

# Psychotherapy Versus Medication for Depression: Challenging the Conventional Wisdom With Data

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**Abstract.** *Antidepressant medications are the most popular treatment for unipolar depression in the United States, although there may be safer alternatives that are equally or more effective. This article reviews a wide range of well-controlled studies comparing psychological and pharmacological treatments for depression. The evidence suggests that the psychological interventions, particularly cognitive—behavioral therapy, are at least as effective as medication in the treatment of depression, even if severe. These conclusions hold for both vegetative and social adjustment symptoms, especially when patient-rated measures are used and long-term follow-up is considered. Some aspirational guidelines for the treatment of depression are proposed.*

The prevalence of unipolar depression is estimated to be between 3% and 13%, with as much as 20% of the adult population experiencing at least some depressive symptoms at any given time (Amenson & Lewinsohn, 1981; Kessler et al., 1994; Oliver & Simmons, 1985). The lifetime incidence of depression is estimated to be between 20% and 55%. Women are consistently found to have rates of depression twice as high as those of men. Somewhere between 9% and 18% of all depressions are the result of an underlying medical condition, suggesting that a physical examination is important in the comprehensive treatment of depression (Hall, Popkin, Devaul, Fallaice, & Stickney, 1978; Koranyi, 1979). However, the vast majority of depressions are not attributable to identifiable medical causes. Other data (Gatz, Pedersen, Plomin, Nesselroade, & McClearn, 1992) suggest that genetic influences account for only 16% of the variance in total depression scores and that life experiences are the most statistically important influence on self-reported depressive symptoms. Genetic influences on major depression, dysthymia, and depressive adjustment disorder appear to be weak and

cannot account for the increases in depression for age cohorts born after World War II (Blehar, Weissman, Gershon, & Hirschfeld, 1988). Despite these data, depression is conventionally viewed as a "medical illness," and drugs are the most commonly delivered treatment for depression in the United States (Narrow, Regier, Rae, Manderscheid, & Locke, 1993).

In stark contrast to the illness model, several psychotherapy models have evolved that use specific nondrug strategies to help alleviate depressive symptoms (Antonuccio, Ward, & Tearnan, 1989). These effective nondrug strategies are often ignored by medical practitioners (Altrocchi, Antonuccio, & Miller, 1986). While not denying that medications have helped many depressed patients, this article addresses the relative effectiveness of drugs and psychotherapy by examining studies that have compared these treatments for nonpsychotic unipolar depression.

## **Cognitive—Behavioral Therapy Versus Antidepressant Medication**

Much of the comparative efficacy research on depression has involved cognitive—behavioral psychotherapy, a subtype of the broader group of psychotherapies. Cognitive—behavioral interventions, or behavior therapies, are active (i.e., skills are taught) and directive (e.g., homework is assigned), have specific achievable goals, and help provide a new perspective for the patient (Stravynski & Greenberg, 1992). Cognitive—behavioral therapies may be broadly classified as pleasant activity therapy, cognitive therapy, and social skills therapy. In the sections to follow, one key comparative study from each subtype of cognitive—behavioral therapy is described, and a listing of other relevant studies is provided.

### ***Pleasant Activity Therapy***

A classic behavioral model of depression (e.g., Lewinsohn, Youngren, & Grosscup, 1979) postulates that depression can result from a stressor that disrupts normal behavior patterns, causing a low rate of response-contingent positive reinforcement. The rate of reinforcement is functionally related to the availability of reinforcing events, personal skills to act on the environment, or the impact of certain types of events. If an individual cannot reverse the negative balance of reinforcement, a heightened state of self-awareness will follow that can lead to self-criticism and behavioral withdrawal (Lewinsohn, Hoberman, Teri, & Hautzinger, 1985). This model also suggests that there may be a negative feedback loop of social reinforcement for depressive behaviors when family members and social networks are mobilized to provide support for the depressed individual. The resulting behavioral psychotherapy involves helping patients increase their frequency and quality of pleasant activities. It has been found that depressed patients have low rates of pleasant activities and obtained pleasure, their mood covaries with rates of pleasant and aversive activities, their mood improves with increases in pleasant activities, and they lack social skills, at least during the depressed phase, which contributes to the depression (Lewinsohn, Sullivan, & Grosscup, 1980).

We are unaware of any published controlled studies that have directly compared pleasant activities treatment with antidepressant medication. However, Wilson (1982) randomly assigned 97 depressed patients to one of three psychological therapies (Lewinsohn's pleasant activity therapy, relaxation therapy, or minimal contact) combined with amitriptyline (150 mg/day) or placebo for a 2-month period. Amitriptyline, a member of the most heavily studied class of tricyclic antidepressants, is theorized to help

alleviate depression by enhancing the availability of neurotransmitters considered to be responsible for normal mood. A total of 64 patients completed treatment, and there was no differential attrition. Significant improvement was noted on most measures for all of the treatments at termination, and these results were maintained at 6-month follow-up. Pleasant activity therapy plus placebo was shown to be just as effective as pleasant activity therapy plus amitriptyline on patient-rated measures of outcome. At midtreatment, pleasant activity therapy resulted in better outcomes than minimal contact. Other studies suggest that similar behavioral interventions are as effective as combined treatment (Stravynski et al., 1994) or add to the efficacy of standard drug treatment with drug-refractory depression (Antonuccio et al., 1984). One study (Roth, Bielski, Jones, Parker, & Osborn, 1982) suggests that adding antidepressant medication to such a behavioral intervention may speed up recovery somewhat, but the outcomes are equivalent at treatment termination.

