Key Words: antidepressants, mechanism of action, serotonin, norepinephrine, SSRI, SNRI, venlafaxine, tricyclic antidepressants, monoamine oxidase inhibitors

Long-Term Treatment Strategies in Anxiety Disorders

By Christer Allgulander, MD, Robert M. A. Hirschfeld, MD, and David J. Nutt, MD, PhD

ABSTRACT *~ Anxiety disorders are prevalent and associated with increased morbidity and mortality. Some chronic anxiety disorders, including generalized anxiety disorder (GAD), may be characterized by an underlying high level of anxiety on which exacerbations of symptoms are superimposed. Effective treatment of anxiety disorders should therefore strive to attain both an acute reduction in the symptoms of anxiety (a response) and sustained resolution of the symptoms of any underlying chronic anxiety (remission). This strategy may necessitate long-term treatment of these disorders by pharmacotherapy and/or psychotherapy. Studies using the serotonin and norepinephrine reuptake inhibitor (SNRI), venlafaxine extended release (XR), suggest that these aims may be achieved using this newer class of drugs. Studies with venlafaxine XR in patients with GAD have demonstrated robust anxiolytic efficacy over placebo, particularly regarding worry, cognitive dysfunction, and muscular tension, which are specific to GAD. Administration of venlafaxine XR over both short- (8-week) and long-term (6-month) periods resulted in a significantly greater number of patients achieving response and remission than obtained with placebo. Long-term treatment with venlafaxine XR in patients with GAD showed greater efficacy than that observed in short-term studies. This was achieved without any loss of short-term efficacy and patients' social functioning was also restored. While available data indicate that venlafaxine XR is an appropriate choice of agent in the long-term treatment of GAD, more studies are needed to determine how to further increase remission rates and to maintain remission beyond 6 months.*
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Introduction

Anxiety disorders are common[1,2] and often undertreated, resulting in significant impairment of daily functioning in a considerable number of people. The availability of newer medications, including the serotonin and norepinephrine reuptake inhibitor (SNRI), venlafaxine extended release (XR), offers the opportunity to re-evaluate the goals in treating anxiety disorders. This article reviews the treatment of

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anxiety disorders, particularly generalized anxiety disorder (GAD), and suggests that there is a need to treat patients until they achieve full resolution of symptoms and complete recovery from the illness. Data obtained from the clinical studies of venlafaxine XR demonstrate that these targets may be approached with longer-term (6 months) therapy of patients with GAD.

PREVALENCE AND TREATMENT OF ANXIETY DISORDERS

Data generated from health surveys of large population samples in Sweden (N=39,379) showed that high proportions of men (8% to 11%) and women (16% to 20%) described themselves as suffering from symptoms of worry, anguish, or anxiety.[3] Results obtained from diagnostic interviews in the general United States population (N>8,000) indicated that 17.2% of people in the US suffer from anxiety disorders for a period of 1 year, and 24.9% live with the disorder all their lives.[2] The proportion of respondents who described symptoms of anxiety did not change appreciably between the Swedish surveys in 1980–1981 (9.7% of men, 19.9% of women) and 1996–1997 (10.9% of men, 20.1% of women), despite increased understanding of anxiety disorders and therapeutic advances during this period. This suggests that, although diagnosis and treatments may have improved, the number of people seeking treatment has not changed significantly. Thus, despite being highly prevalent, anxiety disorders are under-recognized, undertreated, or treated with ineffective agents. Evidence to support this explanation has been reported from studies of populations in the US, Sweden, and the United Kingdom (UK).[2-4]

The Swedish survey also found that 3.2% of the general adult population rated their anxiety symptoms as severe. An evaluation of the treatment received indicated that the proportion of anxious patients receiving treatment was low. Only 30% of respondents with severe anxiety reported being treated with antidepressants or anxiolytics. These findings suggest that, even for patients with severe anxiety, most do not receive appropriate treatment. Similar findings have been reported in a sample population of more than 10,000 individuals in the UK.[4] The proportion of patients receiving treatment for diagnosed anxiety disorders was 8% with GAD, 14% with panic disorder, 19% with obsessive-compulsive disorder, and 11% with anxiety and depression.[4] As found in the Swedish study, the likelihood of any treatment increased with symptom severity.

