Effectiveness of Psychotherapy and Combination Treatment for Chronic Depression

Bruce A. Arnow and Michael J. Constantino
Stanford University Medical Center

Although considerable research has been conducted on the efficacy of psychotherapy for depression, with and without medication, relatively few studies have focused on chronic forms of depression. Approximately 20% of individuals with depression experience episodes that last for two years or longer. We review the controlled research on the effectiveness of treatments separately for dysthymia and chronic major depression, focusing on the practical implications of the research for clinicians. In trials conducted with dysthymics, medication has been superior to psychotherapy, with limited evidence that combined treatment has advantages over medication or psychotherapy alone. In chronic major depression, combined treatment has demonstrated significant superiority over medication or psychotherapy alone. Possible explanations for the discrepant findings among dysthymics and those with chronic major depression are discussed. © 2003 Wiley Periodicals, Inc. J Clin Psychol/In Session 59: 893–905, 2003.

Keywords: dysthymic disorder; chronic major depression; psychotherapy; combination treatment

Typically, depressive episodes are time limited, with a median length of approximately 20 weeks. Although recurrences are common, most depressed patients eventually return to a state they often describe as *feeling myself again*. Over the past 20 years, however, researchers have identified chronically depressed patients whose episodes last for at least two years and sometimes much longer without a return to baseline. Evidence is accumulating that compared to non-chronically depressed patients, this subgroup is notable for poorer subjective well being and impaired social and occupational functioning. Those

Correspondence concerning this article should be addressed to: Bruce A. Arnow, Ph.D., Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center, 401 Quarry Road, Stanford, CA 94305–5722; e-mail: Arnow@stanford.edu.

JCLP/In Session, Vol. 59(8), 893–905 (2003)

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jclp.10181

whose age of onset is early (before 21), demonstrate particularly high rates of recurrence, comorbid personality disorders, psychiatric hospitalizations, and among women, low educational achievement, which may lead to underemployment and reduced income. Such consequences add a financial dimension to the toll that depression can take on an individual.

In this article, we focus on what is currently known about the effectiveness of psychotherapy, with and without medication, for the treatment of dysthymia and chronic major depression. Before discussing these findings, we discuss two important issues with important implications for the treatment of chronic depression: the economic burden and the relation between residual symptoms and relapse.

Economic Burden of Depression and Its Clinical Implications

Overall, the economic burden of depression in 1990 was calculated at 44 billion dollars including direct costs (e.g., psychiatric, medical), mortality costs (i.e., depression-related suicide), and morbidity costs (e.g., reduced work productivity). Depression was the fourth most costly of all illnesses in 1990; by 2020, it is projected to become the second most costly.

Depression is associated with remarkably high rates of functional impairment, and evidence suggests that these effects are even more pronounced in the chronically depressed. Findings reveal lower daily function among depressed patients compared to patients with a number of chronic medical conditions. Among chronically depressed patients, dysthymics demonstrated notably lower physical function than did those suffering from all other sampled general medical conditions, with the exception of congestive heart failure.

In addition to general daily and physical problems, another measure of disability is days of work that are missed as a function of a specific illness. In comparison with both psychiatric and non-psychiatric illness, depression emerges as the condition with most workdays lost—more, for example, than anxiety, neurological problems, diabetes, and history of heart disease and cancer. Depressed patients also have been shown consistently to use 1.5 to 2 times as many medical services as nondepressed patients, even after controlling for chronic medical illness. Further, there is evidence that when compared to those with acute major depressive disorder (MDD), those with chronic depression demonstrate higher rates of suicide attempts and hospitalizations and are notable for high rates of medical use.

Although the economic burden of an illness may at first glance appear to be of more concern to policy makers than to mental-health professionals, we believe it has implications regarding both assessment and treatment for the depressed patient. With respect to the latter, disability-related problems associated with depression should be a target of treatment. Although recovery from depression itself is associated with reductions in disability, there is evidence that changes in social- and work-function lag behind changes in symptoms. Moreover, clinicians often find themselves in the position of requesting treatment authorizations and extensions from third-party payers for patients in their care. The ability to document changes in vocational, social, and physical function is likely to play an important role in assisting patients to obtain authorization and reimbursement, which in turn facilitates participation in necessary treatment. Thus, in addition to monitoring changes in symptoms, measures of daily function, such as the Medical Outcome Study 36-item Short Form (SF-36; Ware & Sherbourne, 1992), and social-adjustment scales such as the Social Adjustment Scale—Self-Report (SAS-SR; Weissman, Prusoff, Thompson, Harding, & Meyers, 1978) should be part of the routine assessment of the depressed patient across the course of treatment.