### ***Cognitive Therapy***

Another approach to treating depression involves addressing the cognitions that mediate the impact of events in patients' lives (e.g., Beck, Rush, Shaw, & Emery, 1979; Beck & Young, 1985). The proponents of this approach assert that it is not necessarily what happens to depressed persons that causes them to be depressed, but rather, what they tell themselves about what happens. Some examples of common thinking patterns that can lead to depression include overgeneralized thinking, perfectionistic thinking, and the tendency to catastrophize. One well-controlled study (Murphy, Simons, Wetzel, & Lustman, 1984) randomly assigned 87 moderately to severely depressed psychiatric outpatients to 12 weeks of cognitive therapy, nortriptyline (a tricyclic antidepressant), cognitive therapy plus nortriptyline, or cognitive therapy plus active placebo. The placebo was designed to have mild sedative and anticholinergic effects to simulate actual medication. The therapists in this study were three psychologists and nine psychiatrists. Although the 70 patients who completed treatment showed significant improvement on the patient-rated Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the clinician-rated Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), the treatment conditions were not differentially effective at treatment termination or at 1-month follow-up. Inclusion of dropout patients' end-point scores did not affect these results. Thus, cognitive therapy alone was as effective as nortriptyline, and there was no additive effect of the combined treatments. Notably, the investigators drew venous blood samples every other week to ensure that plasma nortriptyline levels were in the therapeutic target window of 50-150 ng/ml.

The recovered patients ( $n = 44$ ) from Murphy et al. (1984) were followed for 1 year after treatment termination (Simons, Murphy, Levine, & Wetzel, 1986). Patients who had received cognitive therapy, whether or not they had also received nortriptyline, were less likely to relapse. Patients who had received nortriptyline, whether or not they had also received cognitive therapy, were more likely to relapse. These results suggested that medication treatment not only seemed to make relapse more likely but actually may have interfered with the long-term efficacy of cognitive therapy.

Many other studies have shown cognitive therapy to be more effective than antidepressant medication (Blackburn, Bishop, Glen, Whalley, & Christie, 1981; Evans et al., 1992; Kovacs, Rush, Beck, & Hollon, 1981; Rush, Beck, Kovacs, & Hollon, 1977; Rush, Beck, Kovacs, Weissenburger, & Hollon, 1982). Other studies have shown cognitive therapy to be as effective as antidepressant medication (Hollon et al., 1992) or

combined cognitive-drug treatment (Beck, Hollon, Young, Bedrosian, & Budenz, 1985; Blackburn et al., 1981; Covi & Lipman, 1987; Evans et al., 1992; Hollon et al., 1992). Yet other studies suggest that cognitive therapy adds to the efficacy of standard antidepressant drug treatment (Bowers, 1990; Dunn, 1979; Miller, Norman, Keitner, Bishop, & Dow, 1989; Teasdale, Fennell, Hibbert, & Amies, 1984).

### **Social Skills**

A third cognitive—behavioral approach to treating depression involves addressing social interaction problems experienced by the patient. Very often, depressed patients experience dissatisfaction with family, job, and social relationships (Libet & Lewinsohn, 1973). Depression may result because individuals lack the prerequisite social skills necessary for obtaining a maximum of positive reinforcement and reducing punishment. Depressed individuals often have negative self-perceptions of their social competence and have a negative impact on those around them (Coyne, 1976). Behavioral skill deficits include a tendency to be less assertive and less positive, to have negative facial expressions and poor eye contact, and to display less activity in group interactions (Youngren & Lewinsohn, 1980).

McLean and Hakstian (1979) treated 178 depressed outpatients with 10 weeks of insight-oriented dynamic psychotherapy, behavior therapy emphasizing social skills training, the tricyclic antidepressant amitriptyline (150 mg/day), or a relaxation control condition. All patients met diagnostic criteria for primary unipolar depression and had an average pretreatment BDI score of 27. Behavior therapy involved skills training in communication, behavioral productivity, social interaction, assertiveness, decision making, problem solving, and cognitive self-control. Unannounced blood samples were drawn on two random visits over the treatment period to ensure compliance. Results showed behavior therapy to be superior on 9 of 10 outcome measures (primarily self-report) at the end of treatment and on 7 of 10 measures at the 3-month follow-up. The superiority of behavior therapy included symptomatic measures as well as measures of social adjustment. The behavior therapy had the lowest dropout rate, 5%, as compared with 26% for insight and 36% for the drug condition. Insight-oriented psychotherapy was the least effective on most outcome measures at both evaluation periods; 30% of those patients remained in the moderate to severe range of depression, in comparison with 19% of those in the control condition. There were no significant differences between drug therapy and relaxation therapy on any outcome measure. No treatment had a significantly better outcome with the severely depressed subgroup (McLean & Taylor, 1992).

McLean and Hakstian (1990) conducted a 27-month follow-up of their 1979 study. Of the four treatment conditions, behavior therapy ranked best on six of seven outcome measures and ranked second on the seventh outcome measure. Behavior therapy produced significantly better results than the relaxation control condition on measures of personal activity, social skills, and mood. Behavior therapy was better than dynamic psychotherapy on measures of personal activity. The drug therapy condition was not statistically superior to any of the treatment or control conditions on any dimension. Also, in comparison with those in the other treatment conditions, twice as many behavior therapy patients (i.e., 64%) fell within one standard deviation of the normal, nondepressed control group distribution on depressed mood, a highly significant result. One other study has shown social skills training to be at least as effective as antidepressant medications or the combined social skills-drug treatment of depression

(Hersen, Bellack, Himmelhoch, & Thase, 1984), and another study has demonstrated that adding social skills to standard antidepressant treatment is superior to drugs alone (Miller et al., 1989).

The foregoing evidence suggests that three somewhat different cognitive—behavioral interventions compare favorably with antidepressant medications in the treatment of depression. These treatment options include increasing pleasant activities, changing maladaptive cognitions, and improving social skills. Combining these treatments with antidepressant medications does not appear to appreciably enhance the efficacy of the cognitive—behavioral therapies, although there is some suggestive evidence that cognitive therapy may enhance outcome for medications. These effective cognitive—behavioral psychotherapies seem to have the following factors in common (Zeiss, Lewinsohn, & Muñoz, 1979): (a) a well-elaborated rationale and theory guiding the treatment, (b) training in skills the patient can learn, (c) an emphasis on the independent practice of the skills outside of the therapy session, (d) a time-limited treatment with specific goals, (e) encouragement for patients to attribute changes to their own efforts and skills rather than to the skillfulness of the therapist, and (f) a maintenance plan for follow-up assessment and follow-up intervention.

