Continuation and Maintenance Treatments of Major Depressive Disorder

In view of very high rates of relapse and recurrence, long-term continuation and maintenance therapies for depression have become increasingly important.

by MAURIZIO FAVA, MD, and JUNKO KAJI, BA

The distinction between depressive relapse and depressive recurrence in the long-term treatment of depression has emerged as an important conceptual issue among clinicians and researchers in recent years. According to the definitions proposed by Frank et al.,1 depressive relapse occurs when a patient experiences a return of depressive symptoms qualifying for a diagnosis of Major Depressive Disorder (MDD) after an asymptomatic (i.e., a 17-item Hamilton Rating Scale for Depression [HAM-D-17] score ≤ 7) period lasting up to 6 months after full recovery, while depressive recurrence occurs when depressive symptoms satisfying full criteria for MDD return after an asymptomatic period of ≥ 6 months.

The treatment aimed at preventing MDD relapse during the period immediately following recovery is defined as continuation therapy, while continuous prophylactic treatment against MDD recurrences over a longer time frame is called maintenance therapy. More than 50% of depressed patients will experience relapse within 3 months after discontinuing continuation treatment3,4 and more than 80% will experience recurrence within 3 years following discontinuation of maintenance antidepressant treatment.5 In view of these very high rates of relapse and recurrence, long-term continuation and maintenance therapies for depression have become increasingly important, particularly in populations with a relatively higher risk for relapse and recurrence.

This article reviews studies assessing the efficacy of the three most commonly used strategies in continuation and maintenance treatment of MDD: pharmacotherapy with antidepressant drugs, psychotherapy, and the combination of pharmacotherapy with psychotherapy. One of the most important methodological issues in reviewing this literature is related to the tremendous heterogeneity in the ascertainment of relapse or recurrence. While some studies used relatively infrequent follow-up visits to assess outcome, others assessed patients very frequently, thereby increasing the overall sensitivity in the detection of relapses.

As far as long-term treatment of depression is concerned, an especially interesting new area for investigation is the potential increase in prophylactic efficacy that
Potential increase in prophylactic efficacy might be obtained by combining pharmacotherapy with cognitive therapy.

might be obtained by combining pharmacotherapy with cognitive therapy. While the effects of continued treatment with pharmacotherapy or psychotherapy alone have been extensively studied, very few studies have addressed the question of whether combining psychotherapy and pharmacotherapy in long-term treatment would yield an additional benefit over each therapy by itself. In addition, there is a need to investigate the long-term effects of acute combination treatment as, presumably, acute pharmacotherapy and psychotherapy may have different long-term effects on outcome. In view of promising preliminary results in acute trials of combined psychotherapy and pharmacotherapy, this area stands badly in need of further research.

OPTIMAL LENGTH OF LONG-TERM THERAPIES FOR DEPRESSION

Although varying research methodologies and differences in the definition of “relapse” have led to slightly different estimates of the optimal length of long-term treatments for depression, most investigators estimate that continuation therapy should be carried out until 4 to 6 months after obtaining remission of depressive symptoms. This is consistent with the findings of Prien and Kupfer who reanalyzed data from a multicenter clinical trial and found that the risk of relapse after antidepressant withdrawal abated only after at least 4 months of sustained response, underscoring the importance of continuation therapy.

Much less agreement exists on the optimal duration of maintenance therapy. Kupfer et al found that maintenance therapy with imipramine prevented recurrences significantly more often than placebo for up to 5 years after initial recovery. Other authors, noting that most recovered depressives experience recurrence, have recommended that maintenance therapies be continued indefinitely if they have proved effective for at least 1 year after full recovery. On the other end of the spectrum, however, at least one group of investigators found that only 56% of hospitalized depressives experienced a new depressive episode four or more times over 18 years and concluded that “half of the hospitalized [cases of unipolar depression] do not require long-term medication.” Given the high cost of any long-term antidepressant treatment, identifying patients at relatively high risk for depressive recurrence clearly becomes crucial when deciding whether and how long to continue treatment into the maintenance phase.

