Redefining Antidepressant Efficacy Toward Long-Term Recovery

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Most studies of antidepressant therapy assess short-term or acute phase efficacy and tolerability. However, 30% to 50% of patients with major depression will experience a relapse during the 4 to 6 months following treatment of a depressive episode. Patients who do not remit fully during the acute phase of therapy are at particularly high risk for relapse. In addition, 75% to 80% of patients will experience recurrent depression during their lifetime. Thus, full remission and long-term recovery, rather than short-term response, are the desired outcomes from antidepressant treatment. There is a need for prospective, long-term studies to investigate the response and recovery to antidepressant therapy. Research conducted by our group at the University of Pittsburgh has demonstrated that the rate of recurrence can be significantly reduced across 3 to 5 years of continuous treatment with imipramine. Although relatively little research on longer term, preventative pharmacotherapy has been conducted, studies with newer agents including selective serotonin reuptake inhibitors (SSRIs), nefazodone, and mirtazapine also indicate a lower relapse rate with active drug compared with placebo. The long-term efficacy of venlafaxine has been demonstrated in both an extension study and a recent prospective, double-blind discontinuation study. There is increasing evidence that antidepressants, including the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, are well tolerated and effective options for longer term therapy.
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Most studies of antidepressant therapy assess only short-term efficacy and tolerability. However, unless effective acute phase antidepressant therapy is continued for at least 4 to 6 months, up to 50% of responders will relapse.[1,2] Those who do not remit fully during acute phase therapy are at highest risk for relapse.[2] In addition, major depression is an episodic disorder, and 75% to 80% of patients experience recurrent depression during their lifetime despite previous treatment.[1,3] It is now well recognized that depression causes substantial impairment of social and physical functioning, decreased quality-of-life, increased morbidity, and higher rates of suicide.[4–6] Therefore, rather than short-term response, the optimal outcomes from depression treatment are full remission and long-term recovery. Thus, there is a need for prospective, longer term studies to investigate the response and recovery to antidepressant therapy and the effectiveness of drugs for prevention of relapse and recurrence.

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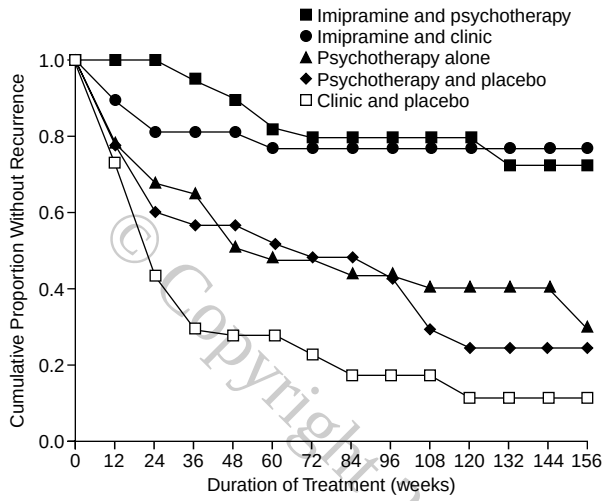
Relapse is defined as the return of symptoms of an index episode of depression during the first few months following a response to treatment or spontaneous remission.[7] Thus, a relapse is presumed to represent a reactivation of the state-dependent illness pathophysiology of the index episode of depression. The period of risk for relapse is highest during the first 4 to 6 months of remission.[8] Thereafter, relapse rates decelerate considerably, suggesting a natural "break" of discontinuity between the events known as relapse and recurrence.[9]

Recurrence, by contrast, is defined as an episode of depression that occurs after a sustained major period of remission. Risk factors for recurrent, antecedent depression include a previous history of episodes of depression, dysthymia, early or late-life onset of depression, long duration of the index episode, family history, poor symptom control during maintenance therapy, and comorbid anxiety disorders.[1,10–12] The chances of a recurrence approach 90% or more once a patient has experienced 3 or more prior depressive episodes.[3,11,13] However, maintenance antidepressant therapy can prevent recurrence and increase the likelihood of sustained recovery.