### **Meta-Analytic Comparisons of Drugs and Psychotherapy**

Isolated studies provide pieces of the puzzle, but meta-analyses, covering all available studies meeting specified criteria, help put the puzzle together. One such meta-analysis of 56 controlled outcome studies considered the relative effectiveness of drug therapy and psychotherapy for treating unipolar depression in adults (Steinbrueck, Maxwell, & Howard, 1983). Effectiveness was measured by the effect size of the treatment condition (i.e., the treatment mean minus the control mean divided by the control standard deviation). The evidence suggested that, in comparison with a control group, psychotherapy had a significantly larger impact (mean effect size = 1.22) than drug therapy (mean effect size = 0.61). Some of the difference in mean effect size may have been due to the different blinding procedures and the different types of control groups. Drug studies were more likely to use a double-blind placebo, whereas psychotherapy studies were more likely to use a waiting list control group.

As part of a quantitative analysis, Dobson (1989) reviewed eight randomized studies ( $N = 721$ ) directly comparing Beck's cognitive therapy and tricyclic medication in the treatment of depressed outpatients. This review suggested that cognitive therapy is superior to drug treatment, as measured by the BDI. The average cognitive therapy recipient did better than 70% of the medication patients, with an average differential effect size of 0.53 in favor of cognitive therapy.

Another meta-analysis (Conte, Plutchik, Wild, & Karasu, 1986) investigated whether combined psychotherapy and pharmacotherapy is superior to either treatment alone for outpatients with unipolar depression. The researchers reviewed 17 controlled studies ( $N = 1,009$ ) reported between 1974 and 1984. In the analysis, studies were given different weights on the basis of the scientific quality of the design, and these weights were multiplied by weights based on the outcome of the study. The results indicated that combined active treatments (drug plus psychotherapy) were appreciably (53% of the weighted evidence) more effective than minimal contact plus placebo and moderately superior to pharmacotherapy alone (29% of the evidence) but only slightly superior to psychotherapy plus placebo (19% of the evidence), psychotherapy alone (18% of the

evidence), or pharmacotherapy plus minimal contact (15% of the evidence). In other words, 82% of the weighted evidence indicated no advantage of combined treatment over psychotherapy alone. A close inspection of the data shows that, of the 4 studies that used a combined behavioral plus drug condition in comparison with a behavioral plus placebo medication, 97% of the evidence indicated no significant difference. Interestingly, 3% of the evidence favored the behavioral intervention when combined with the placebo rather than the tricyclic medication.

Robinson, Berman, and Neimeyer (1990) conducted a unique meta-analytic review of the controlled outcome research on depression. After the results of 8 well-controlled studies had been combined and weighted (on the basis of sample size), psychotherapy had a statistically significant mean effect size that was 0.13 larger than that for drug therapy. Independent raters then judged investigator allegiance on a 5-point scale for each comparison between treatments by reviewing the introductory comments for each study included in the meta-analysis. After investigator allegiance had been controlled through the use of regression procedures, the advantage of psychotherapy shrank to 0.07 and was no longer statistically significant. It should be noted that if investigator allegiance is correlated with a third variable such as scientific rigor or efficacy, statistically controlling for allegiance may disproportionately penalize studies that are well designed or show large effects of a particular treatment. This review also found no advantage to the combined treatment over psychotherapy (in 12 studies) or drug therapy (in 5 studies).

Another meta-analysis (Hollon, Shelton, & Loosen, 1991) reviewed nine randomized controlled studies ( $N = 542$ ) that directly compared cognitive therapy and tricyclic medications in the treatment of nonbipolar depressed outpatients. On the basis of their analysis, Hollon et al. concluded that (a) cognitive therapy appears to be roughly comparable to medication in the treatment of the acute episode; (b) combined cognitive therapy and drug treatment does not appear to be clearly superior to either modality alone, although trends of potential synergistic enhancement justify additional studies with larger samples; and (c) treatment with cognitive therapy (with or without drugs) during the acute episode appears to reduce the risk of subsequent relapse after termination. However, because of limitations in study design and execution, low power, and possible differential retention (i.e., drug conditions might be more likely to retain relapsers), the authors conservatively considered their conclusions to be tentative.

Wexler and Cicchetti (1992) conducted a meta-analysis of treatment success rates, treatment failure rates, and treatment dropout rates from seven well-controlled studies ( $N = 513$ ) comparing psychotherapy and medication for depression. They concluded that combined treatment offers no advantage over treatment with psychotherapy alone and only a modest advantage over treatment with pharmacotherapy alone. When dropout rate was considered together with treatment success rates, the pharmacotherapy alone condition was substantially worse than psychotherapy alone or the combined treatment. They suggested that psychotherapy alone should usually be the initial treatment for depression rather than exposing patients to the unnecessary costs and side effects of combined treatment. Their review suggests that, in a hypothetical cohort of 100 patients with major depression, 29 would recover with pharmacotherapy alone, 47 would recover if given psychotherapy alone, and 47 would recover if given combined treatment. Negative outcomes (i.e., dropouts or no response) would occur in 52 pharmacotherapy patients, 30 psychotherapy patients, and 34

combined patients. Comorbid personality disorder and substance abuse may decrease treatment response (Wexler & Nelson, 1993).

