have interpersonal difficulties, vocational impairment, and poor problem-solving skills. Compared with medication alone, combined treatments were also expected to convey additional benefits over time by reducing demoralization, improving methods of coping with adverse life events, and increasing adherence to medication regimens.

Use of statistics to detect additive effects

Nevertheless, the primary rationale for combining treatments is to obtain truly additive effects. Theoretically, a synergistic interaction between the treatments used in a combination—for example, $.4 + .3 = .9$ —is possible. Unfortunately, such synergy has not been evident in studies of combined treatment for mood disorders (8). In fact, the greatest effect size ever observed in favor of combined treatment was rather modest: $.5 + .5 = .8$ (9).

One of the reasons for “incomplete summation” of additive effects is the progressive loss of measurement sensitivity as improvements in symptoms evolve over time—the so-called ceiling effect. This ceiling might be raised if indicators of wellness—for example, endurance, equanimity, levity, composure, flexibility, reciprocity, creativity, and patience—were added to measures of symptom severity to assess outcomes. Reliable measure-

Editor's Note: This issue of *Psychiatric Services* is distributed free to all attendees at the Institute on Psychiatric Services, the annual fall meeting of the American Psychiatric Association. The theme of the 2003 institute is “Access to Integrated Mental Health Care.” We asked three groups of authors to provide overviews of current integrated treatment approaches for a special section in this issue of the journal. In the first article, Ripu D. Jindal, M.D., and Michael E. Thase, M.D., examine integrated treatment of affective disorders. In the second article, Alex Kopelowicz, M.D., and Robert Paul Liberman, M.D., review integrated approaches to psychosocial rehabilitation. In the third article, Roshel Lenroot, M.D., and colleagues describe integrated care for persons with schizophrenia. We have also included in this section a recently accepted submission from Kyle L. Grazier, Ph.D., and associates that describes a unique collaboration among diverse stakeholders in a Wisconsin county to provide integrated care to Medicaid, low-income, and indigent consumers.

ment of such indicators of “above-average” functioning remains a challenge for researchers who are interested in measuring quality of life.

The ceiling effect also results from the fact that a fair proportion of patients with treatment-resistant illness are included in any clinical trial. For example, among approximately 10 to 20 percent of participants in depression studies, depression proves to be refractory to multiple courses of treatment (10). High symptom scores among these nonresponders not only increase the mean scores on key outcome measures but also inflate the standard deviations of the outcome measures. Specifically, the standard deviations of measures such as the Hamilton (11), Beck (12), and Young rating scales (13) typically double across an eight-week randomized controlled trial.

Given that effect size is based on the difference between treatments by the standard deviation on that dependent measure, the sensitivity for detecting small to moderate differences in symptom ratings is reduced. This problem is amplified when the last-observation-carried-forward (LOCF) method is used to impute the outcomes of patients who drop out of the study (14). Although an intent-to-treat approach to data analysis is preferred, the assumption that those who drop out have the same high scores across multiple time points further distorts the variance structure of a longitudinal data set.

A second factor that adversely affects design sensitivity is the so-called placebo effect. The placebo effect encompasses spontaneous remission (the probability of improvement within a fixed period without any intervention), reactivity to repeated measurement, and the beneficial effects of a helping, professional relationship (15). In contemporary randomized controlled trials of antidepressant medications, placebo effects consistently account for between 60 and 80 percent of the response to pharmacotherapy (15–17). In all likelihood, such nonspecific effects similarly account for a large amount of the action of the depression-focused psychotherapies (18,19). For example, in one randomized controlled trial, a measure of the strength of the helping alliance was as predictive of success with pharmacotherapy, either with imipramine or placebo, as it was of success with cognitive and interpersonal psychotherapies (20). It therefore is important to keep in mind that when two treatments are combined it is likely that there is a common placebo-response component that is not additive.