The consequences of undertreating anxiety disorders are considerable. Patients with anxiety are frequently seen in general medical clinics, where they tend to present with unexplained physical symptoms for which they have often been extensively investigated, before referral to a psychiatrist.[5] In a US study[6] examining the group of high consumers of health care in

a health maintenance organization (HMO), 40% were found to have a history of GAD. Recent evidence has shown that risks to the patient of certain aspects of anxiety, particularly worry in some domains, may include increased liability to myocardial infarction and heart disease.[7] There is also an elevated risk of completed suicide among former inpatients with primary anxiety neurosis.[8] The economic cost of undertreating anxiety disorders are also considerable.[9] Anxiety disorders thus impinge on patients' physical health as well as their psychological well-being. Effective treatment of anxiety disorders is clearly required to enable those patients to return to normal functioning.

TREATMENT OF ANXIETY DISORDER

Anxiety disorders are generally characterized by a chronic course that exhibits a pattern in which periods of remission and relapse are observed.[10-12] The core diagnostic feature of GAD is chronic, excessive worry for at least 6 months (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[13]), but for many patients it may last much longer.[14] Indeed, the Epidemiologic Catchment Area (ECA) study reported that up to 40% of patients with GAD (as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition[15]) had endured their illness for more than 5 years.[1] Furthermore, 27% of patients experiencing full remission from GAD are likely to relapse within 3 years.[14]

It has been suggested that chronic anxiety may exist in two forms: intermittent bouts of severe anxiety, or continuous mild-to-moderate symptoms of anxiety on which intermittent bouts of severe anxiety are superimposed.[16] "Intolerance of uncertainty" has been proposed as a term to describe the worry and associated cognitive dysfunction that is typical of GAD.[17] The episodic exacerbation of symptoms may be transient or escalate into longer-term phases of severe anxiety. An episodic nature to the course of chronic anxiety may have implications for treatment. If patients seek treatment during a prolonged exacerbation of an underlying level of anxiety, there is a risk that only the symptoms of the exacerbation will be treated, rather than the chronic course of the disorder. That is, patients may only be treated short-term to alleviate symptoms (response), rather than long-term for a remission of the symptoms of their condition (Figure 1).

Response Versus Remission

The effect of treatment on the symptoms of anxiety disorders can generally be defined as a response or a remission. A response is a measure of improvement of clinical symptoms specific to the disorder. For GAD, response is typically defined as a reduction of at least 50% from the base-

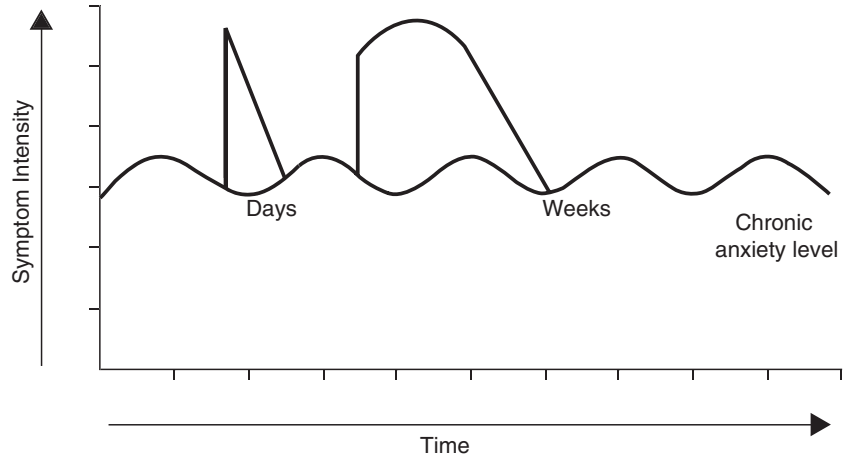
line total score of the Hamilton Rating Scale for Anxiety (HAM-A),[18] and for major depression, response is defined as a similar reduction in score on the Hamilton Rating Scale for Depression (HAM-D).[19] A response to treatment is not usually described in absolute terms, but as a relative change from a pretreatment measure of clinical symptoms. Response indicates a substantial improvement, but not that the patient is well. Indeed, many symptoms often remain.

