*Key Words: chronic major depression, unipolar major depression, serotonin, norepinephrine, SSRI, SNRI, venlafaxine, relapse prevention, recurrence prevention*

# Long-Term Treatment Strategies in Affective Disorders

*By Martin B. Keller, MD*

***ABSTRACT*** *~ Unipolar major depression is a disorder with a high incidence of relapse and recurrence. Some patients with major depression fail to recover from an episode and develop chronic depression. Both episodic and chronic depression are associated with considerable morbidity and mortality. An improved long-term outcome for patients may be achieved by the use of longer courses of treatment in the management of depression, which may ultimately enable recovery from depressive symptoms. The data reviewed in this article indicate that both selective serotonin reuptake inhibitors (SSRIs) and the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine are effective in reducing the incidence of relapse during 6 months of continuation therapy for major depression. In addition, longer-term treatment using imipramine or venlafaxine has shown maintenance therapy to be effective in reducing the risk of recurrence of major depression. Pharmacotherapy using sertraline or imipramine for extended periods of time has also been shown to be effective in attaining remission from, and preventing, recurrence of symptoms in patients with chronic depression. The data reviewed suggest that long-term therapy is beneficial in achieving a sustained return to complete functioning for patients with depression. The significantly higher remission rates attained with venlafaxine treatment as compared with some SSRIs warrant further studies of SNRIs for the long-term treatment of depression.* Psychopharmacology Bulletin. *2002;36(suppl 2):36–48*

## Introduction

Affective disorders are serious, debilitating illnesses associated with significant morbidity and mortality. A review of the epidemiology and characteristics of depression indicates that it is a chronic disorder with a high incidence of relapse and recurrence.[1] Furthermore, findings indicate that there is a great potential for patients with depression to experience marked impairment of social and physical functioning over extended periods of time.[1] These observations suggest a need for such patients to receive longer courses of treatment in the management of depression. It is well documented that various classes of antidepressant medication have the ability to resolve symptoms of depression during acute administration.[2] This article will review the effects of antidepressant therapy given for

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extended periods of time to prevent relapse and recurrence of these symptoms of depression. In addition, the role of antidepressants in the management of chronic mood disorders will be reviewed.

## UNIPOLAR MAJOR DEPRESSION: EPIDEMIOLOGY AND CHARACTERISTICS

Unipolar major depression has a high rate of occurrence in the general population. Data from several worldwide studies conducted since 1988 have confirmed a lifetime prevalence of 16% to 18%.[3] A single episode of major depression can last a long time: approximately 33% of patients experience episodes of more than 2 years' duration. In addition, the longer patients remain depressed, the less likely recovery becomes.[1] Assessment of the cumulative probability of recovery from an episode of major depression indicates that the recovery rate is high during the acute treatment phase, with a probability of 53% of patients recovering within 6 months. The cumulative recovery rate is 70% within 1 year, 81% within 2 years, and 88% within 5 years.[4] Thus, there is a substantial proportion of patients who fail to recover within 5 years of a major depressive episode. Furthermore, the cumulative probability of recovery within 13–15 years of an index episode of depression is 94% (M.B.K., unpublished data, 1997) indicating that some patients remain ill for up to 15 years.



Depressive episodes are associated with a high degree of morbidity and mortality. The risk of suicide is estimated to be 15% among hospitalized depressed patients,[5] and the daily functioning and well-being of patients with major depression are impaired to a degree comparable with or greater than that experienced by patients with other chronic disorders.[1] This study, using measures of morbidity including bed days and disability of daily physical, social, and role functioning, found that patients with depressive symptoms had significantly greater disability than patients diagnosed with hypertension, diabetes, or arthritis, in every measure.[1] Depression was also associated with worse or similar disability in social functioning and current health, compared with patients with lung disease or heart disease.[6]

Despite the chronicity of depression, the risk of recurrence, and the significant impairment of functioning associated with it, the disorder remains undertreated.[7] Therefore, there is a need to recognize depression as a chronic disorder that may require long-term treatment with antidepressants in order to prevent relapse and recurrence of depressive symptoms.

