Attaining Remission in Generalized Anxiety Disorder: Venlafaxine Extended Release Comparative Data

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Generalized anxiety disorder (GAD) is a chronic mental disorder that is characterized by excessive anxiety or worry. Traditionally, the treatment goal for GAD has been the attainment of a treatment response, clinically defined as a 40% to 50% symptomatic improvement relative to baseline. However, there is growing consensus among clinical psychiatrists that the treatment goal should be remission, a virtually asymptomatic state that corresponds to a score of ≤ 7 on the Hamilton Rating Scale for Anxiety (HAM-A) or a ≥ 70% symptomatic improvement from baseline. Venlafaxine extended release (XR), a serotonin-norepinephrine reuptake inhibitor, is the first pharmacotherapeutic agent to be indicated for both depression and GAD. This article reviews the efficacy data from several short- and long-term placebo-controlled studies of venlafaxine conducted to evaluate the potential of this agent to facilitate remission. Total scores on the HAM-A and the Clinical Global Impressions scale were used as the primary variables; scores for the HAM-A psychic and somatic anxiety factors and for the Hospital Anxiety and Depression scale were used as secondary variables. Venlafaxine XR showed a substantial effect size in the individual HAM-A items of worry, anxiety, and behavior at interview. The pooled analysis of 2 long-term studies indicated that the scores of venlafaxine remitters separated from those of responders by the second month, resulting in an overall increase in remitters. The results of these studies demonstrate the strong potential of venlafaxine XR in facilitating remission in GAD.
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Generalized anxiety disorder (GAD) is a common psychiatric illness with a lifetime prevalence of about 5.1%.[1,2] Its hallmark symptoms include excessive, uncontrollable anxiety or worry lasting 6 months or longer, accompanied by 3 or more additional psychic or somatic symptoms including irritability, restlessness, difficulty concentrating, disturbed sleep, muscle tension, and gastrointestinal symptoms.[3] Patients with pure GAD constitute a minority of cases—most patients exhibit comorbid psychiatric (e.g., major depression, substance abuse)[1,4,5] or medical illnesses[6] with GAD. As a distressing ailment that may persist for decades,[7] GAD is a chronic disorder[8] associated with substantial impairment in general life functions (including work, family, and social life)[2,9–11] and high utilization of medical services.[12–14] Despite the significant anxiety-related disabilities that are associated with GAD, however, as many as 50% of individuals with GAD as a core illness neglect seeking medical attention.[15]

Clinical target endpoints (e.g., normal hematocrit, blood pressure, and blood sugar levels) have been established in the treatment guidelines for many types of diseases, but in psychiatry, analogous endpoints are less well defined, particularly with anxiety disorders. Treatment efficacy is generally evaluated based on the attainment of 3 levels of improvement: response, remission, and wellness. Response is defined as a 40% to 50% reduction in anxiety rating scores (relative to baseline), remission is a virtually asymptomatic state, and wellness is an attainment of functional recovery. Empirical data comparing scores on the Hamilton Rating Scale for Anxiety (HAM-A) before and after active treatment in double-blind placebo-controlled studies suggest that end-of-study scores > 14 indicate a weak clinical response, scores of 12 to 14 indicate treatment efficacy, scores of 10 to 12 indicate a highly efficacious pharmacotherapeutic agent, and scores < 10 herald a gold standard.

Now that newer generations of antidepressants have shown efficacy and safety superior to that of earlier-generation agents, there is general consensus among clinical psychiatrists that treatment goals should be set beyond the attainment of simple clinical response. Among patients who attain even a 50% reduction from baseline psychiatric rating scores, residual symptoms often persist. Data de-

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Table 1. Short-Term and Long-Term Studies of Venlafaxine XR in GAD[a]

Study	N	Treatment Duration	Treatment	Dose (mode)	Change in HAM-A Total Scores From Baseline With Venlafaxine XR
Short-term studies					
Rickels et al, 2000[18]	349	8 wk	Placebo		–11.5 at week 8 for the highest dose; statistically significant difference from placebo
			Venlafaxine XR	75, 150, 225 mg/d (fixed dose)	
Davidson et al, 1999[19]	365	8 wk	Placebo		Approximately –10 at week 8; not significantly different from placebo
			Buspirone	30 mg/d	
			Venlafaxine XR	75, 150 mg/d (fixed dose)	
Long-term studies					
Gelenberg et al, 2000[20]	238	28 wk	Placebo		≥ –12 beginning at week 6 through week 28; significant reduction compared with placebo from week 1
			Venlafaxine XR	75, 150, 225 mg/d (flexible dose)	
Allgulander et al, 2001[21]	529	24 wk	Placebo		–16 at week 24 for the highest dose (150 mg/d); significant reduction compared with placebo from week 2
			Venlafaxine XR	37.5, 75, 150 mg/d (fixed dose)	