Remission from a disorder can be defined as the stage at which there is resolution of clinical symptoms and the functional impairment associated with the disorder, ie, the patient is well. The European College of Neuropsychopharmacology consensus meeting[20] proposed that remission from anxiety disorders equates to a score of ≤7 on the HAM-A scale. Hence, remission is defined as an absolute measure, irrespective of the baseline level of anxiety at which patients commence treatment. The attainment of remission is an ambitious target that may require long-term treatment.

The long-term strategy in the treatment of anxiety disorders should therefore ensure that patients receive effective therapy, on which they should be maintained for a sufficient period to maximize the possibility of optimal treatment outcome. Thus, following reduction of the acute symptoms of anxiety (response), continued therapy might enable the full resolution of symptoms and restoration of normal functioning (remission).

FIGURE 1

CLINICAL COURSE OF GENERALIZED ANXIETY DISORDER



Source: Rickels K, Schweizer E. The clinical presentation of generalized anxiety in primary-care settings: practical concepts of classification and management. *J Clin Psychiatry*. 1997;58(suppl 11):4-10. Reprinted with permission of the Physician's Postgraduate Press.

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LONG-TERM TREATMENT OF GAD

GAD is a chronic anxiety disorder that is undertreated[4] and associated with a poor long-term outcome.[14,21] Among typical GAD patients receiving mainly benzodiazepines and tricyclic antidepressants (TCAs) in the 1980s, only 15% attained remission from the disorder within 1 year of diagnosis, rising to just 38% of patients within 5 years.[14] Although the likelihood of partial remission (defined as a decrease in psychiatric status rating of 3, ie, ≤50% of time worrying and accompanied by three symptoms) was higher, still <50% of patients achieved partial remission within 5 years.[14] These data contrast with equivalent data obtained from a study of patients with unipolar major depression, where the probability of remission within the first year (70%) is comparatively high and rises to 88% by 5 years.[22] The reason for this difference in remission rates for patients with GAD compared to those with depression is not fully understood, but may reflect differences in the nature of the two illnesses, such as the chronicity of GAD which, unlike depression, is not episodic. Other reasons for the difference in remission rates may include inappropriate or ineffective treatment of GAD in large numbers of patients; most traditional anxiety treatment is only given short-term. GAD is therefore an anxiety disorder for which long-term therapy may be required to attain the desired treatment goal of remission.

A nonpharmacotherapeutic approach to the treatment of GAD is the use of psychotherapy, particularly forms that target the excessive worry and muscle tension typical in patients with the disorder. A pooled analysis of the few published controlled studies of psychotherapy in GAD showed that treatment with cognitive behavior therapy (CBT) or applied relaxation resulted in recovery 6 months after treatment in 51% and 60% of patients, respectively, although analytical psychotherapy had little effect (recovery rate 4%).[23] However, the Spielberger State-Trait Anxiety Inventory (STAI-T) scale used in this study did not adequately assess items of worry, anxiety, and tension, and this limits the usefulness of this scale for determining the outcome of therapy for GAD. Furthermore, the need to treat the symptoms of worry, anxiety, and tension as the core symptoms of GAD is highlighted.[23] The alternative approach is the use of pharmacotherapeutic agents, either alone or in combination with psychotherapy/CBT, in the long-term therapy of GAD.

A study using the TCA, imipramine, suggested that antidepressants might be more effective than anxiolytics in the acute treatment of GAD.[24] There is good evidence to suggest that abnormality of the serotonin and norepinephrine systems is involved in the neurobiology of both GAD and major depression.[25,26] The SNRI, venlafaxine XR, by virtue of its ability to modulate both of these systems, is therefore likely to be effective in the treatment of GAD.