## RELAPSE AND RECURRENCE OF UNIPOLAR MAJOR DEPRESSION

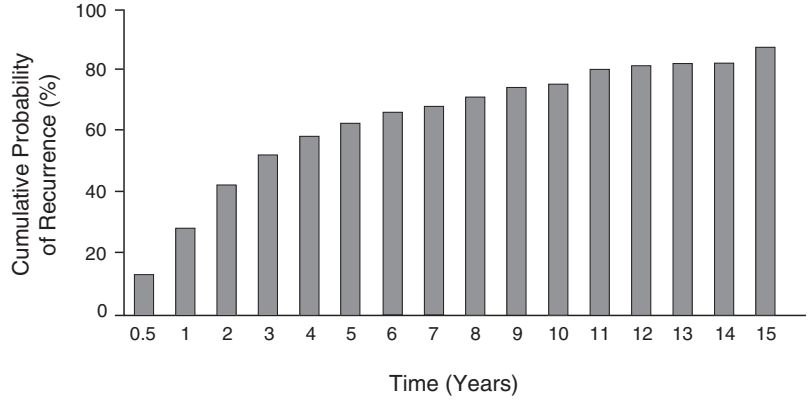
Following resolution of symptoms of depression, there is a risk of relapse or recurrence. Relapse can be defined as a return of the symptoms of the index episode within 6 months of an initial response to treatment in the

patient.[8] Thus, following an initial response to acute antidepressant therapy, most patients benefit from continuation treatment to reduce the risk of relapse. Recurrence of depression is defined as the appearance of a new episode of depression following a period of recovery from the index episode.[8] Although an increasing number of patients recover from the index episode of depression over time, there is a high probability that these patients will experience a recurrence of symptoms. The cumulative probability of recurrence after recovery from the index episode of major depression increases steadily in the 2–3 years after recovery, and there is a 50% probability of recurrence within 3 years.[9] The cumulative probability of recurrence continues to increase for up to 15 years after the index episode, at which point the rate is 85% (Figure 1).[10] The number of prior episodes of depression is a key predictor of recurrence; more than 95% of patients experiencing three or more episodes are predicted to have another within 6 months.[1] Accounting for this risk factor, other patient groups have also been identified as being at high risk for recurrent depression, including those with episodes of depression of long duration, subsyndromal symptoms that do not meet the full criteria for depression, a family history of affective disorder, and the elderly (Table 1).[1] Patients at risk of recurrent depression are most likely to benefit from maintenance treatment with antidepressant therapy.



**FIGURE 1**

**THE CUMULATIVE PROBABILITY OF RECURRENCE OF DEPRESSION AFTER RECOVERY FROM AN INDEX EPISODE OF UNIPOLAR MAJOR DEPRESSION***




* Data shown are obtained from a group of 431 patients followed for up to 15 years following an episode of depression.

Data from: Lavori PW, Keller MB, Mueller TI, Scheftner W, Fawcett J, Coryell W. Recurrence after recovery in unipolar MDD: an observational follow-up study of clinical predictors and somatic treatment as a mediating factor. *Int J Meth Psychiatric Res*. 1994;4:211-229.

Mueller TI, Leon AC, Keller MB, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry*. 1999;156:1000-1006.

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### *Relapse Prevention*

The effects of various antidepressants on relapse rates have been examined in several studies of a "continuation" or "relapse prevention" design (Table 2).[11-16] In these studies, an agent was administered for 4–8 weeks. Patients who responded to treatment and maintained the response for 2–4 weeks prior to randomization continued to receive either medication or placebo for an additional period of up to 52 weeks. The data summarized in Table 2 indicate that there is a highly significant advantage to remaining on active drug treatment following an initial response to either a selective serotonin reuptake inhibitor (SSRI) or a combined serotonergic 5-$HT_2$ receptor antagonist/reuptake inhibitor.[11-16] Comparable data have been obtained using the serotonin

**TABLE 1**

**RISK FACTORS ASSOCIATED WITH RECURRENT DEPRESSION, INDICATING THE PATIENT GROUPS LIKELY TO BENEFIT FROM MAINTENANCE TREATMENT**

*Patient groups identified as having a high risk of recurrent depression*

- History of frequent and/or multiple episodes
- Double depression (major depression plus dysthymia)
- Onset after 60 years of age
- Long duration of individual episodes
- Family history of affective disorder
- Poor symptom control during continuation therapy
- Comorbid anxiety disorder or substance abuse

Adapted from: Keller MB, Boland RJ. Implications of failling to achieve successful long-term maintenance treatment of recurrent unipolar major depression. *Biol Psychiatry*. 1998;44:348-360.
Keller MB. *Psychopharmacology Bulletin*. Vol 36. Suppl 2. 2002.