Residual Symptoms, Chronicity, and Relapse/Recurrence in Major Depression

Much of our knowledge regarding the course of major depression derives from data gathered in the Collaborative Depression Study (CDS), which involved over 500 treatment-seeking patients diagnosed with unipolar major depression over a period of more than 20 years. Findings indicate that over 75% of those who experience major depression suffer more than one episode and over 20% experience chronic depression lasting two years or longer. A number of studies based on CDS data also have highlighted unexpected relations among residual symptoms, time to relapse, chronicity, and recurrence.

In a study of patients followed in the CDS for at least 10 years, those whose recovery was asymptomatic—that is, full remitters—were compared to a group who recovered but continued to suffer subthreshold depressive symptoms, that is, partial remitters (Judd et al., 1998). Compared to the asymptomatic group, patients with subthreshold symptoms relapsed to a major depressive episode more than 3 times more quickly. Put differently, patients whose recovery was asymptomatic remained well for a median of over 4 years compared with slightly more than 1 year for those with subthreshold symptoms. Subsequently, those in the subthreshold group also were found to suffer more chronic episodes (lasting 2 years or longer) and, over a 12-year period, had significantly fewer weeks during which they were free of depressive symptoms (Judd et al., 2000). Other reports based on CDS data have revealed that an individual's probability of recurrence increases as the number of recurrences increase, and decreases with longer duration of recovery (Solomon et al., 2000).

Clinical Implications of Data on Course of Depression

Taken together, these data suggest two important treatment considerations for the psychotherapist. First, the difference in course between those who are full versus partial remitters clearly implies that the goal of treatment for the depressed patient should be full remission. Second, the ubiquity of recurrence, as well as the increasing risk conferred by multiple episodes, suggests the importance of longer-term treatment, even beyond the point where the individual has responded.

Consistent with these data, the most recent American Psychiatric Association Practice Guidelines for Depression (2000) conceptualize treatment as a three-phase process. The goal of the initial, or acute, phase of treatment is full remission of depressive symptoms. Although the guidelines suggest an acute phase length of 6–8 weeks, the latter is predicated on time to response to medication. Because available data suggest that response to psychotherapy takes somewhat longer than response to a single medication, the likely length of acute treatment involving psychotherapy would be 12 weeks or longer. The guidelines suggest that the initial stage of treatment should be followed by a continuation phase of 16–20 weeks. The goal of continuation treatment is preventing relapse. The frequency of visits during this phase, depending upon clinical status, might continue at the same frequency as the acute phase, or may be decreased (e.g., from once per week to biweekly). The third, or maintenance, phase of treatment is designed to prevent recurrences, that is, new episodes of major depression. For patients in psychotherapy, visits during this phase are typically once per month and may continue for a year or longer.

Psychotherapy and Combination Treatment for Dysthymic Disorder

A number of recent studies have focused on the effectiveness of different treatments for dysthymia. As noted by Kocsis (this issue), the efficacy of psychopharmacology for

dysthymic disorder has been relatively well established. Although studies on psychotherapy for dysthymic patients have lagged behind, some researchers recently have reported on the efficacy of psychotherapy for dysthymia.

In an earlier review, Markowitz (1994) identified only seven empirical reports on psychotherapy for dysthymia. Given significant methodological limitations (e.g., small samples) in these reports, Markowitz warned that the findings should be interpreted with caution. With this in mind, the response rate—those meeting criteria for significant clinical improvement—across all studies was 41%, suggesting that some dysthymic patients derive benefit from psychotherapy.

Psychotherapy vs Medication

More recently, three trials have compared psychotherapy and medication for dysthymic disorder without examining the efficacy of combined treatment. Barrett and associates (2001) compared the effectiveness of a brief trial of paroxetine, placebo, and a brief problem-solving psychotherapy (PST) (6 visits over 11 weeks) in adult primary-care patients diagnosed with either minor depression or dysthymia. Findings revealed significant post-treatment reductions in depressive symptoms across both diagnoses and all treatment groups. For the dysthymic sample, there were no significant differences between the three treatments on overall reductions in depressive symptoms. However, remission rates were significantly higher for both active treatment groups than the placebo group, with paroxetine having the most robust effect (paroxetine = 80%; PST = 57%; placebo = 44%).

Within the same research group and using the same design, Williams and associates (2000) examined the impact of these interventions in elderly patients. Although paroxetine was significantly more effective in reducing depressive symptoms than the placebo group, PST was not. These authors did note, however, that during the latter weeks of treatment, those patients treated with psychotherapy showed more-rapid decline in symptomatology than those in the placebo group.

Dunner and colleagues (1996) found that dysthymic patients treated for 16 weeks with either cognitive therapy alone or fluoxetine alone showed equivalent symptomatic improvement over baseline. However, response rates in both groups were smaller than those found in treatment studies for MDD.

Findings from the three trials reviewed here suggest that, with the exception of the Dunner et al. (1996) trial in which the two were equivalent, medication appears to be superior to psychotherapy alone. However, the *dose* of psychotherapy in these trials was relatively low. In the two trials using PST in primary care (Barrett et al., 2001; Williams et al., 2000), six treatment sessions may have been too brief to be effective with chronically depressed patients. When evaluating these findings, it is important also to note that psychotherapy was being compared to medications where the effective dose was well known.