Venlafaxine XR in the Treatment of GAD

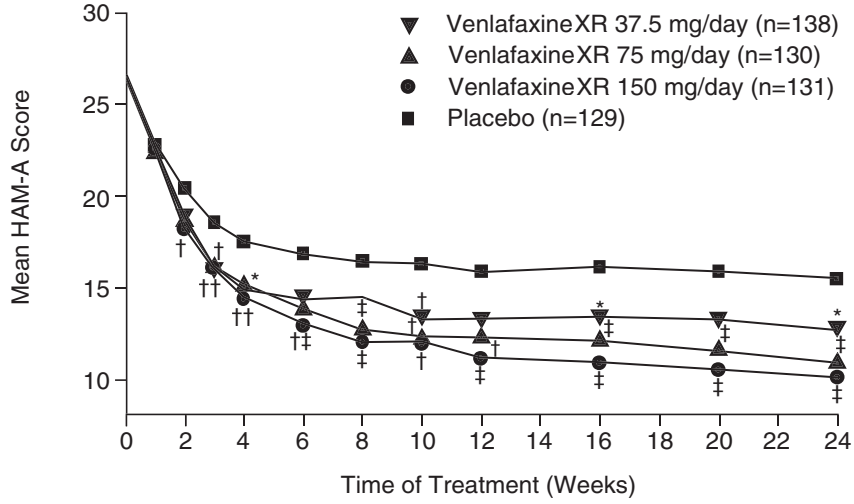
The short-term (8-week) administration of venlafaxine XR to patients with GAD was associated with decreases in HAM-A psychic anxiety, anxious mood, and tension scores that were significantly greater than those achieved by administration of placebo or buspirone (Sheehan, pages 68-78).[27,28] Additional placebo-controlled studies have also evaluated the long-term (6-month) effects of venlafaxine XR in the treatment of GAD.[29]

The administration of fixed doses of venlafaxine XR (37.5, 75, and 150 mg/day) for 6 months to patients with GAD results in a dose-dependent anxiolytic response, determined as a reduction in the mean HAM-A total score that was significantly greater than placebo (Figure 2).[29] A statistically significant effect was evident within 2–3 weeks of commencing treatment, with a clinically meaningful response (defined as ≤50% HAM-A total score) from week 4 of treatment. The anxiolytic effect of venlafaxine XR was sustained and remained greater than placebo for the

FIGURE 2

SYMPTOM REDUCTION DURING 6 MONTHS OF TREATMENT WITH VENLAFAXINE XR OR PLACEBO IN GAD

Mean HAM-A total scores determined at baseline and during 24 weeks of treatment of patients with GAD with placebo or venlafaxine extended release 37.5, 75, or 150 mg/day (ITT, LOCF).



*$P \leq .05$
†$P \leq .01$
‡$P \leq .001$

XR=extended release; GAD=generalized anxiety disorder; HAM-A=Hamilton Rating Scale for Anxiety; ITT=intent-to-treat; LOCF=last observation carried forward.

Adapted from: Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (XR) in the treatment of generalized anxiety disorder: a 24-week placebo-controlled dose-ranging study. *Br J Psychiatry*. 2001;179:15-22. Allgulander C, Hirschfeld RMA, Nutt DJ. *Psychopharmacology Bulletin*. Vol 36. Suppl. 2. 2002.

6-month duration of the study. Furthermore, there was evidence of continued improvement in symptoms over time in patients receiving venlafaxine XR, seen as a progressive decline in the HAM-A total score by 12–24 weeks of treatment, particularly at the higher doses of venlafaxine XR (Figure 2). The onset of anxiolytic effect was observed at weeks 1 and 2 with venlafaxine XR 150 mg, and weeks 2 and 3 with venlafaxine XR 37.5 mg and 75 mg. All doses of venlafaxine XR demonstrated significantly higher treatment response rates versus placebo as early as week 2.[29]

The ability of venlafaxine XR to produce a sustained anxiolytic response in patients with GAD has been confirmed in a long-term, flexible-dose trial, which enabled optimization of the medication that patients received.[30] Administration of venlafaxine XR (75–225 mg/day; mean daily dose 176 mg) produced a rapid reduction in the HAM-A total score that was significantly greater than placebo after only 1 week of treatment, and remained greater in patients treated with venlafaxine XR at study completion, ie, 28 weeks (change in total score -13.4 versus -8.7).[30] Although remission was not a primary outcome measure in this study, determining remission in patients with anxiety disorders is important, since patients in remission have the greatest chance of returning to normal functioning. Thus, data from two long-term studies were analyzed retrospectively by pooling the data sets from each study.