**TABLE 2**

**COMPARISON OF RELAPSE RATES FOLLOWING CONTINUATION TREATMENT WITH ANTIDEPRESSANT MEDICATION OR PLACEBO AFTER AN ACUTE RESPONSE TO THE ACTIVE AGENT**

| *Antidepressant Medication* | *Treatment (weeks)* | *Drug Relapse Rate (%)* | *Placebo Relapse Rate* (%)* |
|---|---|---|---|
| Fluoxetine[11] | 52 | 26 | 57 |
| Paroxetine[12] | 52 | 16 | 43 |
| Sertraline[13] | 44 | 13 | 46 |
| Citalopram[14] | 24 | 11 | 31 |
| Nefazodone[15] | 36 | 17 | 33 |
| Mirtazapine[16] | 20 | 4 | 23 |

* $P<.001$ for placebo versus drug.
Adapted from: Keller MB, Boland RJ. Implications of failling to achieve successful long-term maintenance treatment of recurrent unipolar major depression. *Biol Psychiatry*. 1998;44:348-360.
Keller MB. *Psychopharmacology Bulletin*. Vol 36. Suppl 2. 2002.

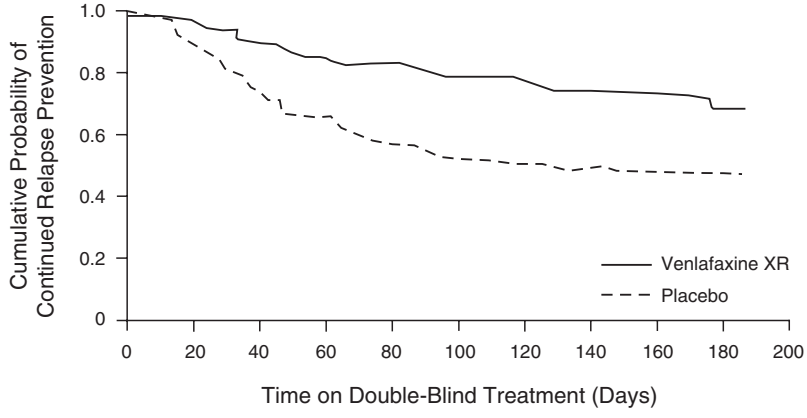
and norepinephrine reuptake inhibitor (SNRI) venlafaxine, which also confers significant protection against relapse of depressive symptoms.[17] Following 6 months of continuation treatment, the probability of relapse was 28% in patients receiving venlafaxine, compared with 52% of those receiving placebo ($P<.001$). In addition to significantly reducing the risk of relapse, continuation therapy with venlafaxine also maintained a low score on the Hamilton Rating Scale for Depression (HAM-D)[18] throughout the 6-month relapse-prevention period, demonstrating continued antidepressant efficacy of venlafaxine (Figure 2A).

Although direct comparisons cannot be made between the antidepressant agents examined in these relapse-prevention studies, a common finding was that most of the benefit of the continuation antidepressant medication was attained in the first 3–6 months of treatment. Plots of the cumulative relapse rate show that, over this initial period, there is a marked separation between the effects of active drug and placebo. Thereafter, the curves plotted for drug and placebo are parallel (Figure 2B). The explanation for such a rapid return of depressive symptoms following early discontinuation of medication is unclear at present, but a continually improving understanding of the neurobiology of depression may enable interpretation of this finding in future studies. However, it has previously been suggested that the rapid return of depressive symptoms may be a direct effect of discontinuation.[19] Nevertheless, the available data provide



FIGURE 2A

**THE EFFECT OF VENLAFAXINE XR COMPARED WITH PLACEBO ON THE CUMULATIVE PROBABILITY OF CONTINUED RELAPSE PREVENTION***




* Determined during 6 months of continuation treatment following an acute response to venlafaxine in patients with major depression.