Combined Treatment

Four studies have reported evaluations of combined medication and psychotherapy for dysthymia. Browne and colleagues (2002) examined the impact of sertraline, brief (10 sessions) interpersonal psychotherapy (IPT), and their combination in a sample of approximately 700 adults recruited in primary-care settings. Treatment lasted for 6 months, followed by an 18-month naturalistic evaluation. At post treatment, combined treatment

and sertraline alone were equivalent and significantly superior to IPT alone. The response rates were 60% for sertraline, 58% for combined treatment, and 47% for IPT. A similar pattern was observed at the 2-year point. However, those patients treated with combined therapy had significantly lower health and social-services costs than the sertraline-alone group at both the 6-month and 2-year points.

One issue regarding the design of this study bears comment. During the naturalistic follow-up period, those assigned to either combination or sertraline alone were offered sertraline for the entire 2-year period. Although all patients were free to pursue treatment, substantially more patients who were in the combined (66%) or sertraline-alone (62%) conditions took sertraline or other antidepressants during the follow-up when compared to the IPT-alone group (12%). This feature of the design, during which there were substantial imbalances in treatment, makes interpretation of the longer-term findings problematic.

In a study carried out in Brazil targeting low SES patients, De Mello and colleagues (2001) compared combined moclobemide/IPT and moclobemide with clinical management in the treatment of a small sample ($N = 35$) of patients with dysthymia. Those in the moclobemide/IPT condition received 16 acute and 6 maintenance psychotherapy sessions. The dropout rate was 37% in the combined group and 58% in the medication-alone group, which is substantially higher than most other published studies. Both groups demonstrated significantly reduced depressive symptoms. Although there was a trend in favor of combined treatment, there were no significant between-group differences. In addition to the high dropout rates, the low sample size and the fact that only one therapist was providing the treatment necessitate cautious interpretation of the results.

In a study comparing placebo, placebo plus brief (12 session) group cognitive–behavioral therapy (GCBT), sertraline, and combined treatment for a sample of 97 adult patients with dysthymia, Ravindran and associates (1999) reported equivalent reductions in depression for the latter two groups. Reductions in depressive symptoms for those in GCBT plus placebo were significantly lower and no different than placebo alone. Response rates were 71% for combined treatment, 54% for sertraline alone, and 33% for both GCBT with placebo and placebo alone. Differences in the response rates between medication alone and combined treatment were not statistically significant in this sample, which was relatively small for a four-group design. However, combined treatment was superior to medication alone on some of the functional measures.

Finally, several studies have reported that CBT (e.g., Fava, Rafanelli, Grandi, Conti, & Belluardo, 1998), mindfulness-based cognitive therapy (Teasdale et al., 2000), and IPT (Frank, Kupfer, Wagner, McEachran, & Cornes, 1990) can be helpful in preventing relapse among depressed patients previously treated with medication. One such study has been reported in the area of chronic depression. Hellerstein and colleagues (2001) compared fluoxetine and combined fluoxetine/cognitive–interpersonal group psychotherapy (CIGP) in 40 dysthymic patients following partial response to medication. CIGP was a 16-session intervention. At post treatment, there were significant differences favoring combined treatment on several measures of depressive symptomatology and global function. Response rates at post treatment were 89% for combined treatment and 76% for medication only. At follow-up, 12 weeks after treatment termination, response rates were 61% for those in combined treatment versus 40% for those in medication only. Although between-group differences were not significant, the sample size was small. These findings are promising and suggest the need for additional trials examining the efficacy of a variety of strategies to treat chronically depressed patients who do not respond fully to medication.

Overall, the findings are somewhat mixed on the question of whether combined treatment is superior to medication alone for dysthymic disorder. Although evidence to

date on reducing depressive symptoms does not reveal a clear advantage for combined treatment, differences in use of health and social services (Browne et al., 2002) and in the studies with smaller samples, differences in response rates (Ravindran et al., 1999), dropout rates (De Mello et al., 2001), and functional improvement (Ravindran et al., 1999), suggest that combined treatment may be superior to medication alone.

Although only one study (Hellerstein et al., 2001) addressed whether combined treatment might be helpful in treating dysthymic patients who partially respond to medication, the findings suggest an advantage for combined treatment. Clearly, substantially more research is needed in this area.

Psychotherapy and Combination Treatment for Chronic Major Depression

In addition to dysthymic disorder, which may occur in the absence of a chronic major depressive episode, at least three other subtypes of chronic depression have been identified. Those with chronic major depression have had an episode of major depression that has lasted for two years or more. A second subtype comprises those with MDD superimposed on antecedent dysthymia, often referred to as *double depressives*. The third subtype are those who suffer recurrent major depressive episodes without full interepisode recovery, that is, who suffer subsyndromal symptoms between episodes, where the entire length of illness is two years or greater.