[a]Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, XR = extended release.

rived from a study in which patients were asked to keep a structured diary that reflected the degree of effective anxiolysis on an hourly basis indicated that 87% of patients considered a functional improvement of < 60% as unacceptable; 70% of the patients felt that a ≥ 70% improvement in functioning was required for the outcome to be considered desirable.[16] This improvement is equivalent to a score of ≤ 7 on the HAM-A, a score of 1 on the Clinical Global Impressions scale (CGI) , and a score of ≤ 5 on the Sheehan Disability Scale.

Long-term studies to date have shown that only about a third of patients with GAD attain remission within a year of follow-up.[8,15,17] In a study[8] in which the pharmacotherapeutic agents used included benzodiazepines, tricyclic antidepressants, and fluoxetine administered as monotherapy or in combination treatment, remission was only infrequently attained, suggesting treatment inadequacy. This outcome was found despite the fact that most of the patients also received concomitant psychotherapy.

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is the first pharmacotherapeutic agent to be indicated for GAD and depression. In this article, published and unpublished controlled studies of venlafaxine extended release (XR) in the treatment of GAD are summarized with emphasis on assessing the extent to which the reported efficacy of this drug satisfies the above-mentioned criteria for acceptable improvement. All of the studies were placebo-controlled and adhered to the following inclusion criteria: (1) fulfillment of GAD criteria according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV); (2) baseline HAM-A score ≥ 20, with scores on HAM-A items 1 (anxious mood) and 2 (tension) ≥ 2 at baseline (i.e., indicative of moderate severity); and (3) Covi anxiety score exceeding the Raskin depression score, where the Raskin score was ≤ 9 (i.e., lack of apparent depressive symptoms). Table 1 summarizes the parameters in the studies using venlafaxine XR in this review.

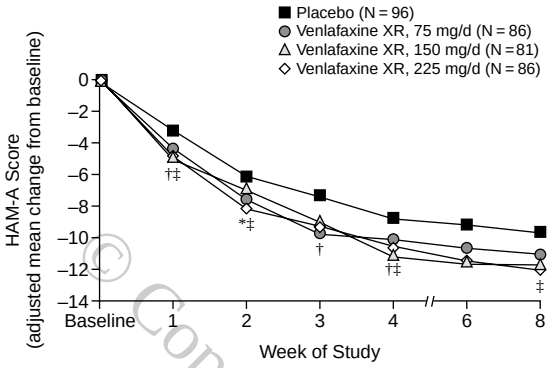
SHORT-TERM STUDIES

Both of the short-term studies[18,19] were 8-week multicenter studies. One compared venlafaxine XR with placebo in outpatients with GAD.[18] Efficacy results were based on the last-observation-carried-forward (LOCF) method of analysis. Of 349 patients included in the efficacy analysis, 96 received placebo and a total of 253 received venlafaxine XR; 86 received 75 mg/day, 81 received 150 mg/day, and 86 received 225 mg/day. The primary efficacy variables were the final on-therapy scores on the CGI-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales, the total HAM-A scores, and the HAM-A psychic anxiety factor scores; secondary efficacy variables were the HAM-A somatic anxiety factor scores and the scores on the anxiety subscale of the Hospital Anxiety and Depression (HAD) scale.

Venlafaxine XR separated statistically from placebo as early as week 1, as well as at weeks 2, 3, 4, and 8 (Figure 1).[18,22] The magnitude of the change from baseline attained a clinically meaningful level from the fourth week of the study, at which time the HAM-A total score decreased by about 10 points from baseline (average baseline scores ranged from 23.6 to 24.7). While all 3 venlafaxine XR doses demonstrated efficacy, the 225-mg/day dose elicited the most positive results, based on the primary and secondary efficacy variables. For example, the 75-mg/day dose differed significantly from placebo only for scores on the HAD scale, but the 225-mg/day dose differed significantly from placebo on most measures, including the HAM-A total scores, the HAM-A psychic anxiety factor scores, and the scores on the CGI scales (Table 2).[18]

The other 8-week study[19] compared 2 fixed dosages of venlafaxine XR with buspirone and placebo in outpatients with GAD. This study showed similar results to the other study. Data were analyzed for the intent-to-treat population using the LOCF method. In this study, 98 patients received

Figure 1. Change From Baseline in HAM-A Total Score in Patients Receiving Venlafaxine XR or Placebo[a]



[a]Adapted from Rickels et al.[18] Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, XR = extended release.
*p < .05 for venlafaxine XR, 75 mg/day, vs. placebo.
†p < .05 for venlafaxine XR, 150 mg/day, vs. placebo.
‡p < .05 for venlafaxine XR, 225 mg/day, vs. placebo.