PATIENTS AT RISK FOR RELAPSE AND RECURRENCE

There are several robust predictors of depressive relapse and recurrence that might identify those who may most benefit from continuation and maintenance treatment of MDD following initial recovery. One of the most powerful predictors of relapse or recurrence is a chronic or highly recurrent course of depression. In fact, patients with three or more previous episodes of depression and patients with double depression (i.e., patients with a major depressive episode superimposed on dysthymia) have a greatly increased chance of relapse/recurrence after recovery.

Two other important predictors of relapse/recurrence are long duration of the index episode prior to assessment and treatment and the presence of residual depressive symptoms at the end of the acute treatment. Several additional variables may predict relapse/recurrence and provide information on the patient populations that would most benefit from continuation and maintenance therapy. For example, married individuals were significantly less likely to suffer a relapse/recurrence than unmarried individuals; both greater dysfunctional attitudes and more negative self-appraisal are associated with a relatively higher probability of relapse/recurrence; younger age has been found to predict relapse/recurrence; and greater neuroticism and personality disorder traits are associated with a relatively higher risk of relapse/recurrence.

Although responsiveness to acute antidepressant treatment can vary across different depressive subgroups of patients, it is not known whether different populations of patients with relatively high risk for relapse/recurrence differ in their response to the prophylactic effects of various treatments. Future research might therefore concentrate on identifying clinical features of those patients best suited for specific long-term strategies.

One promising study along these lines is Aronson and Shukla's report on a group of patients displaying a full response to antidepressant treatment and a quick relapse (within 2 months) following antidepressant discontinuation. Unlike fully recovered, "episodic" patients who experience recurrences only after 6 months or longer without medica-
TABLE 1

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of Study</th>
<th>Class of Drug</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loonen et al 23</td>
<td>meta-analysis of placebo-controlled trials</td>
<td>tricyclics</td>
<td>tricyclics &gt; placebo in prevention of relapse</td>
</tr>
<tr>
<td>Prien and Kupfer 3</td>
<td>literature review</td>
<td>tricyclics, lithium</td>
<td>tricyclics or lithium &gt; placebo in prevention of relapse</td>
</tr>
<tr>
<td>Harrison et al 24</td>
<td>double-blind, placebo-controlled trial</td>
<td>phenelzine</td>
<td>phenelzine &gt; placebo in prevention of relapse</td>
</tr>
<tr>
<td>Robinson et al 25</td>
<td>uncontrolled trial</td>
<td>phenelzine</td>
<td>phenelzine effective in preventing relapse (8.2% relapse rate over 16 weeks), but associated with frequent side effects</td>
</tr>
<tr>
<td>Rosenbaum et al 26</td>
<td>placebo-controlled multicenter trial</td>
<td>fluoxetine</td>
<td>fluoxetine &gt; placebo in prevention of relapse over 3 months</td>
</tr>
<tr>
<td>Doogan and Caillard 28</td>
<td>placebo-controlled multicenter trial</td>
<td>sertraline</td>
<td>sertraline &gt; placebo in prevention of relapse over 3 months</td>
</tr>
<tr>
<td>Dunbar and Montgomery 29</td>
<td>placebo-controlled multicenter trial</td>
<td>paroxetine</td>
<td>paroxetine &gt; placebo in prevention of relapse over 3 months</td>
</tr>
</tbody>
</table>

Efficacy of Continuation Treatment with Antidepressants

As mentioned before, one of the most widely prescribed therapeutic approaches to the continuation treatment of MDD is to continue to treat recovered patients with antidepressant drugs after obtaining remission from the index episode. Continuation treatment with antidepressants is usually defined as the administration of an antidepressant drug for up to 6 months following the disappearance of acute depressive symptoms. This definition applies to all classes of antidepressants, including tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and the selective serotonin reuptake inhibitors (SSRIs). Table 1 lists the conclusions of some typical studies involving different classes of drugs.