Antidepressant treatment can be divided into 3 phases, acute, continuation, and maintenance, which cover treatment from response through remission and recovery.[14,15] The acute phase consists of the therapy necessary to produce a response (i.e., an easy-to-treat patient) and may last as little as a few weeks to months in duration (i.e., a treatment-refractory patient). Continuation therapy con-

Figure 1. Three-Year Outcome From Treatment of Recurrent Depression[a]

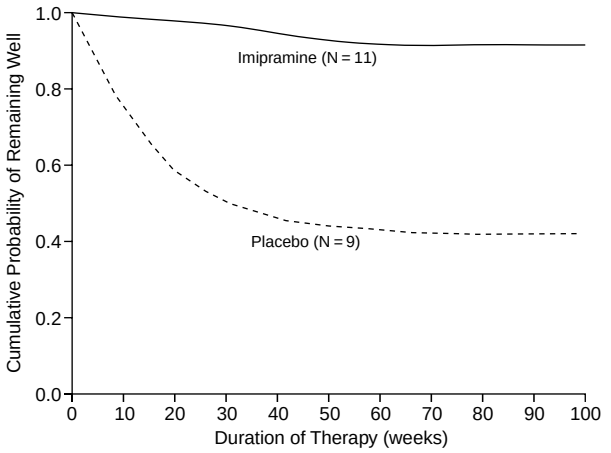


[a]Adapted from reference 3, with permission.

tinues an effective medication for an additional 4 to 6 months with the goal of inducing a remission and preventing a relapse. For those at high risk of recurrence, an extended course of maintenance therapy is needed to prevent recurrence and establish long-term recovery.[1,3]

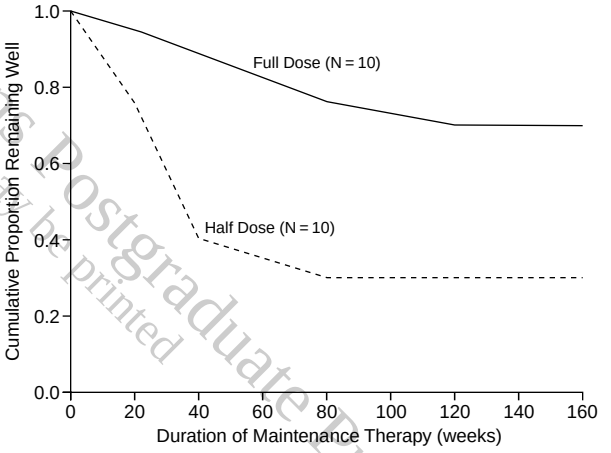
In an influential study of long-term maintenance antidepressant therapy conducted at the University of Pittsburgh, patients with highly recurrent depression were treated initially with the combination of weekly sessions of interpersonal psychotherapy (IPT) and imipramine. Those who responded to treatment and were able to maintain a stable remission across 4 months of therapy were randomly assigned to continue with imipramine, placebo, IPT, or their combination for 3 years.[3] The time to recurrence of depression was significantly ($p < .0001$) longer with imipramine than with placebo, with or without psychotherapy (Figure 1).[3] Although not as effective as imipramine, monthly sessions of IPT also had a significant preventative effect. Maintenance IPT was particularly effective for the subsets of patients with more normal sleep profiles and those who were able to engage in more focused therapy sessions.[16] However, for the portion of patients who had decreased slow wave sleep and below average therapy, IPT was no more effective than placebo. Two smaller trials derived from the Pittsburgh study extended these findings. At the end of the maintenance study, 20 patients without recurrence after 3 years agreed to be re-randomized to receive an additional 2 years of either imipramine or placebo.[17] Only 1 of 11 patients who remained on imipramine therapy had a recurrence compared with 6 of 9 patients switched to placebo ($p = .006$) (Figure 2). It would thus appear that even $3^1/_2$ years of sustained recovery are not sufficient to overcome the risk of highly recurrent depression.