Table 2. Venlafaxine Dose-Finding Results: Pairwise Comparison (least squares test) With Placebo[a]

	Venlafaxine XR		
Outcome Measure	75 mg (N = 86)	150 mg (N = 81)	225 mg (N = 86)
HAM-A total	.20	.07	.03
HAM-A psychic	.10	.03	.01
CGI-Improvement	.15	.15	.02
CGI-Severity of Illness	.13	.06	.01
HAM-A somatic	.60	.29	.12
HAD anxiety	.02	.01	< .001
Covi anxiety	.21	.07	.03
No. of tests with clinically meaningful outcomes	1	2	6

[a]Adapted from Rickels et al.[18] Abbreviations: CGI = Clinical Global Impressions scale, HAD = Hospital Anxiety and Depression scale, HAM-A = Hamilton Rating Scale for Anxiety, XR = extended release. Values shown are p values unless specified otherwise. Statistical significance set at p ≤ .05.

placebo; 93 received buspirone, 30 mg/day, in a split dose; 87 received venlafaxine XR, 75 mg/day; and 87 received venlafaxine XR, 150 mg/day. No significant differences in HAM-A total scores were observed between any of the treatment groups and the placebo group. However, patients in both of the venlafaxine XR groups showed significant improvement compared with placebo patients on HAM-A psychic anxiety scores, HAM-A anxious mood scores, HAM-A tension scores, HAD anxiety subscale scores, and CGI scores at week 8 and earlier (in some measures, starting at week 2). In addition, the 2 doses of venlafaxine XR elicited significantly greater improvement than buspirone treatment on the HAD anxiety subscale and the CGI scales at various timepoints (HAD at all timepoints after week 1). In contrast, buspirone treatment demonstrated superiority over placebo based only on CGI-I scores of 1 or 2 at weeks 6 and 8 but otherwise did not differ significantly from placebo on any other measure.[19]

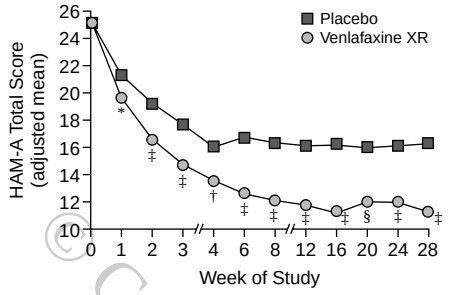
The lack of significant differences in HAM-A total scores between the placebo and venlafaxine XR groups in the second study[19] despite significant changes in other measures is somewhat perplexing. Relative to the cohort in the first study,[18] however, the cohort in the second study[19] collectively appeared to have a longer duration of current episode at baseline, which suggests a greater severity of illness; moreover, the degree of heterogeneity in the duration of treatment between groups may have diminished the differentiation in efficacy results.

It is possible that longer durations of treatment may be necessary before patients with severe anxiety can achieve clinically meaningful levels of improvement. This hypothesis was tested by comparing the time to remission (within a 6-month period) using placebo and venlafaxine XR treatment in patients with moderate anxiety (HAM-A score ≤ 25 at baseline) and severe anxiety (HAM-A score > 25 at baseline).[23] As would be expected among the patients receiving placebo, fewer of those with severe anxiety achieved remission than did those with moderate anxiety at all timepoints. In the short term (up to 8 weeks), severely anxious patients exhibited lower remission rates than patients with moderate anxiety, regardless of whether they received placebo or venlafaxine XR; however, in contrast with the placebo patients, continued treatment with venlafaxine XR in both the moderately anxious and the severely anxious patients produced similar levels of remission by 24 weeks. Thus, these data provide clinical evidence that, in cases of severe anxiety, prolonged treatment may be necessary to achieve remission; such extended treatment using venlafaxine XR facilitates the attainment of levels of symptomatic improvement comparable to those demonstrated by patients with moderate anxiety.