In summary, several meta-analyses—reported in both psychiatry and psychology journals—covering multiple studies with thousands of patients are remarkably consistent in support of the perspective that psychotherapy is at least as effective as medication in the treatment of depression. Although there is some overlap of included studies, all of these meta-analyses were conducted independently. Except for the meta-analyses of Dobson (1989) and Hollon et al. (1991), which used only studies including cognitive—behavioral interventions, the meta-analyses combined all brands of psychotherapy for depression. This may have obscured differences in outcome between the different brands of treatment. Different types of psychotherapy may have different outcomes, as in the study by McLean and Hakstian (1979). It should also be noted that none of these meta-analyses attempted to estimate any possible effect of the type of outcome measure (i.e., self-report vs. clinician ratings) on the relative effectiveness of psychotherapy and medication. Despite the foregoing evidence to the contrary, the conventional wisdom in medicine, among the lay public, in the media, and even within the mental health profession continues to be that drugs are more effective than psychotherapy for depression (e.g., Kramer, 1993), especially severe depression, and that the combination treatment is superior to either one alone.

## **Support for Drugs or Combined Treatment Over Psychotherapy Alone**

The studies by Weissman and Klerman are usually cited to support the superior efficacy of combined psychotherapy and drug treatment (DiMascio et al., 1979; Weissman, Klerman, Prusoff, Sholomskas, & Padian, 1981; Weissman et al., 1979). These researchers conducted a randomized controlled trial comparing 16 weeks of combined amitriptyline (flexible divided dose of 100—200 mg/day) and short-term interpersonal psychotherapy, either treatment alone, and nonscheduled supportive psychotherapy in 96 acute, nonbipolar, nonpsychotic depressed outpatients. Interpersonal psychotherapy focuses on clarifying and resolving current interpersonal difficulties related to the depression. All of the treatment conditions produced better outcomes than the nonscheduled control group; interpersonal therapy outperformed drug treatment on adjustment measures (e.g., mood, apathy, suicidal ideation, work, and interest), whereas the drug treatment was superior on vegetative symptom (e.g., sleep and appetite) measures. From another perspective, the side effects of sedation and weight gain may not necessarily be signs of improvement. However, on the basis of the differential impact of the single treatments, these investigators concluded that the combined treatment outcome was additive, even though the combined treatment condition was not statistically superior to the single treatments on any outcome measures. It should be noted that the interpersonal psychotherapy relied heavily on insight and did not require behavioral homework assignments between sessions. Also, these studies relied exclusively on clinician-rated outcome measures. Note that, at 1-year follow-up, there was a statistically superior outcome on social functioning for patients who had received interpersonal psychotherapy, whether or not they had received medications. There were no statistically detectable effects of the medication condition at follow-up. It is possible that the type of psychotherapy may make a difference. Psychodynamic insight-oriented treatment of depression has performed relatively poorly in several studies (Covi & Lipman, 1987; Covi, Lipman, Derogatis, Smith, & Pattison, 1974; McLean & Hakstian, 1979; Sanchez, Lewinsohn, & Larson, 1980), and, in one study, marital therapy not specifically targeting depression resulted in slower improvement than amitriptyline (Friedman, 1975).

The recent multisite National Institute of Mental Health (NIMH) collaborative study on the treatment of depression (Elkin et al., 1989) has been cited to suggest that drugs are superior to psychotherapy in the treatment of severe depression. This ambitious project compared Beck's version of cognitive therapy, Klerman and Weissman's interpersonal therapy, imipramine (median of 185 mg/day, with a median plasma level of 231 ng/ml), and a pill placebo group. The authors concluded that there were no differences in overall effectiveness, but imipramine appeared to be more effective with severely depressed patients. The results of the analysis actually showed that imipramine did marginally better than the placebo condition with severely depressed patients at termination on clinician-rated measures such as the HRSD or the Global Assessment Scale (GAS; Endicott, Spitzer, Fleiss, & Cohen, 1976) but not on patient-rated measures like the BDI. Despite media reports to the contrary, drugs were not significantly better than either of the psychotherapies with severely depressed patients on any measures. Because the placebo was inert, clinician raters may have been inadvertently "unblinded" by side effects, a problem with many drug studies (Fisher & Greenberg, 1993). Also, the medication condition may have functioned more like a combined treatment condition because the clinical management provided "supportive psychotherapy." It is noteworthy that patients in the medication condition were still on

medication when the termination assessments were done, whereas the comparison conditions were actually terminated before assessment. This is a common practice in studies using a drug condition.

An 18-month follow-up (Shea et al., 1992) of the original NIMH collaborative study was conducted. Although the differences were not statistically significant, the psychotherapies outperformed imipramine on almost every outcome measure. In fact, cognitive therapy was ranked best on 11 of the 13 outcome measures reported in the published tables. There was a slight advantage of the psychotherapies over drug treatment with the milder depressions. The treatment outcomes were not statistically different in cases of severe depression. There did appear to be a reduced risk for relapse among the cognitive—behavioral therapy patients. Of all patients entering treatment, the cognitive—behavioral condition had the highest percentage of patients recover, the highest percentage of patients recover without a subsequent major depressive relapse, and the highest percentage of patients recover without major depressive relapse or treatment seeking. Patients who had received imipramine were most likely to seek treatment during the follow-up period, had the highest probability of relapse, and had the fewest weeks of minimal or no symptoms. These results are consistent with the relatively poor long-term drug outcomes reported in the studies cited earlier.

Some investigators have argued that the relatively high relapse rate after drug treatment indicates that depression should be treated like a chronic medical disease requiring ongoing, long-term, high-dose medication treatment indefinitely (e.g., Fava & Kaji, 1994; Frank et al., 1990; Kupfer et al., 1992; Paykel, Dimascio, Haskell, & Prusoff, 1975; Reynolds et al., 1992). This logic appears tautological: Drug treatment results in a higher relapse rate than cognitive—behavioral therapy; therefore, patients should be maintained on drugs to prevent relapse. Such maintenance studies typically rely on clinician ratings of outcome, and all patients are initially given combined treatment or drug treatment only. The maintenance phase of treatment is conducted only with the responders. Because psychotherapy alone is not offered to patients initially, the maintenance phase of treatment is essentially restricted to drug responders. Therefore, patient samples in these drug maintenance studies should not be considered representative of the general population of depressed patients.