XR=extended release.

Source: Kunz NR, Entsuah R, Lei D, Rudolph RL, Hackett D. Venlafaxine in the preventive treatment of recurrent major depressive disorder. Poster presented at: Annual Meeting of the European College of Neuropsychopharmacology; Munich, Germany; 2000.

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compelling evidence for treatment regimens that, on achieving a satisfactory therapeutic response, involve continuation therapy for 6–12 months to prevent relapse.

### *Recurrence Prevention*

Recurrence of depression is defined as the development of a new episode of depression following a period of recovery after an index episode.[8] There is a high probability of recurrence (Figure 1), particularly in a number of high-risk patient groups (Table 2),[11-16] and treatment is needed to control this redevelopment of depressive symptoms. In this respect, treatment can be viewed as prophylactic or maintenance therapy in the long-term control of depression.

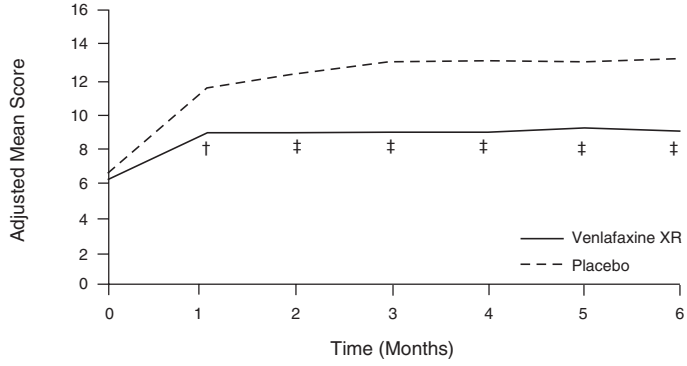
The type of maintenance therapy given could involve long-term use of pharmacotherapeutic agents in addition to psychotherapy. In a placebo-controlled maintenance study involving patients with recurrent depression, the rate of recurrence in patients receiving monthly sessions of interpersonal psychotherapy (IPT) over 3 years (62% IPT alone, 65% IPT+placebo) was lower than that observed in those receiving placebo (78%). However, these rates were higher than those achieved using treatment with imipramine alone (22%) or combined with IPT (24%).[20]



Although the maintenance therapy study suggested that long-term pharmacotherapy offered the greatest benefit in prevention of recur-

**FIGURE 2B**

**THE EFFECT OF VENLAFAXINE XR COMPARED WITH PLACEBO ON HAM-D TOTAL SCORES***




* Determined during 6 months of continuation treatment following an acute response to venlafaxine in patients with major depression.
† *P*<.003
‡ *P*<.001 for venlafaxine XR versus placebo.
HAM-D=Hamilton Rating Scale for Depression; XR=extended release.

Source: Kunz NR, Entsuah R, Lei D, Rudolph RL, Hackett D. Venlafaxine in the preventive treatment of recurrent major depressive disorder. Poster presented at: Annual Meeting of the European College of Neuropsychopharmacology; Munich, Germany; 2000.

rence, the recommended duration and dosage of maintenance therapy for prevention of recurrence is uncertain. An extension of this study indicated that even after full-dose maintenance therapy with imipramine for 3 years, the risk remains that withdrawal of treatment will result in recurrence of depression. Twenty patients with a high probability of recurrent depression who were maintained in remission by treatment with full-dose imipramine for 3 years, either continued to receive imipramine for 2 years or were switched to placebo medication. Discontinuation of imipramine treatment was associated with a 50% probability that depression would recur within approximately 6 months of stopping treatment.[21] Thus, long-term prophylaxis may be required in patients with recurrent depression. However, the long-term use of tricyclic antidepressants, such as imipramine, is not recommended due to the incidence of adverse events and high risks of toxicity and overdose. Alternative long-term medication is preferable.

A recent study[17] has shown that long-term treatment with venlafaxine may offer significant benefit in preventing recurrence of depression. Patients responding to venlafaxine and in remission (HAM-D, score <12) during a 6-month, open-label study were eligible to enter a 12-month, double-blind, randomized recurrence-prevention study. Patients were randomized to receive venlafaxine or placebo during this 12-month recurrence-prevention evaluation period. Switching from active medication to placebo was associated with a higher probability of recurrence, increasing from 34% to 55% between 3 and 12 months after stopping active treatment (Figure 3). The probability of recurrence in patients receiving venlafaxine was much lower (13% versus 22% in those receiving placebo), indicating that venlafaxine was significantly more effective than placebo in preventing the recurrence of depression.