Data obtained in both of these 6-month studies were pooled and used to assess the longer-term effects of venlafaxine XR treatment on response and remission rates in patients with GAD.[31] The number of patients identified as responders (≥50% improvement in baseline HAM-A total score) during venlafaxine XR treatment was significantly ($P \leq .05$) higher than placebo (8% of the venlafaxine XR group, versus 3% of the placebo group) as early as week 1 of treatment.[31] There was then progressive accumulation of patients responding to venlafaxine XR such that, by week 8 of the study, approximately 60% of patients in the venlafaxine XR group were categorized as responders, compared with approximately 35% of patients receiving placebo ($P \leq .001$). At the completion of the 6-month study, 66% of patients in the venlafaxine XR group were responders, compared with 39% of those receiving placebo ($P \leq .001$).[30]

The long-term effectiveness of venlafaxine XR in the treatment of GAD was also demonstrated by the observation that significantly fewer patients discontinued venlafaxine XR therapy for lack of efficacy than did patients receiving placebo.[31] Survival analysis showed that, while patients receiving placebo discontinued therapy at an almost constant rate from the first month of treatment onwards, discontinuations in the venlafaxine XR group either slowed or stopped from the second month of treatment (Figure 3). Thus, after 6 months of fixed or flexible daily doses of venlafaxine XR (≥150 mg), only 4% to 8% of patients had dis-

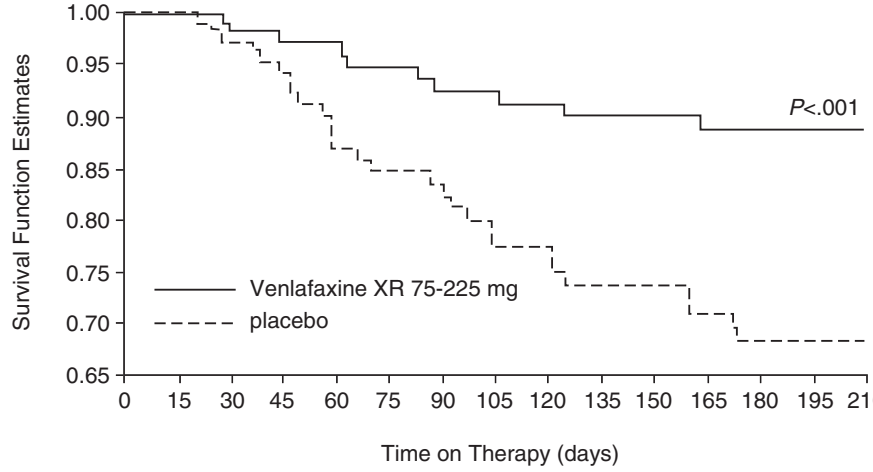
continued for lack of efficacy, compared with 21% to 22% of those receiving placebo (Figure 3).[32]

Venlafaxine XR appears to be particularly effective in reducing the psychic symptoms of anxiety. Assessment of a number of HAM-A items indicated that 6 months of treatment with venlafaxine XR was associated with a greater effect size (difference between baseline and 6-month scores for each item of interest) than placebo in most items, with particularly marked effects (effect size of ≥1) on anxious/worried mood, tension, intellectual function (poor memory, difficulty in concentration), somatic (muscular aches and pains) complaints, and behavior at interview items.[33]

The robust efficacy of venlafaxine XR in reducing symptoms of GAD translates to an ability to attain the goal of remission during treatment. Analysis of the data pooled from the two studies cited above indicated that, following 6 months of treatment with venlafaxine XR, 43% of all patients who started treatment could be defined as in remission (HAM-A total score of ≤7), compared with only 19% of patients receiving placebo ($P \leq .001$).[30] Furthermore, there was evidence that with continued treatment, increasing numbers of patients remitted as indicated by a progressive increase in the proportion of patients in remission during weeks 8–24 of treatment (Figure 4). This trend was confirmed by an analysis comparing response and remission rates at 8 weeks and at study completion.