A notable exception is a recent well-controlled study with 2 years of follow-up evaluating the impact of continuing medication (Evans et al., 1992; Hollon et al., 1992). The investigators randomly assigned 107 nonpsychotic, nonbipolar depressed patients to 12 weeks of cognitive therapy alone, imipramine hydrochloride alone (mean of 232 mg/day, with plasma levels of at least 180 ng/ml), or combined treatment. Sixty-four patients completed treatment, and there was no differential attrition. Cognitive therapy and pharmacotherapy did not differ in terms of symptomatic response, even in severely depressed patients, on patient-rated or clinician-rated measures. Initial severity predicted poorer response within the pharmacotherapy condition but not within the cognitive therapy condition. The combined treatment was not significantly more effective than the single treatments. Two patients committed suicide with study medication, and a third patient made a nonlethal attempt. Two other patients were withdrawn from pharmacotherapy alone because of severe suicidal risk. Three other patients were withdrawn from pharmacotherapy alone because of severe side effects. Half of the patients treated with pharmacotherapy alone continued to receive study medications for

the 1st year of follow-up. Among those showing at least partial response, patients previously treated cognitively (with or without medications) showed a significantly lower relapse rate than imipramine patients from whom medications were withdrawn. Thus, patients treated with 3 months of cognitive therapy (either alone or in combination with medications) had less than half the relapse rate of patients who received 3 months of medication alone. The relapse rate after 3 months of cognitive therapy did not differ from that of patients provided with 15 months of medication. Rather than supporting long-term drug treatment, these data support the cost-effectiveness of treating depression with brief cognitive—behavioral therapy.

In summary, the preponderance of the evidence suggests that drug treatments do less well than psychotherapy during follow-up (e.g., Blackburn, Eunson, & Bishop, 1986; Evans et al., 1992; Hersen et al., 1984; Hollon et al., 1991; Kovacs et al., 1981; McLean & Hakstian, 1990; Rush et al., 1977; Shea et al., 1992; Simons et al., 1986; Weissman et al., 1981) and are not more effective than psychotherapy with endogenous (Blackburn et al., 1981; Greenberg, Bornstein, Greenberg, & Fisher, 1992a), severe (Hollon et al., 1992; McLean & Taylor, 1992; Shea et al., 1992); or chronic (Rush, Hollon, Beck, & Kovacs, 1978) depression. The American Psychiatric Association's own committee review of 12 studies concluded that there was no demonstrable relationship between endogenous depression and treatment outcome (Zimmerman & Spitzer, 1989). In a recent naturalistic prospective study (Brugha, Bebbington, MacCarthy, Sturt, & Wykes, 1992), even depressed inpatients on antidepressant medications showed a nonsignificant trend for a lesser degree of improvement in comparison with equally depressed inpatients who were not put on antidepressants. Part of the problem in finding differential responsiveness for endogenous depression may be that there is little support for the distinction between endogenous and reactive depression (Free & Oei, 1989), and endogeneity is highly correlated with severity (Greenberg et al., 1992a).

## Methodological Issues in Studies Involving a Drug Condition

It is generally assumed that antidepressants have been clearly established as more effective than placebo in double-blind controlled research. Morris and Beck (1974) conducted a comprehensive literature review that revealed that tricyclic antidepressants were superior to a placebo in 63 of 91 controlled studies conducted between 1958 and 1972. Although this review would appear to support the efficacy of antidepressants, there may be some problems that diminish the strength of the results. For example, studies with negative results are much less likely to be published (Greenberg & Fisher, 1989). Also, most controlled drug studies use an inert placebo that may, in effect, unblind the studies because the clinician raters can determine who is receiving the active medication by determining who is having side effects (Hughes & Krahn, 1985; Margraf et al., 1991). This could be a serious flaw because most drug studies rely primarily on potentially biased clinician-rated measures (e.g., the HRSD and the GAS) rather than on patient-rated measures (e.g., the BDI). It has been shown, in an extensive meta-analysis (Lambert, Hatch, Kingston, & Edwards, 1986), that patient-rated measures show a significantly smaller effect size than clinician-rated measures (i.e., patient raters tend to see less improvement than clinician raters). Another concern is that most antidepressant drug studies use a "washout" phase during which all prospective participants are placed on placebo (Greenberg & Fisher, 1989). Those prospective participants who show improvement during the washout phase are eliminated from the pool of participants. This routine procedure very likely creates a bias against the placebo condition in such drug studies before they even start by eliminating those individuals who may be "placebo responders." Thus, the actual placebo response rate may be seriously underestimated in most antidepressant studies.

Using the same study pool reviewed by Morris and Beck (1974), Thomson (1982) reviewed 75 placebo-controlled double-blind studies of tricyclic antidepressants conducted between 1958 and 1972 that met somewhat stricter methodological criteria. Only 7 of these studies used an active placebo, and only 1 of the studies using an active placebo showed the antidepressant to have a superior outcome to the placebo.

Despite the excitement about the newer antidepressants such as fluoxetine, a recent meta-analysis of nine controlled fluoxetine outcome studies showed only a modest mean effect size of 0.39 in comparison with controls on patient-rated measures (Greenberg, Bornstein, Zborowski, Fisher, & Greenberg, 1994). This effect size is comparable but not larger than that obtained in previous meta-analyses of tricyclic antidepressants. Interestingly, both clinician and patient outcome ratings correlated significantly with the percentage of patients experiencing side effects, suggesting that side effects may unblind these studies and bias the outcome measures.