LONG-TERM STUDIES

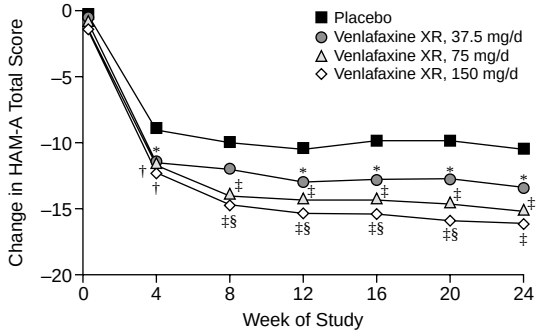
Long-term studies of GAD have previously been performed,[24] but the results from these studies are inconclusive because many were not placebo-controlled. More importantly, all of these studies used the DSM-III criteria, wherein GAD was considered a "residual" category.[24] The following studies using venlafaxine XR are the first long-term, placebo-controlled studies using the DSM-IV criteria for GAD (i.e., as an autonomous disorder). The 2 long-term studies that have been conducted with venlafaxine XR in GAD were both 6-month multicenter studies, 1 using flexible dosing[20] and the other using fixed dosing.[21] The flexible-dose trial tested the efficacy and safety of venlafaxine XR dosages of 75, 150, and 225 mg/day in outpatients with GAD (123 patients received placebo and 115 received venlafaxine).[20] Patients were seen weekly for the first month, every 2 weeks for the second month, and once per month thereafter. Treatment efficacy was evaluated using observed cases and LOCF analyses. Venlafax-

Figure 2. Long-Term Efficacy of Venlafaxine XR (N = 115) and Placebo (N = 123)[a]



[a]Adapted, with permission, from Gelenberg et al.[20] Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, XR = extended release.
*p ≤ .003 vs. placebo.
†p ≤ .002 vs. placebo.
‡p ≤ .001 vs. placebo.
§p ≤ .007 vs. placebo.

Figure 3. Long-Term Changes in HAM-A Total Score With Venlafaxine Versus Placebo[a]



[a]Adapted, with permission, from Allgulander et al.[21] Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, XR = extended release.
*p < .05 venlafaxine XR vs. placebo.
†p < .01 venlafaxine XR vs. placebo.
‡p < .001 venlafaxine XR vs. placebo.
§p < .05 venlafaxine XR, 150 mg/day, vs. venlafaxine XR, 37.5 mg/day.

ine XR was significantly superior to placebo at the following timepoints: from week 1 to the end of the study on the basis of HAM-A total scores and HAM-A psychic anxiety scores, from week 2 to the end of the study on the basis of CGI-I and CGI-S scores, and at several other timepoints on the basis of secondary measures including the HAD anxiety subscale of Covi Anxiety Scale, HAM-A anxious mood and tension items, and HAM-A somatic anxiety factor. LOCF analysis demonstrated that average HAM-A total scores in the venlafaxine group reached clinically meaningful levels by week 4, when the scores dropped below 14, a > 10-point decrease from baseline. By the end of the study, the average HAM-A total score was approximately 11 in the active treatment group, suggesting that venlafaxine XR is a highly effective anxiolytic (Figure 2).[20]

In the double-blind, fixed-dose study involving 541 nondepressed outpatients with GAD,[21,25] patients were randomly assigned to 1 of 4 treatment groups (i.e., placebo or venlafaxine, 37.5 mg/day, 75 mg/day, or 150 mg/day); 529 patients were included in the intent-to-treat analysis. The primary outcome parameters used included the HAM-A total score, HAM-A psychic anxiety factor score, HAD score, and CGI-I score. The Social Adjustment Scale Self-Report was used to evaluate impairment in social functioning. Observed cases and LOCF analyses were the bases for evaluating treatment efficacy. For most variables, anxiolytic effect was seen at weeks 1 and 2 with the highest dose of venlafaxine XR (150 mg/day); for venlafaxine XR doses of 37.5 mg/day and 75 mg/day, anxiolytic onset was apparent at weeks 2 and 3. All active treatment doses, however, showed significantly higher response rates as early as week 2 compared with placebo (based on both HAM-A and CGI-I scores)—an effect that was maintained continuously through week 24 using the 2 higher dosages. A dose-response relationship was observed (Figure 3).[21] Moreover, the 2 higher doses of venlafaxine XR elicited an improvement in social adjustment.

In long-term studies, patients who respond to medication are expected to exhibit symptomatic improvement over time. This hypothesis was tested by analyzing data pooled from these 2 long-term studies, since they had similar designs. In each of the studies, the proportion of patients who showed a response (defined as ≥ 50% reduction in HAM-A scores from baseline) or remission (defined as HAM-A score ≤ 7) was evaluated for the duration of the study. In the pooled analysis,[23] approximately 40% of venlafaxine XR patients satisfied the definition of a responder by month 2, while slightly more patients from this active treatment group (approximately 42%) had achieved remission by this time. By the end of the study, the number of venlafaxine XR responders declined to approximately 20% and the number of remitters increased to approximately 60% as more patients who initially showed a response to venlafaxine XR reached remission. In contrast, in the placebo group, the proportion of patients throughout the study who achieved remission did not exceed 40%. Thus, a substantial proportion of patients treated with venlafaxine XR progressively achieved remission.