Figure 2. Outcome After 3-Years' Treatment With Imipramine[a]



[a]Adapted from reference 17, with permission. $p = .006$ for comparison of imipramine vs. placebo.

Figure 3. Effects of Full- and Half-Dose Maintenance Therapy With Imipramine on the Prevention of Recurrent Depression[a]



[a]Adapted from reference 18, with permission.

If, indeed, preventative treatment must be maintained indefinitely, then concerns about safety and tolerability are amplified. Historically, a reduced dose of medication was recommended to lessen side effects during maintenance therapy. However, this strategy had never been compared, side-by-side, with full-dose maintenance therapy. The full dose-half dose question was examined prospectively in a study of 20 patients from the original cohort who had experienced a recurrence of depression during treatment with placebo.[18] Patients were restabilized on imipramine and, after attaining a sustained remission, were randomly assigned to a 50% dose reduction or continued full-dose therapy. During the 3-year trial, the recurrence rate was

Table 1. Summary of Results From Selected Continuation Phase Studies of Newer Antidepressants in Major Depression

Reference	Drug	Duration (months)	Relapse Rate (%) Active Drug	Relapse Rate (%) Placebo
Montgomery et al[33]	Fluoxetine	6	18	37
Montgomery and Dunbar[25]	Paroxetine	4	3	19
Doogan and Caillard[24]	Sertraline	4	13	46
Montgomery et al[27]	Citalopram	6	11	31
Anton et al[29]	Nefazodone	12	9	25

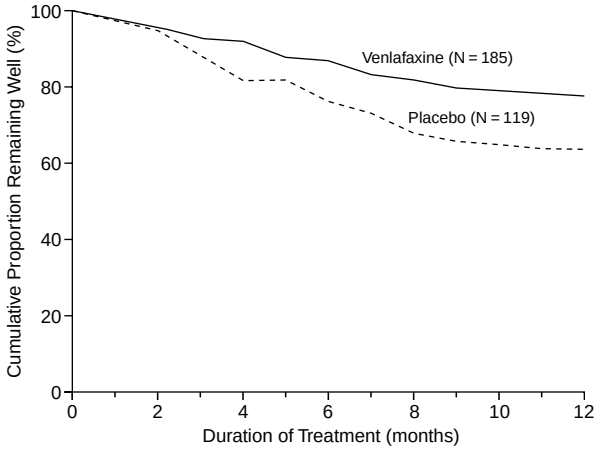
30% with full-dose imipramine and 70% with half-dose imipramine (Figure 3). At least with the tricyclic antidepressant imipramine, a half-dose strategy is not a useful option.

OTHER STUDIES ON LONG-TERM MAINTENANCE PHARMACOTHERAPY OF DEPRESSION

The World Health Organization, the National Institute of Mental Health, and others have presented recommendations for further study of long-term treatment of depression.[19–21] Key among these are prospectively determined eligibility criteria, which include definitions of remission, relapse, and recurrence. It is also important to focus the study on patients with a history of recurrent depression to ensure an efficient study that can be completed in 3 to 5 years. In addition, patients optimally should be enrolled in an open-label phase of long enough duration, e.g., 4 to 6 months, to identify true drug responders and screen out patients with labile or transient responses and to differentiate further between relapse and recurrence. Ideally, the endpoint of open-label treatment and entry criterion for double-blind treatment should be remission (relapse prevention) or recovery (prophylaxis against recurrence) on active drug. Finally, unless the patient group is known to be at particularly high risk, the study design should include a placebo-controlled arm and double-blind assignment during the maintenance phase.