Fisher and Greenberg (1993) conducted a worldwide literature search for psychotropic drug studies that evaluated whether or not the double blind had been penetrated. Of the 26 reports they were able to locate, 23 (88%) indicated that both patients and physicians were able to differentiate who was receiving the drug or placebo at rates significantly better than chance. Another recent study showed that clinical evaluators' subjective ratings of treatment outcome were significantly different depending on whether the clinical evaluator had correctly guessed the patients' condition (Carroll, Rounsaville, & Nich, 1994). This is likely to be a problem for both psychotherapy and drug treatment conditions but is likely to especially affect drug—placebo comparisons

as a result of the presence or absence of drug side effects.

A recent meta-analysis (Greenberg, Bornstein, Greenberg, & Fisher, 1992b) reviewed 22 controlled studies ( $N = 2,230$ ) that compared a placebo (usually inert) with an "old" antidepressant and a "new" antidepressant. Even if the clinician rater were unblinded by side effects, he or she would have difficulty distinguishing which of the active medications the patient was receiving, in effect making these studies somewhat "blinder." Overall, the old antidepressants and the new antidepressants showed a small (average effect sizes of 0.25 and 0.31, respectively) advantage over placebo on clinician-rated measures. Considering that most studies with nonsignificant findings are not published, the authors speculated that this advantage may, in fact, have been negligible. Interestingly, when patient-rated outcome measures were used, the old antidepressants were not significantly more effective than the placebo and showed an effect size of only 0.06. The data suggested that the new antidepressants did not fare much better. These effect sizes were far smaller than the effect sizes, ranging from 0.44 to 0.79, that had emerged from the earlier meta-analyses of tricyclic antidepressants (Morris & Beck, 1974; Thomson, 1982). These data suggest that relying on clinician ratings alone could lead to significant biases whenever the blind is penetrated.

## **Side Effects**

If one accepts the data and the argument that drug treatment of depression may not be as effective as conventional wisdom would suggest, it does not necessarily follow that drugs should be relegated to a second-class treatment status. Some patients prefer medications to psychotherapy and strongly believe in their efficacy. By prescribing medication, a clinician could take advantage of any nonspecific and placebo factors associated with drug treatment. However, some of the costs of medications are underappreciated. Research suggests that antidepressants are the most common agents used in suicide by poisoning (Kapur, Mieczkowski, & Mann, 1992) and are responsible for half of serious adult overdoses (Kathol & Henn, 1982). We are aware of no data about the relative risk of suicide in patients treated with drugs in comparison with those treated with psychotherapy. Although a suicidal patient treated with psychotherapy may commit suicide, the treatment itself does not become the agent of death.

Even at therapeutic levels, there are many potential side effects of tricyclic antidepressants. The anticholinergic side effects include dry mouth, blurred vision, urinary retention, constipation, and delirium (Settle, 1992). There may also be sedative effects, cognitive deficits, speech blockage, excessive perspiration, weight gain, and dental caries. There is some evidence of risk for extrapyramidal symptoms, seizures, sleep disruption, and mania, depending on the type of antidepressant. The cardiovascular risks include heart failure (especially with bundle branch block), hypertension, hypotension, arrhythmias, and sudden death (Jefferson, 1992). Tricyclic antidepressants appear to increase the risk of sudden unexpected death by more than 400% for patients diagnosed with cardiac disease (Moir et al., 1972). Sexual side effects have commonly included low libido, erectile disorder, orgasm or ejaculatory impairment, and, less commonly, painful ejaculation, penile anesthesia, spontaneous orgasm, and even yawning combined with orgasm (Seagraves, 1992). There is a well-documented withdrawal phenomenon associated with tricyclic medication (Dilsaver & Greden, 1984). The most common withdrawal symptoms include general somatic or gastrointestinal distress with or without anxiety and agitation, sleep disturbance

characterized by excessive and vivid dreaming and initial and middle insomnia, movement disorder, and psychic and behavioral activation extending on a continuum to mania. In one study, use of antidepressants in medically ill inpatients resulted in a 60% unfavorable response rate, and 32% had to be discontinued because of significant side effects, the most common of which was delirium (Popkin, Callies, & Mackenzie, 1985). Thus, there is much evidence that antidepressant medications are not benign treatments.

Despite recommendations for "adequate" doses to achieve therapeutic response, there are only weak relationships between plasma levels and clinical response to imipramine or amitriptyline (Kocsis, Hanin, Bowden, & Brunswick, 1986; Simpson et al., 1982). There is also new evidence that improvement in cognitive therapy (in patients with obsessive-compulsive disorder) is associated with therapeutic alterations in brain chemistry without the use of any medication (Baxter et al., 1992) and without the attendant medical risks.

Newer antidepressants, the so-called selective serotonin reuptake inhibitors (SSRIs), were developed on the theory that depression results from a deficiency in serotonin levels, even though studies have not shown that serotonergic activity is lowered in depressive states (Hallman & Oreland, 1989). The SSRIs theoretically increase the serotonin available to the brain by interfering with its reuptake. However, the brain quickly (as soon as 2 days in animal studies) compensates for this artificial intrusion of extra serotonin (through a process called *down regulation*) and reduces the number of serotonin receptors (Breggin, 1994). It has been demonstrated that, with other drugs, compensatory receptor changes can become permanent (Breggin, 1994), potentially creating serious long-term problems.