Tricyclic Antidepressants

A meta-analysis by Loonen et al 23 of studies on the efficacy of antidepressant drug treatment in patients with recurrent major depression found that continuation therapy with tricyclic antidepressants was more effective than placebo in preventing relapses. This conclusion is consistent with the earlier work of Prien and Kupfer, 3 who reviewed results from a number of early investigations on the efficacy of long-term antidepressant drug treatment in depressed patients. They also concluded that the risk of relapse was approximately 50% when recently improved patients were switched to placebo, as opposed to 22% in patients receiving ongoing treatment with lithium or tricyclic antidepressants.

Monoamine Oxidase Inhibitors (MAOIs)

Harrison et al reported the results of a double-blind, placebo-controlled study on the efficacy of phenelzine in preventing relapse over 6 months in 12 dysthyemic patients. 24 All patients had previously responded to acute treatment with phenelzine and had maintained their response for at least 6 weeks before randomization. A statistically significant difference in outcome emerged between the two treatment groups. In fact, while all seven patients switched to placebo suffered a relapse within 42 days, only one of five patients remaining on phenelzine relapsed.

Similarly, a large study by Robinson et al 25 showed that only 6 of 73 (8.2%) patients who had responded to acute treatment with phenelzine and who were kept on a flexible dose of open-label phenelzine for up to 16 weeks experienced a relapse in their depressive symptoms. These investigators also reported that 11 of their 73 subjects on continuation treatment with phenelzine ultimately discontinued treatment because of side effects such as insomnia, weight gain, orthostasis, and sexual dysfunction. When the dose of phenelzine was reduced in these patients, the
There is much disagreement on the optimal duration of maintenance therapy.

side effects improved but the remission of the patients' depressive symptoms was not sustained. It is unclear whether the side-effect profile and dropout rate observed in this study are significantly higher than what would be expected with other classes of antidepressants, as no comparative studies have yet been conducted.

Selective Serotonin Reuptake Inhibitors (SSRIs)

The US multicenter "Fluoxetine vs. Placebo: Long-Term Treatment of MDD" study, whose results have not been published yet, showed that fluoxetine 20 mg per day was significantly better than placebo in preventing relapses. Furthermore, data from our "Pilot Study on Drug and Cognitive Maintenance Therapies of Depression" suggest that higher doses of fluoxetine (e.g., 40 mg to 60 mg per day) may be even more effective than 20 mg per day, although this dose is usually considered as effective as higher doses during short-term treatment.

We have compared data from our pilot study with those obtained at our site in the US multicenter "Fluoxetine vs. Placebo: Long-Term Treatment of MDD" study. While both studies had an initial open-phase treatment with fluoxetine 20 mg per day and had almost identical inclusion and exclusion criteria, our pilot study increased the dose to 40 mg per day at the beginning of the continuation phase, and the "Fluoxetine vs. Placebo: Long-Term Treatment of MDD" study maintained the same dose (20 mg per day). The relapse rate observed during the first 20 weeks of the continuation phase appears to be lower in the study using 40 mg per day as compared to the first 20 weeks of continuation treatment in the study using the dose of 20 mg per day, in spite of the fact that both studies used the same definition of relapse.

The idea that some patients may do best when treated with a higher dose during continuation treatment seems to be supported by the results of a follow-up study that we have conducted on patients relapsing on fluoxetine 20 mg per day at our site during the course of the US multicenter "Fluoxetine vs. Placebo: Long-Term Treatment of MDD" study. In the follow-up study, 83% of the patients who relapsed showed partial or full response to an increase in dose to 40 mg per day, with their positive response being maintained over time.

It is not known whether the other SSRIs also require doses that are somewhat higher than those normally used during acute treatment in order to obtain the best prophylactic effect during continuation. In fact, the only double-blind study on long-term efficacy of sertraline adopted a flexible dose strategy during continuation and maintenance treatment. This approach might have minimized the risk of relapse in some patients due to inadequate dosing, as changes in dosage might have both specific and nonspecific, placebo-like effects on prodromal symptoms of relapse/recurrence, thereby diminishing one's ability to detect actual relapses and recurrences. This multicenter study did show that, after about 3 months of continuation treatment, the estimated relapse rate on a flexible dose of sertraline was only about 4% and was markedly lower than that observed with placebo (30%).