Although maintenance therapy of recurrent unipolar major depression using antidepressant agents has been demonstrated to provide clear benefit, a number of issues remain unresolved. Future studies will need to assess the dose and duration of maintenance antidepressant medication, and to evaluate whether the efficacy of these agents is sustained over long periods of time. Furthermore, after extended periods of pharmacotherapy, cessation of treatment will require assessment in terms of determining rates of relapse and recurrence, and safe tapering of doses during discontinuation of treatment.

### *Current Recommendations for the Treatment of Unipolar Major Depression*

The data presented demonstrate that continuation of acute therapy is required to prevent relapse of an index episode of depression, and that

maintenance therapy is recommended to achieve the long-term goal of preventing the development of new (recurrent) depressive episodes.

Candidates for maintenance therapy are those patients at high risk of recurrent depressive episodes: patients with more than three episodes of major depression or those with more than two episodes plus a family history of mood disorder; a rapid recurrence; onset after 60 years of age; or particularly severe episodes. The available data indicate that during maintenance therapy, patients should be given the dosage of drug that was effective in providing the initial resolution of depressive symptoms. The duration of this treatment has been suggested to cover two episodic cycles, which in some patients (with previous episodes less than 2.5 years apart) may equate to 4–5 years of therapy followed by a slow, tapered discontinuation of medication. Concomitant psychotherapy has shown some benefit in preliminary studies, although the role of nonpharmacotherapeutic treatment in the maintenance therapy of recurrent depression has yet to be fully established.

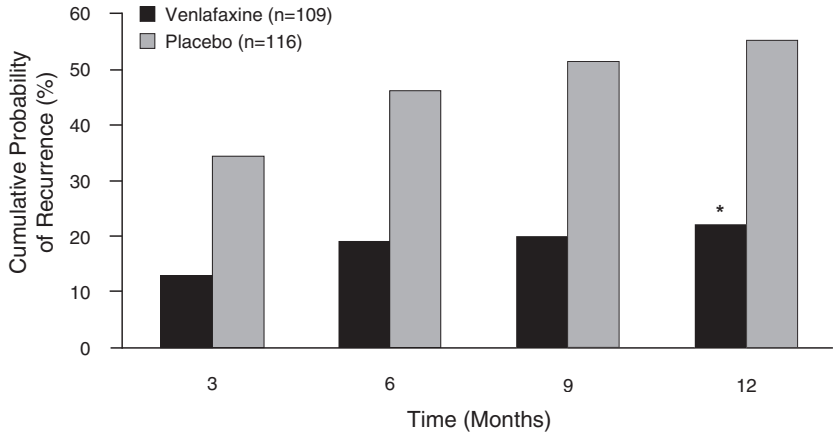
## CHRONIC DEPRESSION

Some patients with depression do not recover from the index episode, developing chronic depression of at least 2 years' duration. Indeed, 10% of patients remain clinically depressed for at least 5 years.[3] Chronic depression is estimated to affect as many as 30% to 35% of patients presenting with depression,[6] and its prevalence is high (3% to 5%).[22] However, the disorder remains underrecognized and undertreated.[23]



**FIGURE 3**

**CUMULATIVE PROBABILITY OF RECURRENCE OF DEPRESSION IN PATIENTS WITH MAJOR DEPRESSION DURING 12 MONTHS OF MAINTENANCE TREATMENT WITH VENLAFAXINE OR PLACEBO**




* *P*<.001.

Data from: Kunz NR, Entsuah R, Lei D, Rudolph RL, Hackett D. Venlafaxine in the preventive treatment of recurrent major depressive disorder. Poster presented at: Annual Meeting of the European College of Neuropsychopharmacology; Munich, Germany; 2000.

Keller MB. *Psychopharmacology Bulletin*. Vol 36. Suppl 2. 2002.