Existing studies of combined treatments need to be reexamined in light of this information about design sensitivity, ceiling effects, and nonspecific placebo effects. When these considerations are taken into account, it becomes clear that the study by Keller and colleagues (9), cited above as an example of incomplete summation,

found additive or even synergistic effects. On the basis of previous studies (21,22), at least 30 percent of the patients in the study would have responded to a credible placebo-expectancy intervention. With the active components of pharmacotherapy and psychotherapy each delivering about a 20 percent "specific" response rate (50 percent total response rate minus 30 percent placebo-expectancy rate, an additive effect of 70 percent would be expected (30 percent plus 20 percent plus 20 percent). In fact, the investigators observed a 72 percent intent-to-treat response rate in the group that received combined therapy.

Once it has been recognized that the specific effects of antidepressant interventions are small, it is imperative to pay close attention to the concept of statistical power. At least 250 patients need to be enrolled in each study group to provide 80 percent power to detect a 15 percent difference in response rates (23). If an even more modest difference of 10 percent is anticipated, at least 500 patients will be needed in each group (24).

Practical issues in integrating treatment

Combined treatment is provided in two different models: the single-provider model (for example, a psychiatrist or selected nurse practitioners), and a split-treatment model, in which a psychotherapist collaborates with a primary care physician or a psychiatrist. We are not aware of any controlled studies that have established the superiority of one approach over the other. Proponents of an integrated model contend that a single provider is more likely to impart clear, nonconflicting information about the treatment plan than a pair of providers, and they highlight the possibility of splitting of communication. However, the evidence supporting disruption of care as a result of splitting of communication is purely anecdotal.

Most community mental health centers and managed care organizations favor a split-treatment model as a way of reducing costs. In base terms, the hourly fee of a psychiatrist is higher than that of other mental health providers. Whether split care does in fact reduce costs is still open

to some debate. Compared with non-medical therapists, psychiatrists tend to treat patients who are more severely ill (25), and, after case complexity is controlled for, the presumed cost differential disappears (26). In fact, Dewan (27), demonstrated that integrated care by a psychiatrist was somewhat less costly than split treatment in analysis of an insurance database.

Nevertheless, even if an integrated model proved to be both superior in efficacy and no more costly, there are simply not enough psychiatrists to treat all the patients who might benefit from combined therapy. Service use data reveal that psychiatrists provide no more than 10 percent of psychotherapy and only about 35 percent of the pharmacotherapy provided to patients with mental disorders in the United States (25,28). These percentages may be even lower for patients with depressive disorders.

Another way of reducing costs is to have a primary care physician handle the prescribing. To our knowledge, no randomized comparative studies have been conducted of the outcomes of pharmacotherapy by psychiatrists and by primary care physicians. In one study, pharmacotherapy provided by psychiatrists was markedly more effective than pharmacotherapy provided by primary care physicians (29). However, the patients were not randomly assigned to the two treatment settings. In two other studies, the outcomes of treatment as usual provided by primary care physicians were poor (30,31). However, in the latter study, advanced training and the use of a carefully outlined pharmacotherapy protocol greatly improved the outcomes of patients who were treated by primary care physicians. Even in the absence of sufficient controlled data, it seems reasonable to say that patients with a complex mood disorder—for example, comorbid agoraphobia, posttraumatic stress disorder, and substance abuse—would be better served through combined treatment provided by a psychiatrist.

Research findings

Major depressive disorder

Controlled clinical studies show that 40 to 70 percent of patients with major depressive disorder (nonpsychotic

nonmelancholic subtype) obtain a satisfactory response with either an antidepressant or one of the newer procedurally specified psychotherapies, such as cognitive-behavioral therapy or interpersonal therapy alone. Such success rates are clearly higher than the spontaneous remission rates observed in control groups of patients on waiting lists and surpass the gains observed in placebo groups or in pseudotherapy attentional control groups about 50 percent of the time. There is a paucity of data on more eclectic psychotherapies, and evidence gathered from randomized controlled trials of well-specified therapies may or may not be applicable.