Although there is a reasonably large literature evaluating cognitive as well as interpersonal therapy for nonchronic or mixed depressed samples, few studies have targeted specifically the above groups of patients. We found only three controlled studies that included patients who met criteria for one of the three subtypes and involved at least 10 patients per treatment. All have examined somewhat different questions with chronically depressed patients and, for the most part, have used different treatments.

One early study (de Jong, Treiber, & Henrich, 1986) found that a comprehensive cognitive–behavioral treatment including activity scheduling, social-competence training, and cognitive restructuring, achieved higher response rates (60%) among patients with double depression than cognitive restructuring alone (30%) or a wait-list control condition (10%).

In a comparison of combined pharmacotherapy and cognitive–behavioral therapy with medication alone, a group of patients with double depression were recruited while inpatients (Miller, Norman, & Keitner, 1999). Treatment continued following discharge from the hospital. At post treatment, those who received combined therapy were significantly more improved on symptoms of depression and social functioning. However, there were no differences between the groups at the 6-month and 1-year follow ups. In addition, overall response rates were low, with 38% meeting criteria for full response at post treatment and a high relapse rate at subsequent assessments.

In a multicenter trial involving nearly 700 patients suffering chronic major depression, Keller and colleagues (2000) compared the efficacy of the antidepressant medication nefazodone alone, cognitive–behavioral analysis system of psychotherapy (CBASP; McCullough, this issue), and their combination. This trial involved acute (12 weeks), continuation (4 months), and maintenance (1 year) phases. In addition, there was a crossover phase for nonresponders to either monotherapy (i.e., nonresponders to medication only were crossed over to CBASP and vice-versa). Nonresponders to combination treatment were dropped from the study. Full and partial responders in the acute phase continued in the treatment to which they responded for continuation. During the maintenance phase, those in combination or nefazodone alone were assigned randomly to drug versus

placebo, whereas those in CBASP alone were assigned randomly to either once-monthly CBASP or assessment only.

The major findings regarding reductions in depressive symptoms were as follows:

1. at the end of the acute phase, combination treatment was associated with significantly better response (approximately 75%) compared to the monotherapies (approximately 50%);
2. in the crossover phase, evidence suggests that those started with medication, who failed to respond, and then received psychotherapy had higher response rates than those who experienced the reverse (Arnow et al., 2000);
3. in the continuation phase, those in remission had lower relapse rates than those who were partial responders (approximately 25% vs less than 10%) (Arnow et al., 2000);
4. the rate of continuation-phase relapse among partial responders who were in combination treatment was much less than those in either monotherapy (approximately 10% vs 25%) (Arnow et al., 2000); and
5. in the maintenance phase, there was a higher rate of relapse in placebo than in nefazodone (Gelenberg et al., in press).

These findings are consistent with practice guidelines that suggest providing combined treatment in more-severe cases of depression, and with prior data suggesting better outcomes among those with full versus partial response. In addition, the results are consistent with evidence that outcomes continue to improve beyond the acute phase of treatment, supporting the importance of longer courses of therapy for those with chronic depression.

Although no single trial is definitive because of the sample size, treatment length, and other methodological strengths, these findings provide the best-available guidance on treating patients with chronic major depression. In this study, medication and psychotherapy were equivalent, and there was a pronounced advantage for combined treatment.

The question arises as to why these findings are different from those in the dysthymia literature, where medication was superior to psychotherapy alone and evidence in favor of combined treatment was far more equivocal. Of the many possible explanations, we will highlight two.

First, it is possible that CBASP, which was specifically developed for the chronically depressed patient, has distinctive efficacy with this population compared with other psychotherapies such as IPT and PST. Second, the dose of psychotherapy in this study was substantially higher than in most of the trials conducted with dysthymic patients (e.g., Browne et al., 2002; Ravindran et al., 1999). Although the acute phase was only 12 weeks, CBASP was provided twice weekly during weeks 1–4 for all patients, with the option for two sessions weekly during weeks 5–8 for patients who were demonstrating that they were not learning the specific problem-solving methodology in CBASP. Thus, the mean number of psychotherapy sessions over the 12 weeks of acute treatment was 18. Furthermore, during the first four weeks there were no differences between medication and combined treatment, but CBASP alone was associated with significantly lower reductions in depressive symptoms. It was only in the latter part of the acute phase that CBASP *caught up* with medication and the superiority of combination therapy became evident. It is possible that the differences in the speed of recovery were due not only to psychotherapy taking a longer period of time to manifest its full effects, but also because patients needed a larger dose of psychotherapy than was delivered during the early part of the acute phase.