FIGURE 3

SURVIVAL FUNCTION ESTIMATES FOR PATIENTS RECEIVING VENLAFAXINE XR (≥150 MG) OR PLACEBO



XR=extended release.

Adapted from: Montgomery SA, Mahe V, Haudiquet V, Hackett D. Survival analyses of discontinuations as evidence of long-term effectiveness of venlafaxine XR in GAD: comparison of venlafaxine XR with placebo. *Eur Neuropsychopharmacol*. 2000;10(suppl 3):S338.

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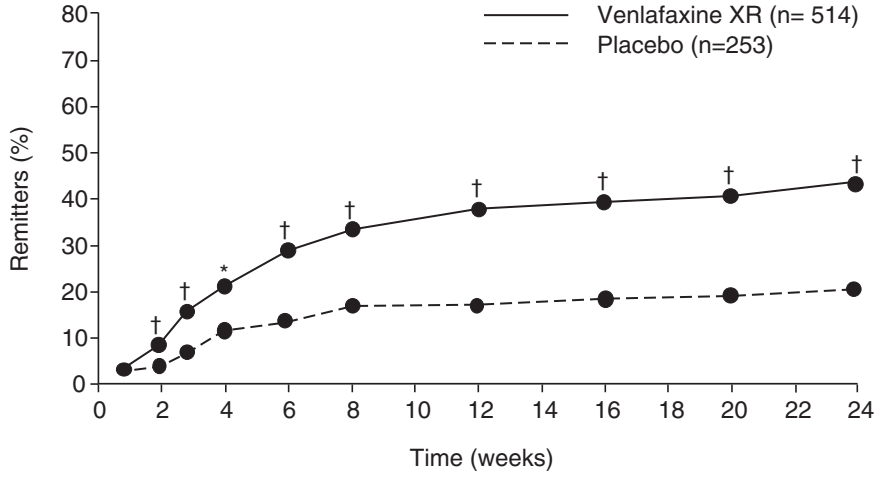
Of patients receiving placebo (n=51) for 8 weeks (short-term), continued administration resulted in remission in 20 (39%) patients. However, of patients responding to 8 weeks of venlafaxine XR therapy (n=131), a remission was observed in 80 (61%) patients by the end of long-term treatment (Figure 5a).[31] Moreover, of patients identified as nonresponders (n=62) after short-term administration of placebo, long-term administration (6 months) resulted in 16 (26%) becoming responders. Of those identified as nonresponders (n=85) after short-term administration of venlafaxine XR, a large proportion of patients (n=54; 64%) subsequently became responders after long-term (6-month) treatment (Figure 5b).[31] These data suggest that continued treatment with venlafaxine XR is associated with longer-term benefits of attaining a response and an eventual remission from symptoms.

FIGURE 4

REMISSION RATES IN GAD PATIENTS TREATED WITH VENLAFAXINE XR OR PLACEBO FOR UP TO 6 MONTHS

The proportion of patients with GAD categorized as in remission (HAM-A total score ≤7) during 24 weeks of treatment with venlafaxine XR or placebo (ITT, LOCF analysis). Figure represents data pooled from two 6-month studies of fixed dose (37.5, 75, or 150 mg/day) or flexible dose (mean dose=176 mg/day) venlafaxine XR compared with placebo.



*$P \leq .05$ versus placebo group.
†$P \leq .001$ versus placebo group.
GAD=generalized anxiety disorder; XR=extended release; HAM-A=Hamilton Rating Scale for Anxiety; ITT=intent-to-treat; LOCF=last observation carried forward.

Adapted from: Montgomery SA, Sheehan DV, Meoni P, Haudiquet V, Hackett D. Characterization of the longitudinal course of improvement in generalized anxiety disorder during long-term treatment with venlafaxine XR. *J Psychiatr Res*. 2002. In press.