Similarly, although the multicenter study by Dunbar and Montgomery showed after 3 months of continuation treatment a relapse rate on paroxetine of 3%, which was significantly lower than that observed with placebo (19%), the mean dose used in this study was about 30 mg per day, slightly higher than the paroxetine dose (20 mg per day) generally recommended for acute treatment. Since the long-term study with paroxetine, whose results have not been published yet, used a relatively high mean dose and the long-term study of sertraline used a flexible dose approach, one cannot establish whether or not all SSRIs need doses, during long-term treatment, that are relatively higher than those commonly used during the acute phase of treatment. If this is the case, it would imply that SSRIs may differ in their long-term efficacy from tricyclic antidepressants and MAOIs. No plausible explanations of the biological mechanisms underlying such differences can be offered at this time.

Preliminary analyses from the US multicenter "Fluoxetine vs. Placebo: Long-Term Treatment of MDD" study suggest that continuation therapy should be carried out until 6 months after obtaining remission of depressive symptoms, consistent with the findings of studies using tricyclic antidepressants.

Because of the relatively benign side-effect profile of this class of antidepressants compared to MAOIs and tricyclics, SSRIs such as fluoxetine, paroxetine, and sertraline have gained increasing popularity among clinicians in the long-term treatment of depression. Investigations conducted with SSRIs suggest that this class of drugs is equally effective as the earlier drugs in preventing relapses and recurrences of depression. However, system-
TABLE 2
Summary of Studies on Efficacy of Maintenance Pharmacotherapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of Study</th>
<th>Class of Drug</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleinman and Schachter*</td>
<td>literature review</td>
<td>tricyclics</td>
<td>insufficient data to support efficacy of maintenance therapy with tricyclics</td>
</tr>
<tr>
<td>Loonen et al*</td>
<td>meta-analysis of placebo-controlled trials</td>
<td>tricyclics (imipramine)</td>
<td>insufficient data to support efficacy of maintenance therapy with tricyclics</td>
</tr>
<tr>
<td>Frank et al</td>
<td>placebo-controlled trial</td>
<td>tricyclics</td>
<td>imipramine &gt; placebo during 3 years after end of continuation treatment</td>
</tr>
<tr>
<td>Robinson et al</td>
<td>placebo-controlled trial</td>
<td>phenelzine</td>
<td>phenelzine &gt; placebo in recurrence prevention 2 years after recovery, but with significant side effects</td>
</tr>
<tr>
<td>Georgotas et al</td>
<td>placebo-controlled trial</td>
<td>nortriptyline, phenelzine</td>
<td>phenelzine &gt; nortriptyline = placebo in recurrence prevention 1 year after recovery</td>
</tr>
<tr>
<td>Montgomery et al</td>
<td>placebo-controlled trial</td>
<td>fluoxetine</td>
<td>fluoxetine &gt; placebo in recurrence prevention during 12 months after end of continuation treatment</td>
</tr>
<tr>
<td>Doogan and Caillard*</td>
<td>placebo-controlled trial</td>
<td>sertraline</td>
<td>sertraline &gt; placebo in recurrence prevention during 7 months after end of continuation treatment</td>
</tr>
<tr>
<td>Dunbar and Montgomery*</td>
<td>placebo-controlled trial</td>
<td>paroxetine</td>
<td>paroxetine &gt; placebo in recurrence prevention during 9 months after end of continuation treatment</td>
</tr>
</tbody>
</table>

Efficacy of Maintenance Treatment with Antidepressants

As mentioned before, pharmacologic maintenance treatment extends beyond the continuation phase and is administered for long periods of time (months or years) to prevent recurrences of depression. During the maintenance phase, the frequency of therapeutic contact typically decreases, often to a level of monthly meetings. Table 2 lists the conclusions of some typical studies on the efficacy of maintenance treatment involving different classes of drugs.