Chronic depression is associated with a high degree of morbidity and mortality. Patients with chronic depression experience a high degree of psychosocial and physical impairment,[24] high rates of comorbidity of anxiety disorder, alcoholism, and personality disorder,[25] and, when the disorder is severe enough to require hospitalization, these patients have a 15% probability of committing suicide.[3]

Chronic forms of depression include dysthymia, chronic major depression, and double depression. Dysthymia is defined as a depressed mood that persists most of the time for at least 2 years (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition-Text Revision [*DSM-IV-TR*]).[26] Although symptom severity may be lower than in episodes of major depression, patients with dysthymia experience considerable functional impairment. Indeed, the impairment of well-being and functional status in patients with chronic affective disorder is significantly worse than that observed in patients with major depression alone.[24] Chronic major depression is defined as an episode of major depression of at least 2 years' duration, and double depression is defined as episodes of major depression superimposed on dysthymia of at least 2 years' duration (*DSM-IV-TR*).[26] Although patients with chronic major depression may have fewer episodes compared with patients with double depression, the duration of the index episode is longer.



Some of these issues are currently under evaluation in a long-term maintenance study of venlafaxine compared with SSRIs in patients with recurrent unipolar major depression (Wyeth Pharmaceuticals, study in progress). This study will examine the effects of venlafaxine in three phases of treatment: acute phase, continuation phase, and maintenance phase. Previous studies have shown the superiority of venlafaxine over SSRIs in the treatment of depression to remission, and this study aims to determine the benefits of long-term treatment with this SNRI compared with SSRIs. The study objectives include evaluation of response and remission in the acute and continuation phases, any loss of efficacy (development of tachyphylaxis) in the continuation phase, and prevention of recurrence of depression in the maintenance phase.[27]

### *Acute Treatment of Chronic Depression*

Patients with chronic depression are often undertreated,[23] possibly due to an assumption that these patients are chronically depressed as a consequence of failure to respond to antidepressant medication. However, acute treatment of patients diagnosed with chronic depression can provide a satisfactory therapeutic response. Patients with chronic major depression (mean duration of episode 8.9 years) or double depression (mean duration of dysthymia 23.4 years) were treat-

ed for 12 weeks with sertraline or imipramine. An intent-to-treat analysis revealed that 52% of patients in the sertraline group and 51% of patients in the imipramine group achieved a satisfactory therapeutic response, defined as a Clinical Global Impressions (CGI)-Improvement score of 1 or 2, a total HAM-D (24-item) score of <15, a ≥50% decrease from the baseline in HAM-D total score, and a final CGI-Severity score of <3. Furthermore, despite the chronicity of the depression recorded in these patients, remission from symptoms could be attained. Remission, defined as a CGI-I score of 1 or 2 and a total HAM-D (24-item) score of <7, was attained in 32% of patients receiving sertraline and 34% of those receiving imipramine (intent-to-treat analysis).[25]

A study of venlafaxine in patients with chronic treatment-resistant depression showed that treatment led to a response in a significant proportion of patients.[28] These patients had previously failed to respond to at least three adequate trials of antidepressants (at least two different antidepressant classes or electroconvulsive therapy and at least one augmentation attempt). The criteria for full response were: HAM-D (21-item) score<8, Montgomery Åsberg Depression Rating Scale (MÅDRS)[29] score<12, and CGI score=1. Partial response was defined as: 50% decrease in HAM-D (21-item) score (final score>8) and MÅDRS score (final score>12), and CGI score=2. Following 12 weeks of treatment with venlafaxine, about one third of patients were considered to be either full or partial responders (32.9% by HAM-D score, 30% by MÅDRS, and 40% by CGI).[28]



The ability of antidepressant medication to achieve remission in patients with chronic depression has major implications for their social functioning. Patients with chronic depression were found to have marked impairment of social functioning, (total score on a social adjustment scale 2.6, compared with 1.6 for normal subjects).[30] This impairment in social functioning was not corrected following attainment of a satisfactory therapeutic response to sertraline or imipramine; the social adjustment scale total score remained significantly elevated for patients with chronic depression compared with normal patients (total score 2.1 versus 1.6, respectively). However, in patients defined as "in remission" (Research Diagnostic Criteria <2) for 8 consecutive weeks following treatment with sertraline or imipramine, the Social Adjustment Scale total score (1.7) was not significantly different from that of normal patients.[31] Thus, normalization of social functioning was only observed in patients remitting during treatment and therefore illustrates the importance of treating to remission.