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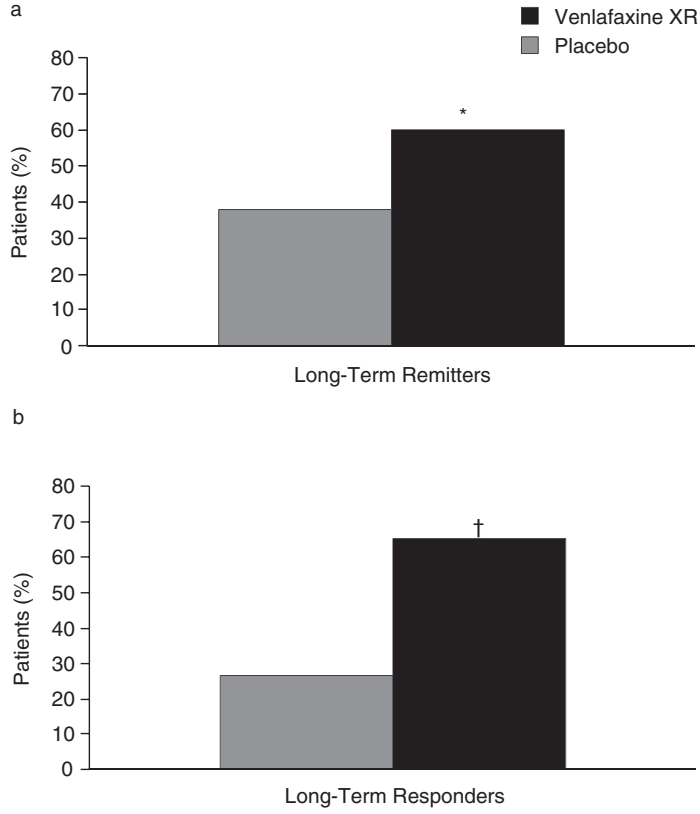
LONGER-TERM BENEFITS OF TREATMENT TO REMISSION

The longer-term administration of effective pharmacotherapy for GAD may be useful in preventing recurrence of symptoms or relapse. In a study of relapse prevention, patients with GAD who responded during 8 weeks of treatment with venlafaxine XR (75–150 mg/day) were allocated to receive either venlafaxine XR or placebo for another 4 months. Continued treatment with venlafaxine XR prevented the return of symptoms of anxiety, whereas switching to placebo was associated with a slow return of symptoms over the 4-month period.[34]

FIGURES 5A, 5B

PROPORTION OF PATIENTS WHO IMPROVE FROM RESPONSE AT 2 MONTHS TO REMISSION AT 6 MONTHS (A), AND FROM NONRESPONSE AT 2 MONTHS TO RESPONSE AFTER 6 MONTHS (B) UPON TREATMENT WITH VENLAFAXINE XR OR PLACEBO

Pooled data were obtained from two 6-month studies of fixed dose (37.5, 75 or 150 mg/day) or flexible dose (mean dose 176 mg/day) venlafaxine XR compared with placebo. Response was defined as a ≥50% decrease in HAM-A total score and remission as a HAM-A total score of ≤7.



* *P*=.007 venlafaxine XR versus placebo (treatment-by-time interaction). † *P*<.001.

XR=extended release; HAM-A=Hamilton Rating Scale for Anxiety.

Adapted from: Montgomery SA, Sheehan DV, Meoni P, Haudiquet V, Hackett D. Characterization of the longitudinal course of improvement in generalized anxiety disorder during long-term treatment with venlafaxine XR. *J Psychiatr Re*s. 2002. In press