Treatment for Chronic Depression: Impact on Comorbid Symptomatology

In addition to recent studies addressing the impact of pharmacotherapy, psychotherapy, and their combination on chronic depression, several studies also have concentrated on the effect of such treatments on comorbid symptoms. Although few in number, these studies make clinical and practical sense considering the broad impact chronic depression has on people's functioning.

Comorbid Anxiety

Given that anxiety symptoms commonly co-occur in MDD and dysthymia, one set of investigators (Ninan et al., 2002) compared improvement in anxiety symptoms among treatment groups in the Keller et al. (2000) multicenter study. The findings were similar to those for depressive symptoms. That is, at the end of the acute phase, combined treatment yielded significantly greater improvement in symptoms of anxiety than either monotherapy.

Comorbid Sleep Dysfunction

Also using data from the same multicenter study, Thase and colleagues (2002) examined the impact of CBASP, nefazodone, and their combination on co-occurring sleep difficulties among patients who had experienced at least one symptom of insomnia. As might be expected based on nefazodone's established effectiveness in reducing insomnia, those patients receiving nefazodone alone or in combination with psychotherapy had significantly greater sleep improvement than did patients receiving CBASP only during the acute phase of treatment. It is unknown whether such findings would generalize to other antidepressants with less favorable impact on sleep.

Comorbid Sexual Difficulties

Given that depression often is associated with sexual dysfunction and that sexual difficulties are known to be part of the side-effect profile for many antidepressant agents, it makes sense to study the effect of treatments for chronic depression on sexual functioning. One group of investigators (Zajecka et al., 2002) indeed found that a high percentage of both men and women in the Keller et al. (2000) sample reported sexual dysfunction at baseline (65% and 48%, respectively). Improvement in depressive symptoms predicted improvement in sexual interest and satisfaction (for men and women) and improved sexual functioning in men across all treatment groups. Furthermore, when controlling for change in depression levels, male and female patients across all 3 groups evidenced significant increases in sexual interest and satisfaction, with the combined group showing the greatest effect. While these findings again point to the benefit of combined treatment for chronic depression and its related symptomatology, nefazodone is associated with fewer sexual side effects than many other antidepressant medications. It is unknown whether these findings would replicate with antidepressants associated with more problematic effects on sexual function.

Comorbid Functional Deficits

Hirschfeld and associates (2002) investigated whether improvement in psychosocial functioning (e.g., work performance, social adjustment) during the acute phase of the

Keller et al. study (2000) differed between treatments and examined relations between psychosocial functioning and changes in depressive symptoms. For most outcomes, combination therapy was associated with greater psychosocial improvement than either monotherapy. Functional improvement progressed more slowly than did reductions in symptoms of depression. Although these findings are encouraging, it should be noted that moderate functional impairment remained following acute treatment. This finding is consistent with other researchers (e.g., Friedman, Markowitz, Parides, Gniwesch, & Kocsis 1999) who have found that despite some improvement in social functioning following continuation pharmacological treatment for dysthymia, significant social problems persisted even when depressive symptoms were low.

The composite findings regarding the impact of treatment on comorbid symptoms of chronic depression are encouraging, particularly regarding combined treatment. That is, combined treatment has been shown to be advantageous specifically over monotherapies in the areas of anxiety reduction, improved sexual interest and satisfaction, and improved psychosocial functioning. However, research in this area is just beginning to emerge and has been predicated mainly on one large sample of patients treated with a specific psychotherapy and antidepressant medication. It remains to be seen whether these findings will be reproduced in future studies.

Process and Outcome in Psychotherapy for the Chronic Depressions

The Therapeutic Alliance

The therapeutic alliance has emerged consistently as a robust predictor of outcome across a variety of treatment approaches and for a wide array of clinical problems (see Constantino, Castonguay, & Schut, 2002). Although studies of the alliance in chronic depression and dysthymia are limited, investigators (Klein et al., in press) recently examined the impact of patient-rated alliance on treatment outcome in the acute phase of the Keller et al. (2000) trial. The quality of the alliance at week two significantly predicted patient improvement in both the combined and psychotherapy-alone treatment conditions (the alliance was not assessed in the nefazodone-alone condition). Moreover, this association held when controlling for patient improvement before alliance ratings, as well as certain patient characteristics. These findings are generally consistent with those from the landmark NIMH Treatment of Depression Collaborative Research Program in which the quality of the therapy alliance significantly predicted outcome across all four treatments (Krupnick et al., 1996).

With regard to predictors of the alliance, Santiago and colleagues (2002), drawing on the multicenter data, found that a history of drug abuse/dependence and lower social adjustment were related negatively to early alliance development in the psychotherapy-alone condition. In the combined psychotherapy/pharmacotherapy group, male gender and emotional distancing significantly predicted a poorer alliance. These authors cautioned, however, that the correlations, although statistically significant, were low and of uncertain clinical significance.