Tricyclic Antidepressants

Very few studies have actually examined the efficacy of maintenance treatment with tricyclic antidepressants against appropriately randomized, placebo-treated, or minimal contact comparison groups. In fact, both the literature review by Kleinman and Schachter* and the meta-analysis by Loonen et al* of the studies published between 1974 and 1987 on the efficacy of maintenance antidepressant drug treatment in patients with recurrent major depression found insufficient data to allow any conclusions about the efficacy of maintenance therapy with tricyclic antidepressants. Overall, the recurrence rates reported in studies with tricyclic antidepressants hovered around 50%, only a modest advantage when compared to placebo.

However, the Maintenance Therapies in Recurrent Depression study by Frank et al* found a significantly lower estimated recurrence rate on imipramine (22%) than on placebo (88%) after 3 years of maintenance treatment. The relatively low recurrence rate on imipramine observed in this study could have been due to the fact that all subjects, including those who were assigned to drug therapy alone during the maintenance phase, had been exposed to prior treatment with interpersonal psychotherapy during the acute phase, possibly augmenting any prophylactic effect of imipramine during maintenance treatment. However, this interpretation does not account for the very high relapse rate of patients on placebo, since any prophylactic effect of interpersonal therapy during the acute phase would
presumably protect the subjects on placebo as well as those on imipramine.

Monoamine Oxidase Inhibitors (MAOIs)

In one double-blind maintenance therapy study involving phenelzine by Robinson et al., 47 subjects who had responded to phenelzine and had maintained their response for at least 16 weeks during continuation treatment were randomized to receive either phenelzine 60 mg per day, phenelzine 45 mg per day, or placebo for 2 years. Patients in both groups receiving phenelzine had fewer recurrences (26% and 33%, respectively) during the course of 2 years than patients receiving placebo (81%), with a nonsignificant difference between phenelzine 60 mg and phenelzine 45 mg up to the 16th month of treatment. Because side effects such as weight gain were more severe in the group receiving the higher dose of phenelzine, the authors recommend that maintenance treatment with phenelzine should be conducted at a dose of 45 mg per day for at least 1 year after response to drug treatment.

In another double-blind, placebo-controlled study, Georgotas et al. followed for 1 year 51 elderly depressed outpatients who had responded to antidepressants and completed continuation therapy. Twenty-three were switched to placebo, while 13 and 15 took nortriptyline and phenelzine, respectively. Patients administered phenelzine did significantly better (13.3% recurrences) than patients administered either nortriptyline (53.8% recurrences) or placebo (65.2% recurrences). These investigators speculate that the high recurrence rate for patients on nortriptyline may have been due to the accumulation over time of its metabolite 10-hydroxynortriptyline, which in high enough concentrations might interfere with nortriptyline's antidepressant effect and produce an apparent "tolerance" effect.

Overall, nonreversible MAOIs seem to be effective in preventing recurrences, but their side-effect profile might interfere with compliance whenever treatment is extended beyond 1 year following recovery.

Selective Serotonin Reuptake Inhibitors (SSRIs)

The estimated 12-month recurrence rate on fluoxetine 40 mg per day (26.1%) was significantly lower than that observed with placebo (57.4%) in a multicenter study conducted in Europe by Montgomery et al. Two other multicenter studies examined the efficacy of SSRIs in the maintenance treatment of MDD. While the study by Doogan and Caillard found a 7-month estimated recurrence rate of about 8% on sertraline and of about 18% on placebo among patients surviving for 3 months after remission, the study by Dunbar and Montgomery observed a 9-month cumulative recurrence rate of 14% on paroxetine and of 30% on placebo following a similar period of continuation treatment.

Overall, all SSRIs show prophylactic efficacy in the maintenance treatment of depression, although the duration of the maintenance phases has been relatively short, particularly in the study by Doogan and Caillard.