Beyond the work of the Pittsburgh group, there have been several properly controlled longitudinal studies of tricyclic antidepressants (TCAs), the older, nonselective monoamine oxidase inhibitors (MAOIs), and lithium salts for prevention of recurrent depressive episodes (see, for example, the review by Thase and Sullivan[1]). Recently, Stewart et al.[22] extended the evidence for the efficacy of phenelzine for prevention of recurrent episodes of atypical depression, and Kocsis et al.[23] demonstrated that patients who had presented with chronic depressive syndromes also benefited from maintenance treatment with TCAs. These classes of medications are rapidly becoming outmoded, however. It is now imperative to document both the benefits and potential risks of longer term therapy with the newer antidepressants.

Figure 4. Continuation Phase Study of Venlafaxine and Placebo Responders With Major Depression[a]



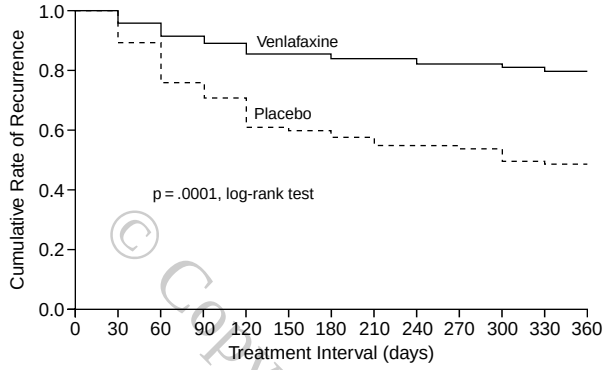
[a]Adapted from reference 35, with permission. p = .022 for comparison of venlafaxine and placebo.

The effectiveness of SSRIs, nefazodone, and mirtazapine has been evaluated in longer term studies.[24–34] The results from the preventative trials consistently show a lower relapse rate with active drug therapy compared with placebo (Table 1). However, most of these studies have at least one limitation in the study design. Some[26,29,31] were simply extensions of short-term studies and were not prospectively designed to evaluate prevention of relapse or recurrence. Specifically, patients were not re-randomized to active drug or placebo for the extension phase. Also, several of these studies did not select patients with a history of recurrent depression. Some studies used imprecise definitions of relapse.[29,31] Only 3 studies could really be considered maintenance phase trials.[32–34] Two studies[30,32] lacked a placebo control group. Despite so many differences in definitions, the time period of observation, and patient selection, the similarity of findings is remarkable. It should be noted that relapse rates of placebo responders during continuation therapy are generally much lower than those of patients switched from active medication to placebo.[1]

VENLAFAXINE FOR PREVENTION OF DEPRESSION RECURRENCE

Long-term antidepressant efficacy data are starting to emerge for venlafaxine from extension phases of short-term clinical studies as well as a prospective study for the prevention of recurrence. Pooled analysis of relapse rates was performed from 4 double-blind, randomized trials of venlafaxine and the active comparators, imipramine and trazodone, extended over 12 months.[35] A relapse was defined as 2 consecutive Clinical Global Impressions (CGI) severity scores greater than 3, a CGI severity score higher

Figure 5. Cumulative Rate of Recurrence in Placebo and Venlafaxine Groups[a]



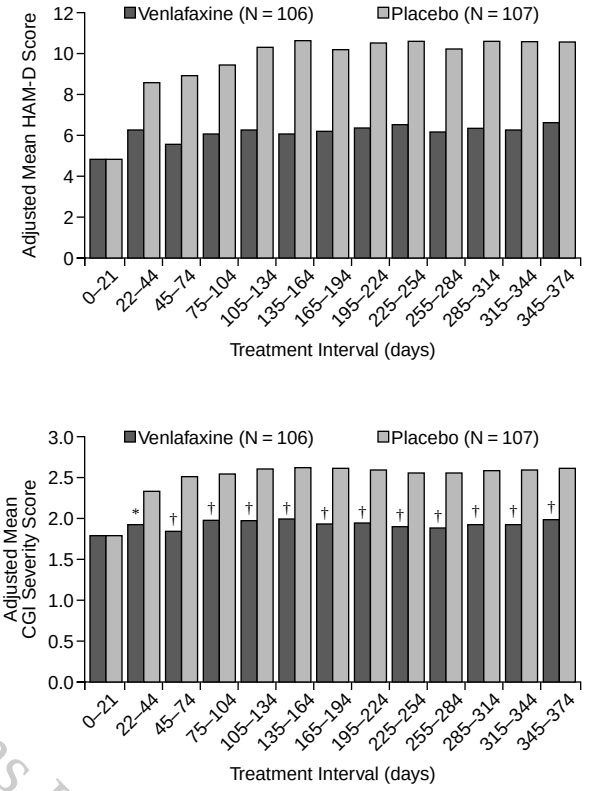
[a]From reference 36, with permission.