Meta-analyses of early randomized controlled trials among outpatients with depression have shown relatively small additive effect sizes (3,32). Most of the early studies that used cognitive or behavioral therapies did not detect a statistically significant additive benefit of combined treatment (33–36). However, as noted above, interpretation based on these studies must be tempered by concerns about research methods and design sensitivity. More recently, a pooled analysis of nearly 600 outpatients with depression (37) revealed that a combination of pharmacotherapy and interpersonal therapy was associated with remission rates that were about 15 percent higher than those associated with psychotherapy alone among patients with milder major depressive episodes. Although this is a modest effect, it would nevertheless have significant public health implications. Moreover, combined treatment was associated with a more substantial additive effect in a subgroup of patients with severe, recurrent depressive episodes. The major shortcoming of the study was the absence of a group that received pharmacotherapy alone.

In perhaps the most influential early study, DiMascio and colleagues (38) studied outcomes with interpersonal therapy and amitriptyline, singly and in combination, compared with a low-contact control condition ("treatment on demand"). In terms of symptom measures, the two component monotherapies were superior to the control condition, and the combination was superior to monotherapies.

Results of a secondary analysis of the same data (39) suggested that the three active treatment groups were comparably effective for the subgroup of patients who met research diagnostic criteria (40) for situational, nonendogenous major depressive disorder. By contrast, combined treatment was superior to both monotherapies among the patients with nonsituational, endogenous depression. These findings essentially mirror those observed in the pooled analysis referred to above (37). Thus it appears that a severity (endogenous) grouping can be used to select patients for whom combined treatment is likely to be more cost-effective than either pharmacotherapy or psychotherapy alone.

In another recent randomized study of outpatients with major depression, combined treatment was found to be more acceptable to patients and was associated with a significantly lower dropout rate and a significantly higher remission rate than medication alone (41). The study used short-term psychodynamic supportive psychotherapy and a three-step successive medication regimen—fluoxetine, amitriptyline, and moclobemide, in that order, depending on intolerability or inefficacy—as pharmacotherapy.

Two small studies of hospitalized patients with depression produced evidence favoring a combined strategy over medication management (42,43). In a secondary analysis, Miller and colleagues (44) observed a particularly large additive effect for combined treatment among patients with high levels of dysfunctional attitudes. Because patients with this pattern of negative thinking also tend to respond less favorably to cognitive-behavioral therapy alone (45), one would presume that the advantage of combined treatment over psychotherapy alone would be evident. Although the data from controlled trials are sparse, it appears that the combination of cognitive-behavioral therapy and pharmacotherapy may be especially useful for patients with depression during and after an acute psychiatric hospitalization.

Three randomized controlled trials have been published of combined

treatment among chronically depressed outpatients. Ravindran and colleagues (21) found no additive benefit of a combination of group cognitive-behavioral therapy and sertraline in a study of 97 outpatients with dysthymia. The group cognitive-behavioral therapy was no more effective than placebo, which calls into question the efficacy of the psychosocial intervention.

Browne and associates (46) conducted a randomized controlled trial among 707 patients with chronic depression who were randomly assigned to one of three treatment groups: interpersonal therapy alone, sertraline therapy alone, and a combination of sertraline and interpersonal therapy. Although all treatment modalities proved to be reasonably effective over a two-year period, sertraline alone or in combination was more effective than interpersonal therapy alone. The major finding in support of combined treatment was that patients had lower overall health and social service costs than patients receiving monotherapies.

In a multicenter trial of more than 650 patients with chronic depression (9), combined treatment was associated with substantially better response and remission rates than both monotherapies, which had virtually identical outcomes. The study used the cognitive-behavioral analysis system of psychotherapy, an individual therapy specifically developed for the treatment of chronic depression (47), as the psychotherapeutic intervention and nefazodone as pharmacotherapy.