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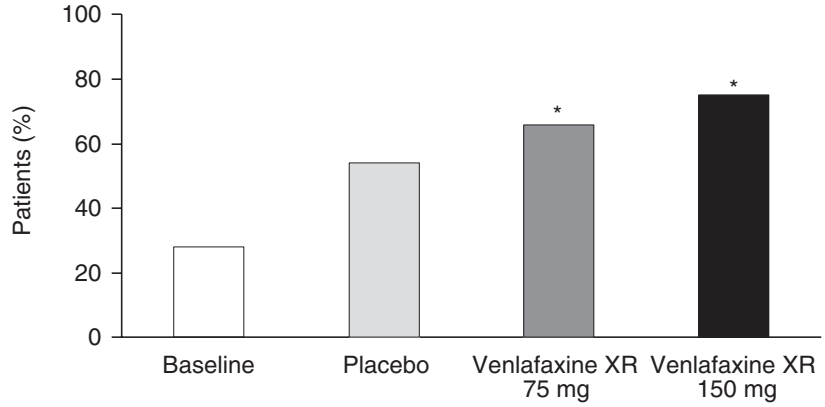
The ability of venlafaxine XR, currently the only antidepressant indicated for the long-term treatment of GAD, in attaining remission and preventing relapse in a substantial proportion of patients with GAD is likely to have a significant impact on the mortality and morbidity associated with the disorder. The daily functioning of patients with GAD is markedly impaired. The degree of impairment in social adjustment can be estimated by use of the Social Adjustment Rating Scale (SAS), which covers six areas of social adaptation (work, social and leisure, extended family, primary relationship, parental, family unit). SAS scores may be categorized and standardized using T-scores. A high T-score, defined as >70, indicates an atypical score representative of marked impairment of social adjustment. Analysis of the study sample revealed that 72% of patients with GAD had a T-score of >70 at baseline.[35] This is in marked contrast to a previous observation in which an estimated 16% of people from a community sample were reported to experience impairment in social adjustment.[36] Treatment of patients with fixed-doses of venlafaxine XR for 6 months was associated with a significant improvement in social adjustment.[35] The proportion of patients with a T-score of ≤60 (minimal or no impairment) increased from 28% at baseline to up to 75% following treatment with venlafaxine XR (Figure 6), thereby approaching the proportions expected in a community sample.[35]

FIGURE 6

RESTORATION OF SELF-RATED SOCIAL FUNCTIONING AFTER 6 MONTHS OF TREATMENT FOR GAD WITH VENLAFAXINE XR OR PLACEBO

The proportion of patients with SAS-SR T-score of ≤60 (minimal or no impairment of social adjustment) at baseline and following 6 months of treatment with placebo or venlafaxine (ITT, LOCF analysis).



* *P*<.05 venlafaxine XR versus placebo; SAS-SR=Social Adjustment Rating Scale; ITT=intent-to-treat; LOCF=last observation carried forward.

Source: Boyer P, Mahe V, Hackett D, Haudiquet V. Efficacy of venlafaxine XR in social adjustment in patients with generalized anxiety disorder. *Eur Neuropsychopharmacol.* 2000;10(suppl 3):S336.

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Another report has noted that following treatment with an SSRI for 4–6 months, patients with GAD become less harm avoidant, and more cooperative, self-confident, and responsible.[37] Moreover, effective long-term treatment of GAD may reduce the risk of suicide, which is increased approximately five- to sevenfold amongst patients with anxiety neurosis.[8] Recent analysis of statistical data from Sweden has indicated that the number of suicides decreased by 25% between 1992 and 1997, coincident with an increased use of antidepressants during this time. An association between these statistics is likely.[38] The improved efficacy and long-term benefits demonstrated by administration of venlafaxine XR to patients with GAD suggests that increasing availability and use of SNRIs in the future may continue to improve long-term outcomes for patients with chronic anxiety disorders.

Conclusion

The attainment of remission and resolution of the symptoms of anxiety during treatment is associated with considerable long-term benefit to patients with anxiety disorders, including reduction in mortality and morbidity risks, and the prevention of relapse. Studies using the SNRI, venlafaxine XR, suggest that these aims may be achieved using this newer class of drugs. Administration of venlafaxine XR is effective for the treatment of GAD in terms of both short-term anxiolytic and sustained anxiolytic activity for up to 6 months. In addition, there is evidence that the benefit of venlafaxine XR may continue to grow with continued treatment, as evidenced by a widening separation from the effects of placebo over time. Furthermore, there is progressive conversion of patients over time from being non-responsive to treatment, to attaining both an anxiolytic response and remission from symptoms. Further studies are therefore required to examine the precise long-term benefits of venlafaxine XR beyond 6 months of treatment. There also remains the possibility of increasing remission rates further, perhaps by combining psychotherapy and venlafaxine XR in the treatment of GAD, which may form the basis of future investigations. In conclusion, the available data indicate that venlafaxine XR would appear to be an appropriate first-line treatment option in the long-term treatment of GAD. ✤

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