DRUG AUGMENTATION STRATEGIES IN LONG-TERM TREATMENT

Most research on augmentation strategies involving the addition of lithium, thyroid hormone, or other agents to ongoing antidepressant treatment has concentrated on treatment-refractory patients nonresponsive to initial antidepressant therapy. Because this literature deals mainly with acute treatment, no controlled data are available yet on the long-term efficacy of these strategies. However, some investigators have used augmentation strategies in the treatment of relapses and recurrences.

For example, a study by Jacobsen examined buspirone augmentation in nine individuals (five unipolar, two bipolar I, and two bipolar II with a history of winter/fall worsening of mood and who experienced remission and subsequent relapse of depressive symptoms while on antidepressants including fluoxetine, nortriptyline, imipramine, and desipramine. After buspirone augmentation of their current medication was initiated, six displayed complete resolution of depressive symptoms, one showed partial improvement, and the remaining two showed no improvement. An extension of these findings might possibly indicate that augmentation could be a viable means not only of reversing depressive relapse but also of preventing it. However, further research is needed in this area.

ISSUES RELATED TO THE USE OF PLACEBO IN LONG-TERM DRUG STUDIES

A methodological issue in long-term drug trials concerns the ecological validity of using
a placebo-control condition as opposed to a "no pill" condition, which parallels actual clinical practice more closely. Although most maintenance studies on depression have preferred to use a placebo arm as opposed to a "no pill" condition, the question may be raised whether there may be differences in outcome between maintaining patients on a placebo versus withdrawing patients from medication.

Despite this concern, there are several reasons why investigators should probably refrain from replacing a placebo-controlled group with a no-pill condition. Although the no-pill condition is a more accurate reflection of the usual clinical practice of withdrawing patients from active treatment, using such a condition would unblind both patients and clinicians to treatment status and therefore jeopardize the investigators' ability to draw meaningful conclusions about the specific efficacy of pharmacotherapy. The discontinuation of those non-specific treatment elements inherent in a pharmacological study (i.e., the confidence that the pills will continue to help the depression) could be associated with some rebound/withdrawal phenomena, and depressive relapse has been observed following termination of several forms of psychotherapies in patients who had responded to these treatments. Furthermore, compliance with follow-up assessments may deteriorate if the medication is discontinued.

**EFFICACY OF ELECTROCONVULSIVE THERAPY IN PREVENTING RELAPSES AND RECURRENCES**

Several investigators have described patients with unipolar or bipolar depression who, upon initial remission of their symptoms, sustain their recovery while receiving regular "prophylactic" ECT treatments, but relapse soon after they miss a scheduled ECT treatment or if the interval between treatments is lengthened. Although these reports suggest that ECT might provide long-term protection against depressive relapse and recurrence, no double-blind study has yet compared the prophylactic effect of ECT versus simulated ECT in a well-defined patient population with major depression, making it impossible to draw firm conclusions concerning the efficacy of long-term treatment with ECT.

**LONG-TERM EFFICACY OF PSYCHOTHERAPY ALONE OR WITH PHARMACOTHERAPY**

Two forms of psychotherapy have been studied extensively in regard to their prophylactic efficacy: cognitive therapy and interpersonal therapy. Cognitive therapy is a problem-oriented, systematic treatment approach to depression developed by Beck and his colleagues. Interpersonal psychotherapy, as described by Klerman et al, focuses on the social context of the depression rather than on the exploration of intrapsychic material or past experiences. Whereas cognitive therapy aims to identify and challenge specific thoughts that engender patients' "distorted conceptualizations and dysfunctional beliefs" that are seen to cause and maintain depression, interpersonal psychotherapy employs a less directive approach aimed at ameliorating depression through improving a patient's interpersonal and social functioning.

**Cognitive Therapy**

Hollon reviewed four studies examining the prophylactic efficacy of cognitive therapy in depression. He found that patients did better following termination of cognitive therapy than patients originally treated pharmacologically, with a relapse/recurrence rate of 26% following cognitive therapy termination (with or without concomitant pharmacotherapy) and of 64% following pharmacotherapy discontinuation. However, Hollon offers no systematic statistical analysis to indicate the significance of these figures.