The newer antidepressants are touted as being just as effective as the older antidepressants, but the newer drug studies suffer from the same problems outlined earlier. So far, the newer SSRIs appear to be a safer alternative to the tricyclic antidepressants. Although they appear to have about the same risk of overdose, death appears to be a less likely outcome with the SSRIs (Kapur et al., 1992). Although the newer SSRIs may be safer when used alone, there are data to suggest that, when combined with other medications, they are more dangerous as a result of their pharmacodynamic and pharmacokinetic properties (e.g., Settle, 1992). For example, they are lethal when combined with monoamine oxidase inhibitors. Given the common use of multiple concurrent medications, it is not clear that the newer antidepressants will actually result in safer outcomes. Even when they are used alone, SSRIs have fairly common side effects, including agitation, sleep disruption, nausea, and sexual problems (Settle, 1992). For a minority of patients, these new medications also appear to carry a significant risk for suicide induction, mania, akathisia, and extrapyramidal effects (Lenhoff, 1994). To be fair, one might legitimately ask about the side effects (i.e., the unintentional negative effects) of psychotherapy. Although controversial, there are apparently instances in psychotherapy of false memory syndrome caused by suggestions of abuse or inappropriate hypnotic interventions under certain narrow conditions (Loftus, 1993). However, this syndrome is probably rare and irrelevant to most treatments of depression, which typically do not use hypnosis or suggestions of abuse. As mentioned earlier, McLean and Hakstian (1979) found that patients in the insight-oriented psychotherapy condition were more likely than those in the control condition to remain in the moderate to severe range of depression. This could be

considered a negative side effect of this type of therapy if it is replicated in other studies. In comparison with the medical risks associated with drug treatments, psychotherapy is relatively benign. If malpractice rates are any indication, the risks associated with prescribing drugs are much higher than those associated with psychotherapy.

## **Ethnocultural, Gender, and Age Issues**

The roles of ethnicity, gender, and developmental stage in treatment responsiveness merit clinical attention and have been nicely summarized elsewhere (e.g., Lin, Poland, & Nakasaki, 1993; Muñoz, Hollon, McGrath, Rehm, & VandenBos, 1994). Although this area has been sorely neglected, there is evidence that drug compliance and metabolism appear to be affected by ethnocultural issues. Also, minorities are much less likely to seek mental health treatment than nonminorities. Practitioners need to be trained to provide psychotherapeutic treatment in a culturally and linguistically competent manner, or the only treatment accessible to minorities will be pharmacotherapy (Muñoz et al., 1994). In comparative efficacy studies, the ethnic makeup of the sample is often not reported, and when it is the sample is typically 90% Caucasian (e.g., Elkin et al., 1989; Hollon et al., 1992). It remains to be seen how the overall results reported here apply to minorities. None of the meta-analyses described in this article examined the role of ethnicity in the relative efficacy of drugs and psychotherapy.

Meta-analyses of studies comparing drugs and psychotherapy show that women constitute from 69% (Robinson et al., 1990) to 85% (Conte et al., 1986) of all participants. Therefore, most of the results from the comparative outcome studies may be considered representative of depression in women. However, the results may not readily generalize to depression in men. Almost all studies describe the gender makeup of the sample; rarely however, is the impact of this variable considered in the outcome analysis. The Dobson (1989) meta-analysis found an insignificant correlation between the proportion of women in the included studies and the amount of BDI change. None of the other meta-analyses described herein reported on the impact of gender on the relative efficacy of drugs and psychotherapy. An entire meta-analysis of the comparative efficacy literature could be devoted to addressing that issue alone. It is important to note that about 70% of antidepressants are prescribed to women (Olfson & Klerman, 1993), many of whom are of childbearing age, with significant risks to the fetus (e.g., see Pastuszak et al., 1993). This also raises a concern that women appear to be disproportionately exposed to the risks of these medications, even though they are more likely than men to experience adverse side effects (Muñoz et al., 1994).

The average patient in comparative efficacy studies is about 41 years old (e.g., Robinson et al., 1990). Not enough data exist bearing on the relative efficacy of these treatments for elderly people or children. It is worth noting that side effects of antidepressants are more severe in the elderly population. For example, a panel of 13 experts in geriatrics and pharmacology considered amitriptyline a medication that should be entirely avoided in patients more than 65 years of age because of the serious risk for anticholinergic effects and orthostatic hypotension (Beers et al., 1991). Dobson (1989) found suggestive evidence that age may be negatively related to outcome with cognitive therapy. None of the comparative efficacy studies were conducted in a geriatric population.

With regard to younger people, a recent review suggested that there is no credible evidence that antidepressants are an effective treatment for depressed children or

adolescents (Ambrosini, Bianchi, Rabinovich, & Elia, 1993). These data are particularly disturbing given the 6 million prescriptions for antidepressants that are written for children each year (Goleman, 1993) and anecdotal evidence of unexpected sudden death in several children prescribed these medications ("Sudden Death," 1990).

## **Conclusions and Recommendations**

Several conclusions may be drawn from the foregoing information. The preponderance of the evidence suggests that the psychological interventions, particularly cognitive—behavioral therapy, are at least as effective as medication in the treatment of depression, even if severe. These treatments are effective for both vegetative and social adjustment symptoms, especially when outcome is assessed with patient-rated measures and when long-term follow-up is considered. It should be noted that these general conclusions are consistent with findings drawn from the psychiatry literature (e.g., Beck et al., 1985; Murphy et al., 1984; Wexler & Cicchetti, 1992) as well as the psychology literature. Pharmacologic approaches do not directly affect psychosocial factors. Medications result in relatively poorer compliance than psychotherapy, have a higher dropout rate, and result in as much as a 60% nonresponse rate with some patient populations. Many antidepressants are cardiotoxic, have dangerous side effects, and are often used in suicide attempts. Psychotherapy can teach skills to help prevent depression, making such treatment an attractive, cost-effective alternative to drug treatments.

One might legitimately ask how medications have become the predominant treatment in the United States despite the considerable risks and side effects and despite the considerable evidence demonstrating the efficacy of psychotherapy. At least part of the answer, effective marketing, has been well-documented elsewhere ("Miracle Drugs," 1992; "Pushing Drugs," 1992; Breggin, 1991). Other factors contributing to high use of antidepressant medications include the higher rate of reimbursement by some third-party payers for medical interventions relative to psychotherapy (usually 80% vs. 50%) and the pressure from some managed care organizations to use a seemingly quicker, apparently cost-effective drug treatment. However, it should be noted that cognitive—behavioral treatments appear to be quite effective when delivered in a group format (e.g., Brown & Lewinsohn, 1984), providing a safe, time-efficient, cost-effective alternative to standard individual drug treatment, especially when side effects, dropout rate, and long-term outcome are taken into consideration (Wexler & Cicchetti, 1992).