The longer term effects of combined treatment have been documented in three studies. In the first study of continuation therapy, Klerman and colleagues (48) did not detect significant benefits of combined treatment over pharmacotherapy alone in preventing relapses. However, there was a later emerging trend of a higher level of social adjustment in a subgroup of patients who received individual psychotherapy. Moreover, the study may have underestimated the benefit of the psychotherapeutic intervention, because all the patients had responded to amitriptyline before they began psychotherapy. (The study group was preselected for re-

sponsiveness to pharmacotherapy, not psychotherapy.)

Two more recent studies have evaluated the efficacy of combined treatment in the maintenance phase of recurrent depression. In both these studies, all patients received combined treatment during the acute and continuation phases. In the first study (49), which involved 125 outpatients with highly recurrent major depression who were between the ages of 19 and 65 years, combined maintenance phase treatment—interpersonal therapy sessions plus imipramine—was not associated with better prophylaxis than imipramine alone during a 36-month blinded maintenance phase.

In the second study, 107 depressed outpatients aged 60 or older who had stabilized during the acute and continuation phases of treatment with nortriptyline and interpersonal therapy participated in a double-blind, placebo-controlled maintenance-phase study (50). The patients who continued to receive combination treatment were less likely to have a recurrence than were those in either of the monotherapy conditions. Interestingly, the outcome of pharmacotherapy alone in that study was less robust than the results of Frank and colleagues (49), which probably points to the relatively greater advantage of combined therapy when patients have higher inherent risk of recurrent depression.

Sequential treatment strategies have also been investigated. In one study, a three-month course of cognitive-behavioral therapy among 40 patients who had responded to pharmacotherapy but whose illness was not in remission was shown to have additive effects on residual depressive symptoms (51). In follow-up reports, the group that received cognitive-behavioral therapy had a significantly better chance of discontinuing medication without relapse (52) as well as a sustained decrease in the risk of recurrence (53). Paykel and colleagues (54) replicated these findings in a larger two-center study of 158 patients with incomplete remission who were taking antidepressants. The patients received 18 sessions of individual cognitive-behavioral therapy. The group that received cognitive-beh-

ioral therapy in addition to pharmacotherapy had about a 50 percent reduction in relapse risk.

A third study investigated the efficacy of sequential cognitive-behavioral therapy treatment during the maintenance phase (55). In that study, 40 patients whose illness was in full remission and who had a history of highly recurrent depression were randomly assigned to receive either 14 sessions of cognitive-behavioral therapy or supportive medication management during withdrawal of antidepressant pharmacotherapy. Again, the addition of cognitive-behavioral therapy was associated with a significantly reduced risk of recurrence over the next two years.

Bipolar disorder

There is a broad consensus that mania should not be treated with psychotherapy alone (56). Specifically, the efficacy of several types of pharmacotherapy has been established for mania, whereas there is virtually no evidence that psychotherapy alone is effective. An exception may be made if a manic patient refuses pharmacotherapy. Even then, the ability of a manic individual to make informed treatment choices is always worrisome. In such cases, involuntary treatment, guardianship procedures, and mental health advance directives—depending on the jurisdiction—are some of the options.

Some of the information discussed in another paper in this issue of *Psychiatric Services* (57), about combined treatment for schizophrenia, could also be relevant to mania. Perhaps surprisingly, combined treatments for mania have received much less systematic inquiry than have those for schizophrenia, possibly because the therapeutic benefits of pharmacotherapy were overvalued until the early 1990s (58). Eventually, it became clear that bipolar disorder is more often than not a recurrent and life-disrupting severe mental illness associated with profound morbidity and elevated mortality (59). Furthermore, evidence of the effects of psychosocial factors such as stressful life events (60), high levels of expressed emotion (61), marital discord (62), and social support (63) on relapse rates among

patients with mania led to the studies of various modalities of psychosocial interventions in relapse prevention.

In the first large study of combined treatment, Perry and associates (64) evaluated a brief individual psychoeducation intervention (average duration of seven sessions). Apart from the information about the disorder and its treatment, patients were informed of the early warning signs of impending relapse and were provided assistance in developing relapse prevention plans. Compared with treatment as usual, the additional psychoeducational sessions were associated with significantly lower rates of relapses of manic episodes.