Another set of investigators (Zuroff et al., 2000) using a different data set found that patients with high levels of a particular depressogenic cognition—perfectionism—had greater difficulty establishing strong alliances during the course of treatment than nonperfectionistic patients across all forms of treatment. Moreover, the difficulty in establishing a robust alliance was a mediating factor for the negative relation between perfectionism and outcome (Blatt, Quinlan, Pilkonis, & Shea, 1995). It should be noted,

however, that these findings related mainly to patients with episodic depression. Whether they would generalize to chronic forms of depression is unknown. However, it could be the case that perfectionism is particularly common in chronic depressives. Indirect support for this notion has been reported by Klein and colleagues (1988) who found that self-criticism is higher in chronic versus episodic depressives.

Conclusions and Unanswered Questions

In general, relatively few clinical trials have been conducted on the treatment of chronically depressed patients. Based on available data, we advance four recommendations for clinical practice. First, for chronic major depression, the evidence supports recommending combined treatment, which has displayed advantages in reducing not only depressive symptoms, but also comorbid problems. In studies on dysthymia, evidence suggests that medication is superior to psychotherapy alone, while comparisons of medication versus combined treatment suggest an advantage for the latter, particularly when a broad range of outcome measures are considered. The dose of psychotherapy was probably too low to provide an adequate test in the studies carried out with dysthymics.

Second, while few psychotherapies have been evaluated rigorously for chronic depression, CBT, IPT and CBASP have all demonstrated effectiveness in many cases. No direct head–head comparisons have been performed to test whether one of these psychotherapies is more effective than the others.

Third, evidence indicates that the goal of treatment for chronically depressed patients should be full response or remission. Moreover, effective treatment involves not only acute-phase therapy aimed at symptom reduction, but also longer-term treatment aimed at enhancing response where necessary and preventing relapse and recurrence.

Fourth, we recommend that clinicians treating chronically depressed patients assess not only depressive symptoms, but also work and social function. These areas are compromised in this population and appear to improve more slowly than the depressive symptoms themselves.

We can highlight only a few of the many questions that remain unanswered regarding the treatment of this challenging population. First, many practitioners are not familiar with the psychotherapies that have been tested for chronic depression. For example, even where combined treatment has been superior to medication, the psychotherapies studied are limited to CBT or CBASP. In the latter case, only a relative handful of therapists are familiar with the therapy model. It is unclear how similar the findings we summarized would be with other forms of psychotherapy.

Second, most of the studies we reviewed relied on a single medication. Thus, response rates we reported for medication may be somewhat lower than those that might be achieved in a clinical setting where there is access to a variety of medications. On the other hand, approximately half of all depressed patients are treated in primary-care settings, where evidence suggests that under dosing of medication is common and response rates are lower than those achieved in specialty mental-health settings. Although combined treatment may continue to demonstrate the most-robust effects with the chronically depressed patient, it will be important to test whether it is superior to medication alone where prescribing physicians have access to a variety of medications.

Finally, the viability of different treatments will rest not only on their efficacy, but also on their cost effectiveness. Studies comparing the cost effectiveness of treatment for chronic depression remain to be completed.

Select References/Recommended Readings

Arnow, B.A., Blalock, J., Rothbaum, B.O., McCullough, J.P., Markowitz, J.C., & Barlow, D.H. (2000, August). Comparison of medication, psychotherapy and combination treatment for chronic depression. Symposium presented at the 108th annual meeting of the American Psychological Association, Washington, DC.

Barrett, J.E., Williams, J.W., Oxman, T.E., Frank, E., Katon, W., Sullivan, M., Hegel, M.T., Cornell, J.E., & Sengupta, A.S. (2001). Treatment of dysthymia and minor depression in primary care: A randomized trial in patients aged 18–59 years. Journal of Family Practice, 50, 405–412.

Blatt, S.J., Quinlan, D.M., Pilkonis, P.A., & Shea, M.T. (1995). Impact of perfectionism and need for approval on the brief treatment of depression: The National Institute of Mental Health treatment of depression collaborative research program revisited. Journal of Consulting and Clinical Psychology, 63, 125–132.

Browne, G., Steiner, M., Roberts, J., Gafni, A., Byrne, C., Dunn, E., Bell, B., Mills, M., Chalklin, L., Wallik, D., & Kraemer, J. (2002). Sertraline, and/or interpersonal psychotherapy for patients with dysthymic disorder in primary care: 6-month comparison with longitudinal 2-year follow-up of effectiveness and costs. Journal of Affective Disorders, 68, 317–330.

Constantino, M.J., Castonguay, L.G., & Schut, A.J. (2002). The working alliance: A flagship for the "scientist–practitioner" model in psychotherapy. In G.S. Tryon (Ed.), Counseling based on process research: Applying what we know (pp. 81–131). Boston, MA: Allyn & Bacon.