### *Long-Term Treatment of Chronic Depression*

The data reviewed above indicate the benefit of continuation therapy and maintenance therapy with antidepressants in the prevention of

relapse and recurrence of an episode of major depression. Since treatment can produce a response and remission in patients with chronic depression,[32] it seems likely that these patients would also benefit by changing to long-term or maintenance antidepressant therapy. A maintenance-phase study (18 months) of the efficacy of sertraline in the treatment of chronic depression indicated that a significantly lower number of patients treated with sertraline showed recurrence of depression compared with those receiving placebo (6% versus 23%, respectively; Figure 4).[32]

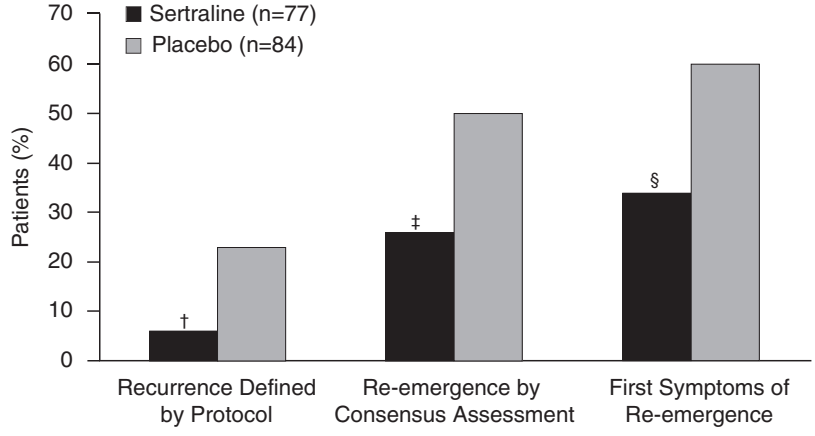
### *Role of Psychotherapy in the Treatment of Chronic Depression*

Psychotherapy may have potential as an adjunct to pharmacotherapy in the long-term treatment of chronic depression. The effects of nefazodone and a cognitive-behavioral analysis system of psychotherapy administered alone and in combination, have been evaluated in patients with chronic depression. In an acute phase of treatment (12 weeks) the overall rate of response (both remission and satisfactory response) was 46% in both the nefazodone group and the psychotherapy group, compared with 73% in the combined-treatment group (intent-to-treat analysis).[33] Thus, the combination of treatment was significantly more efficacious than either treatment alone.



FIGURE 4

**PROPORTION OF PATIENTS WITH CHRONIC DEPRESSION EXPERIENCING RECURRENCE OF DEPRESSIVE SYMPTOMS FOLLOWING 18 MONTHS OF MAINTENANCE TREATMENT WITH SERTRALINE OR PLACEBO***




* Assessed by protocol, consensus assessment, or by re-emergence of first symptoms of depression.
† *P*=.002
‡ *P*=.001
§ *P*<.001 for sertraline versus placebo.

Data from: Keller MB, Kocsis TH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA*. 1998;280:1665-1672.

Keller MB. *Psychopharmacology Bulletin*. Vol 36. Suppl 2. 2002.

## CONCLUSION

In conclusion, data show that in both unipolar major depression and chronic depression there is considerable benefit in extending antidepressant therapy beyond acute-phase treatment. Once a therapeutic response has been obtained, continuation therapy significantly reduces the incidence of relapse. Furthermore, prophylactic treatment using maintenance therapy significantly reduces the incidence of recurrence of depressive symptoms. Data from studies of episodic major depression and chronic depression indicate that long-term therapy is both recommended and efficacious for most depressed patients. The ability of the SNRI venlafaxine to inhibit both serotonin and norepinephrine reuptake, and the demonstrable efficacy of this agent in improving response and remission rates and preventing relapse and recurrence, suggest that venlafaxine may be of particular use in the long-term treatment of depression. Further studies are ongoing to investigate the role of SNRIs as long-term treatment in the management of depressive disorders. ✤

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## DISCLOSURE

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