The second study (65) evaluated a longer term model of family-focused therapy provided soon after discharge from inpatient treatment. All participants received pharmacotherapy as part of the study and were randomly assigned to receive either clinical management (N=70) or 21 sessions of family-focused therapy over a nine-month period (N=31). A preliminary report on the outcomes of nine patients who received family-focused therapy yielded promising results—one relapse, or 11 percent, compared with 14 relapses in a historical control group of 23, or 61 percent.

Results of the prospective study confirmed the benefit of family-focused therapy over the comparison condition for the first year, in terms of both fewer depressive relapses and lower levels of depressive symptoms. No significant association with risk of manic relapse was found. Adherence to medication regimens and reduced levels of expressed emotion were associated with outcome independent of treatment assignment. Thus, it seems that improved outcome with family-focused therapy was not mediated by medication adherence or lower levels of expressed emotion. However, the advantage of family-focused therapy was most pronounced among patients who lived in households with high levels of expressed emotions, particularly if the patient had not fully recovered from the index episode.

The third study examined a modified form of interpersonal therapy, adapted to help patients develop more stable social rhythms, known as

interpersonal social rhythms therapy (IPSRT) (66). All patients received appropriate pharmacotherapy for their index episodes. In addition, the study used a 2 × 2 sequential design for psychosocial intervention; half the patients received IPSRT for acute-phase management, and the other half received clinical management. During the maintenance phase of the study, half the patients in remission in each group continued to undergo the same treatment strategy, and half switched treatment strategies—that is, from IPSRT to clinical management or vice versa. As expected, IPSRT was not significantly associated with enhancement of patients' lifestyle regularity (67). Moreover, the patients who received maintenance IPSRT experienced a significant reduction in depressive symptoms and an increase in the number of euthymic days (68). However, IPSRT was not associated with improvement in acute-phase treatment outcomes or time to remission (69,70). Furthermore, discontinuation of acute-phase IPSRT was associated with an increase in risk of relapse, whereas the addition of maintenance IPSRT was not associated with a lower risk of relapse (71).

Individual and group cognitive therapy also are being investigated as adjunctive treatments for bipolar disorder (72,73). Although results of controlled studies are pending, the results of preliminary studies suggest that these modalities have antidepressant effects (74) and are likely to lower the risk of relapse among patients with mania (75–77).

Taken together, the results of these studies provide support for the addition of focused psychosocial treatment for patients receiving pharmacotherapy for bipolar disorder. Family-focused and interpersonal therapeutic interventions appear to help with depressive symptoms. Psychoeducation and relapse prevention training may even reduce the risk of manic relapse.

Conclusions

Sufficient evidence now exists that focused psychosocial interventions have significant benefit when combined with pharmacotherapy for some pa-

tients. The added benefit of combined treatment is best established for severe, recurrent, and chronic major depressive disorder and bipolar affective disorder. It is possible that the added benefits of psychotherapy are nonspecific—for example, mediated by low levels of expressed emotion in a household or improved medication adherence. It remains to be seen whether there are also therapy-specific outcomes.

Little evidence exists that combined psychotherapy and pharmacotherapy should be considered a routine standard of care for less pervasive or milder depression. On the basis of this evidence—or lack thereof—it seems reasonable that patients with these forms of depression should receive one of the monotherapies first, based on availability and patient preference, and the alternative strategy considered in sequence or in combination for patients who are less responsive to treatment.

Resolution of several issues calls for future research. One such issue is determination of whether combined treatment by a single provider offers additional advantages. Another is replication of findings from specialty research clinics to everyday practice settings. Treatments that convey only benefit when provided by highly skilled expert therapists in tertiary care settings may not be the same as the ones provided to patients who are treated in busy urban clinics or community mental health centers. Much work remains to be done before we can truly make informed choices. ♦

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