than 3 at the time of withdrawal for any reason, or withdrawal from the study for lack of efficacy. The analysis included 304 patients (185 venlafaxine, 119 placebo). Cumulative relapse rates were 11% for venlafaxine and 23% for placebo (p = .019) at 6 months and 20% with venlafaxine and 34% with placebo (p = .022) at 12 months (Figure 4).

More recently, a 12-month, prospective, double-blind, randomized, placebo-controlled study assessed the efficacy and tolerability of venlafaxine, 100 to 200 mg/day, for prevention of recurrence in patients with recurrent major depression.[36] Patients who responded to an 8-week acute phase trial of venlafaxine were continued on open-label therapy for a total of 6 months. Those patients who remained well entered a double-blind, placebo-controlled phase of treatment with venlafaxine for up to 12 months. This study design incorporated several important features: (1) prospective definitions for entry, response, and recurrence; (2) a 6-month period of continuation therapy; (3) selection of patients with a prior history of recurrence; and (4) use of survival analysis to establish the time to recurrence across the 12-month double-blind maintenance phase. Discontinuation for lack of efficacy was reported with 48% of patients in the placebo group and 21% in the venlafaxine group ($p \leq .001$). Life table analysis documented a large difference in survival time (p = .0001; Figure 5). Importantly, the incidence of common adverse events was similar with venlafaxine and placebo during the double-blind phase of treatment. Venlafaxine proved to be both effective and well tolerated (Figure 6).

An ongoing study of similar design is evaluating the effectiveness of once-daily venlafaxine extended release (XR) for prevention of depression recurrence.[37] Patients responding to venlafaxine XR during an 8-week treatment phase are randomly assigned to venlafaxine XR or placebo for a 6-month continuation phase. An interim safety analysis of 214 patients at 6 months revealed an overall rate of adverse events with venlafaxine XR that was comparable to that of placebo. It is anticipated that the results from this study will provide further evidence for relapse prevention with venlafaxine.

Figure 6. Adjusted Mean Scores Over Time for the Hamilton Rating Scale for Depression (HAM-D) Total (top) and Clinical Global Impressions (CGI) Severity Scales (bottom)[a]



[a]From reference 36, with permission.
*$p < .05$, † $p \leq .001$ vs. placebo.

SUMMARY

Full remission and sustained long-term recovery are the optimal outcomes from antidepressant treatment. There is increasing evidence from studies using placebo-controlled, double-blind discontinuation designs to support the effectiveness and safety of preventative pharmacotherapy. Recent studies indicate that venlafaxine is a safe and effective treatment for the prevention of recurrent episodes of major depression. Current recommendations call for the use of the maximum tolerated doses of antidepressants to achieve a full remission and, subsequently, a course of continuation therapy of at least 4 to 6 months' duration.[1] For patients with histories of highly recurrent depressive episodes, long-term, indefinite treatment with maximally tolerated doses of antidepressants may be necessary to reverse a potentially chronic and pro-

gressively deteriorating clinical course. When considering the high rates of recurrence, we now need to emphasize the role of preventative pharmacotherapy to improve the long-term course of depression and to reduce its associated suffering.

Drug names: citalopram (Celexa), fluoxetine (Prozac), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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