Although the recent depression treatment guidelines published by the Agency for Health Care Policy and Research (Depression Guideline Panel, 1993) are a step toward helping physicians identify previously undetected depression, they appear to overrely on the biological model, overemphasize the benefits of antidepressant medications, underemphasize the risks and side effects of these drugs, and underemphasize the efficacy of psychotherapy (see Muñoz et al., 1994). As an example, the summary guidelines recommend two unsuccessful trials of antidepressant medication before consideration of referral for psychotherapy.

We offer the following alternative aspirational guidelines for treating depression based on our review of the scientific literature.

Psychotherapy, notably cognitive—behavioral intervention or interpersonal psychotherapy, should be considered the treatment of first choice for depression

primarily because of superior long-term outcome and fewer medical risks than drugs or combined treatment; medications, combined treatment, or another brand of psychotherapy may be considered for nonresponders after the costs and benefits have been carefully weighed.

Clinicians should be cautious about intervening with insight-oriented psychotherapy alone because evidence suggests that this form of therapy may produce relatively poorer outcomes.

If antidepressants are used, psychotherapy should be included because of the higher risk for relapse with medication alone.

Whenever possible, a single medication should be used until controlled research studies have adequately evaluated the safety risks and efficacy of combined medications.

If antidepressant medication is used, clinicians should use the lowest, safest therapeutic dose for the shortest possible duration because of side effects, cardiotoxic risks, risk of suicide, possible increased dropout rates, and scarcity of long-term outcome or risk data.

Clinicians should be cautious about prescribing antidepressants (especially tricyclics) to hospitalized medical patients, especially those diagnosed with cardiac disease, because of high nonresponse rates, intolerance of side effects, and risk of sudden death.

Clinicians should be cautious about prescribing antidepressants (especially tricyclics) to acutely suicidal patients because of the danger of serious overdose.

Clinicians should not prescribe antidepressants to children or adolescents because there is no evidence that these medications are effective with children or adolescents and little is known about the health risks for young people.

Caution should be used in prescribing antidepressants to elderly people as a result of increased risks of anticholinergic side effects and hypotension.

Clinicians should avoid the use of regular minor tranquilizers alone, which have resulted in worse outcomes than no depression treatment at all (Sturm & Wells, 1995).

These guidelines directed at the use of antidepressant medications apply primarily to tricyclic medications. There are not enough accumulated data yet to know how they apply to the newer SSRIs. In fact, we are unaware of any studies directly comparing the efficacy of the SSRIs and psychotherapy.

One of the most important areas for future outcome research on drugs, psychotherapy, and their comparative efficacy involves identifying the essential ingredients of an effective treatment for depression. For example, what are the essential components of cognitive—behavioral therapy? What is the impact of the type, amount, or expectation of homework? How important is practice of the skills during and outside of the session? With antidepressant medication, is it just the presence of side effects or something specific to the action of the drug on neurotransmitters that results in improvement? What role does the type of outcome measure play? How often is the double blind

penetrated, and what impact does this have on measured outcome? How selective are drug studies that exclude large numbers of patients during the washout period? What happens to the excluded patients? How do differential dropout rates affect outcomes? What happens after psychotherapy or antidepressant medications are withdrawn? In our view, a treatment study is not over until patients are assessed after all treatments are terminated and follow-up outcome is evaluated. This is especially important in the case of drug treatments because of the continuing risk of side effects, medical problems, withdrawal symptoms, and potential for relapse. What are the unique challenges faced by special populations (i.e., children, elderly people, men, and minorities)? We would prefer to see more data before drug treatments with significant medical risks achieve widespread acceptance with untested populations. How well do the treatment outcome studies generalize to the real world? What happens if nonresponders to one treatment are offered a different treatment?

Future treatment outcome studies designed to compare psychotherapy and drug therapy can be improved by (a) including an active drug placebo or comparison treatment condition whenever possible; (b) evaluating the integrity of the double blind and its impact on outcome by asking patients and clinician raters to guess the actual treatment condition; (c) conducting a concurrent but separate outcome analysis of patients who are excluded from a study after the placebo washout to obtain a better understanding of what happens to these patients and how they differ from the treatment participants; (d) always including a separate report and analysis of patient-rated measures along with clinician-rated measures, especially when an inert placebo or a waiting list control is used; (e) assessing treatment compliance by counting pills, taking venous blood samples, or monitoring homework compliance; (f) always evaluating outcome beyond the point at which patients have their treatments terminated; (g) conducting an end-point analysis that includes drop-outs; (h) conducting longer term safety and outcome follow-ups; (i) evaluating the impact of ethnocultural, gender, and age-related variables on outcome; (j) supplementing factorial studies with real-world studies of outcomes in naturalistic settings; and (k) designing crossover studies in which nonresponders to one treatment are switched to a different treatment.

In our view, there is a tendency to underestimate the power and cost-effectiveness of a caring, confidential psychotherapeutic relationship in the treatment of depression. If we as therapists can learn to be patient in dealing with the emotional suffering of depressed individuals and help guide them through it with specific psychotherapeutic strategies, as many as 50% to 80% will respond within 8 to 16 weeks of treatment, without drugs and without the associated medical risks. For those who do not respond to psychotherapy, the costs and benefits of drug treatment or combined treatment can then be carefully weighed. While organized psychology pursues prescription privileges, the costs of attaining such privileges should also be carefully weighed against the potential benefits (DeNelsky, 1991). Despite the conventional wisdom, the data suggest that there is no stronger medicine than psychotherapy in the treatment of depression, even if severe.

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