De Mello, M.F., Myczcowisk, L.M., & Menezes, P.R. (2001). A randomized controlled trial comparing moclobemide and moclobemide plus interpersonal psychotherapy in the treatment of dysthymic disorder. Journal of Psychotherapy Practice & Research, 10, 117–123.

de Jong, R., Treiber, R., & Henrich, G. (1986). Effectiveness of two psychological treatments for inpatients with severe and chronic depressions. Cognitive Therapy Research, 10, 645–663.

Dunner, D.L., Schmaling, K.B., Hendrickson, H., Becker, J., Lehman, A., & Bea, C. (1996). Cognitive therapy versus fluoxetine in the treatment of dysthymic disorder. Depression, 4, 34–41.

Fava, G.A., Rafanelli, C., Grandi, S., Conti, S., & Belluardo, P. (1998). Prevention of recurrent depression with cognitive behavioral therapy: Preliminary findings. Archives of General Psychiatry, 55, 816–820.

Frank, E., Kupfer, D.J., Wagner, E.F., McEachran, A.B., & Cornes, C. (1990). Efficacy of interpersonal psychotherapy as a maintenance treatment of recurrent depression. Archives of General Psychiatry, 48, 1053–1059.

Friedman, R.A., Markowitz, J.C., Parides, M., Gniwesch, L., & Kocsis, J.H. (1999). Six months of desipramine for dysthymia: Can dysthymic patients achieve normal social functioning? Journal of Affective Disorders, 54, 283–286.

Gelenberg, A.J., Trivedi, M.H., Rush, A.J., Thase, M.E., Howland, R., Klein, D.N., Kornstein, S.G., Dunner, D.L., Markowitz, J.C., Hirschfeld, R.M.A., Keitner, G.I., Zajecka, J., Kocsis, J.H., Russell, J.M., Miller, I., Manber, R., Arnow, B., Rothbaum, B., Munsaka, M., Banks, P., Borian, F.E., & Keller, M.B. (in press). Randomized, placebo-controlled trial of Nefazodone maintenance treatment in preventing recurrence in chronic depression. Biological Psychiatry.

Hellerstein, D.J., Little, S.A., Samstag, L.W., Batchelder, S., Muran, J.C., Fedak, M., Kreditor, D., Rosenthal, R.N., & Winston, A. (2001). Adding group psychotherapy to medication treatment in dysthymia. A randomized prospective pilot study. Journal of Psychotherapy Practice, 10, 93–103.

Hirschfeld, R.M., Dunner, D.L., Keitner, G., Klein, D.N., Koran, L.M., Kornstein, S.G., Markowitz, J.C., Miller, I., Nemeroff, C.B., Ninan, P.T., Rush, A.J., Schatzberg, A.F., Thase, M.E., Trivedi, M.H., Borian, F.E., Crits-Christoph, P., & Keller, M.B. (2002). Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. Biological Psychiatry, 51, 123–133.

Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A., & Keller, M.B. (1998). Major depressive disorder: A

prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. Journal of Affective Disorders, 50, 97–108.

Judd, L.L., Paulus, M.J., Schettler, P.J., Akiskal, H.S., Endicott, J., Leon, A.C., Maser, J.D., Mueller, T., Solomon, D.A., & Keller, M.B. (2000). Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? American Journal of Psychiatry, 157, 1501–1504.

Keller, M.B., McCullough, J.P., Klein, D.N., Arnow, B., Dunner, D.L., Gelenberg, A.J., Markowitz, J., Nemeroff, C.B., Russell, J.M., Thase, M.E., Trivedi, M.H., Zajecka, J., Blalock, J.A., Borian, F.E., Fawcett, J., Hirschfeld, R., Jody, D.N., Keitner, G., Kocsis, J.H., Koran, L.M., Kornstein, S.G., Manber, R., Miller, I., Ninan, P.T., Rothbaum, B., Rush, A.J., Schatzberg, A.F., & Vivian, D. (2000). A comparison of Nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. New England Journal of Medicine, 342, 1462–1470.

Klein, D.N., Harding, K., Taylor, E.B., & Dickstein, S. (1988). Dependency and self-criticism in depression: Evaluation in a clinical population. Journal of Abnormal Psychology, 97, 399–404.

Klein, D.N., Schatzberg, A.F., McCullough, J.P., Dowling, F., Goodman, D., Howland, R.H., Markowitz, J.C., Smith, C., Thase, M.E., Rush, A.J., LaVange, L., Harrison, W.M., & Keller, M.B. (1999). Age of onset in chronic major depression: Relation to demographic and clinical variables, family history, and treatment response. Journal of Affective Disorder, 55, 149–157.

Klein, D.N., Schwartz, J.E., Santiago, N.J., Vivian, D., Vocisano, C., Castonguay, L.G., Arnow, B.A., Blalock, J.A., Manber, R., Markowitz, J.C., Riso, L.P., Rothbaum, B., McCullough, J.P., Thase, M.E., Borian, F., Miller, I., & Keller, M.B. (in press). The therapeutic alliance in chronic depression: Prediction of treatment response after controlling for prior change and patient characteristics. Journal of Consulting and Clinical Psychology.