An 18-month naturalistic follow-up study of patients originally assigned to one of four treatment cells in the Treatment of Depression Collaborative Research Program study found that 36% of patients experienced a relapse/recurrence during the 18 months following 16 weeks of cognitive therapy, as opposed to the 50% relapse/recurrence rate among patients who had responded to imipramine alone. We performed a chi-square analysis on their data and found that this difference did not reach significance (chi-square: 0.30).

Two uncontrolled studies observed a relapse/recurrence rate of 34% and 30% in depressed patients followed for 1 year after successful acute treatment with cognitive therapy. As Hollon points out, however, the bulk of the naturalistic follow-ups used brief treatments and relatively short posttreatment follow-ups, so that they probably suggest efficacy in relapse prevention rather than in recurrence prevention. Therefore, the question of whether cognitive therapy alone does indeed prevent recurrences during maintenance treatment remains to be addressed empirically.
No study has yet truly examined the efficacy of the combination of continued cognitive therapy and pharmacotherapy.

Furthermore, no study has yet truly examined the efficacy of the combination of continued cognitive therapy and pharmacotherapy. This approach is actually considered by many to be a standard of clinical practice, established with the goal of reducing residual symptoms and consolidating improvement. The need to address residual symptoms by adding intensive cognitive therapy to drug treatment of patients whose depression is in remission is supported by the observation that patients with higher levels of dysfunctional attitudes have a relatively higher probability of relapse. A study on 40 patients who had responded to open treatment with tricyclic antidepressants showed that cognitive therapy, initiated after obtaining clinical improvement and added to ongoing drug treatment, reduced residual symptoms significantly more than drug therapy alone.

Interpersonal Psychotherapy

Weissman et al found that, after 1 year of follow-up, depressed patients who received interpersonal psychotherapy combined with amitriptyline experienced a greater improvement in some measures of social adjustment than patients receiving amitriptyline alone. The Maintenance Therapies in Recurrent Depression Study compared the long-term efficacy of interpersonal psychotherapy alone with interpersonal psychotherapy plus placebo, the combination of interpersonal and drug therapy, drug therapy alone, and placebo. In this study, acutely ill patients with two or more prior episodes of unipolar depression received the same short-term treatment regimen consisting of a combination of imipramine (150 mg to 300 mg) and interpersonal psychotherapy.

Once patients had achieved clinical remission for 3 consecutive weeks, they continued to receive combined treatment for an additional 17 weeks. If they continued to be stable, a third evaluation was then conducted and patients were randomly assigned to one of the five above mentioned maintenance treat-
limitation of most maintenance studies is that the duration of the treatment has been relatively short. More studies are needed to evaluate the efficacy of antidepressants over a period of several years as well as to determine the optimal dosage for extended treatment.

Of the two forms of psychotherapy used in clinical research studies to treat depression, there is some evidence suggesting efficacy of cognitive therapy in relapse prevention rather than in recurrence prevention, while interpersonal psychotherapy seems to provide some prophylaxis against recurrences in the maintenance treatment of depression. A promising though relatively neglected area is the combination of pharmacotherapy with continuing psychotherapies such as cognitive therapy throughout the continuation and maintenance phases of treatment of depression. As this type of psychotherapy addresses residual symptoms such as dysfunctional attitudes and social functioning, it may provide depressed patients with improved cognitive and social skills, thus protecting against relapses and recurrences, and, in combination with pharmacotherapy, may show efficacy superior to either approach in isolation.

REFERENCES
35. Weissman MM, Klerman GL, Prusoff BA, Sholomskas D, Fadian N. Depressed outpatients: results one year

Psychiatric Annals 24/6/June 1994
after treatment with drugs and/or interpersonal psychotherapy. Arch Gen Psychiatry. 1981; 38:51-55.