Krupnick, J.L., Sotsky, S.M., Simmens, S., Moyer, J., Elkin, I., Watkins, J., & Pilkonis, P.A. (1996). The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: Findings in the National Institute of Mental Health treatment of depression collaborative research program. Journal of Consulting and Clinical Psychology, 64, 532–539.

Markowitz, J.C. (1994). Psychotherapy of dysthymia. American Journal of Psychiatry, 151, 1114–1121.

Miller, I.W., Norman, W.H., & Keitner, G.I. (1999). Combined treatment for patients with double depression. Psychotherapy & Psychosomatics, 68, 180–185.

Ninan, P.T., Rush, A.J., Kornstein, S.G., Manber, R., Thase, M.E., Trivedi, M.H., Rothbaum, B.O., Zajecka, J., & Borian, F.E. (2002). Symptomatic anxiety in outpatients with chronic depression: Effect of nefazadone, cognitive–behavioral analysis system of psychotherapy, and their combination. Journal of Clinical Psychology, 63, 434–441.

Ravindran, A.V., Anisman, H., Merali, Z., Charbonneau, Y., Telner, J., Bialik, R., Wiens, A., Ellis, J., & Griffiths, J. (1999). Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: Clinical symptoms and functional impairments. American Journal of Psychiatry, 156, 1608–1617.

Santiago, N.J., Klein, D.N., Vivian, D., Vocisano, C., Dowling, F., Arnow, B.A., Manber, R., Markowitz, J.C., McCullough, J.P., Riso, L.P.L., Rothbaum, B.O., Rush, A.J., Thase, M.E., & Keller, M.B. (2002). Pretreatment correlates of the therapeutic alliance in the chronically depressed. Journal of Contemporary Psychotherapy, 32, 281–290.

Solomon, D., Keller, M.B., Leon, A.C., Mueller, T.I., Shea, M.T., Warshaw, M., Maser, J.D., Coryell, W., & Endicott, J. (1997). Recovery from major depression: A ten-year prospective follow-up across multiple episodes. Archives of General Psychiatry, 54, 1001–1006.

Solomon, D.A., Keller, M.B., Leon, A.C., Mueller, T.I., Lavori, P.W., Shea, T., Coryell, W., Warshaw, M., Turvey, C., Maser, J.D., & Endicott, J. (2000). Multiple recurrences of major depressive disorder. American Journal of Psychiatry, 157, 229–233.

Teasdale, J.D., Segal, Z.V., Williams, J.M.G., Ridgeway, V.A., Soulsby, J., & Lau, M.A. (2000). Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. Journal of Consulting and Clinical Psychology, 6, 615–623.

Thase, M.E., Rush, J.A., Manber, R., Kornstein, S.G., Klein, D.N., Markowitz, J.C., Ninan, P.T., Friedman, E.S., Dunner, D.L., Schatzberg, A.F., Borian, F.E., Trivedi, M.H., & Keller, M.B. (2002). Differential effects of nefazadone and cognitive behavioral analysis system of psychotherapy on insomnia associated with chronic forms of major depression. Journal of Clinical Psychiatry, 63, 493–500.

Ware, J.E., Jr., & Sherbourne, C.D. (1992). The MOS 36-item short-form health survey (SF-36). I: Conceptual framework and item selection. Medical Care, 30, 473–83.

Weissman, M.M., Prusoff, B.A., Thompson, W.D., Harding, P., & Meyers, K. (1978). Social adjustment by self-report in a community sample and psychiatric outpatients. Journal of Nervous & Mental Disease, 166, 317–326.

Williams, J.W., Jr., Barrett, J., Oxman, T., Frank, E., Katon, W., Sullivan, M., Cornell, J., & Sengupta, A. (2000). Treatment of dysthymia and minor depression in primary care: A randomized controlled trial in older adults. Journal of the American Medical Association, 284, 1519–1526.

Zajecka, J., Dunner, D.L., Gelenberg, A.J., Hirschfeld, R.M.A., Kornstein, S.G., Ninan, P.T., Rush, A.J., Thase, M.E., Trivedi, M.H., Arnow, B.A., Borian, F.E., Manber, R., & Keller, M.B. (2002). Sexual function and satisfaction in the treatment of chronic major depression with nefazadone, psychotherapy, and their combination. Journal of Clinical Psychiatry, 63, 709–716.

Zuroff, D.C., Blatt, S.J., Sotsky, S.M., Krupnick, J.L., Martin, D.J., Sanislow, C.A., III, & Simmens, S. (2000). Relation of therapeutic alliance and perfectionism to outcome in brief outpatient treatment of depression. Journal of Consulting and Clinical Psychology, 68, 114–124.