EFFECT SIZE

Individual items of multi-item scales such as the HAM-A may be useful indicators to elucidate specific effects of medications. However, inferential methods of statistical analysis have limited usefulness in evaluating individual items of multi-item instruments, due to the masking of differences among individual items by the overall score, differences in sample sizes across treatment groups, and type I errors (due to multiple comparisons).[26] Effect

size is a descriptive statistic that avoids these difficulties. Effect size is calculated as the change from baseline to post-treatment divided by the standard deviation of the change found in the treatment group.[26] An effect size of 0.6 is considered clinically observable and meaningful, an effect size of 0.8 is impressive, and an effect size of 1.0 is excellent.

Effect size was used to evaluate the effects of venlafaxine XR on individual items of the HAM-A in 5 placebo-controlled studies of venlafaxine XR in the treatment of GAD, including the 2 short-term and 2 long-term studies described above.[27] Venlafaxine XR produced the largest effect sizes (> 1.0) for anxious mood and worry, tension, and behavior at interview. In addition, the difference between venlafaxine XR and placebo produced the largest effect sizes (> 0.3) for the same items.[27] Consequently, venlafaxine XR appears to have the greatest impact on the items of worry, anxiety, and tension, which are the key psychological aspects of GAD; benzodiazepines, on the other hand, tend to demonstrate stronger effect sizes on somatic items. Thus, by using an analog scale based on the items of worry, anxiety, and tension, it may be possible to more accurately separate drug effects from placebo effects.

SURVIVAL ANALYSIS

An analysis of the proportion of patients who discontinue treatment due to lack of efficacy or adverse events during a study (survival analysis) is a useful, supplemental method for evaluating efficacy. The 2 long-term studies[20,21] described above were reanalyzed using a Kaplan-Meier method of survival analysis.[28] In the flexible-dose study,[20] discontinuations due to lack of efficacy were significantly greater in the placebo group than in the venlafaxine XR group. Patients taking placebo dropped out at a relatively constant rate from the fourth week forward at a significantly greater rate than the venlafaxine XR patients. Likewise, in the fixed-dose study,[21,25] venlafaxine XR patients taking doses of 75 mg/day and 150 mg/day discontinued significantly less frequently than did placebo patients.[28]

A dose-response relationship was apparent in these long-term studies. The observation that the venlafaxine 150-mg/day group achieved earlier stabilization of survival function than the 75-mg/day group is consistent with the dose-response curve associated with venlafaxine XR. There were no significant differences between the placebo and venlafaxine XR groups in discontinuation rates due to adverse events in either long-term study.

The lower rate of discontinuations due to lack of drug efficacy among patients treated with venlafaxine XR (compared with placebo) supports current clinical guidelines for antidepressant treatment.[29] These guidelines highlight the importance of using adequate doses and maintaining these dosage levels for an adequate duration in order to achieve optimal clinical outcomes. There are currently no consensus guidelines specifically developed for GAD. However, because about two thirds of patients with GAD have a comorbid mood disorder,[4,5] treatment for the depression should be part of the management strategy directed toward achieving remission in GAD. The high incidence of comorbid anxiety and depression is associated with greater illness severity.[30] In these situations, prolonged treatment duration is key to the attainment and maintenance of remission.

SUMMARY

The findings from short-term and long-term studies of venlafaxine XR, using various measures of efficacy, confirm the effectiveness of this SNRI in the treatment of GAD. The substantial effect size of venlafaxine XR in the individual HAM-A items of worry, anxiety, and behavior at interview confirms its efficacy in alleviating key psychiatric symptoms of GAD; the significantly lower discontinuation rates due to lack of efficacy among patients taking venlafaxine XR compared with those taking placebo concur with these findings. Because patients with major depression were excluded from these studies, the efficacy of venlafaxine XR in GAD appears to be independent of its antidepressant activity, thus confirming its anxiolytic effect.

The HAM-A data in these studies were mainly presented as the mean change in scores relative to baseline. Based on treatment responses of the study population, a mean reduction in HAM-A total score of 12 points or more from baseline resulted in significant differences from placebo. In the long-term studies, these changes were apparent by week 1 or 2. Based on the criteria for response (50% or more symptomatic improvement) and remission (HAM-A score ≤ 7), the pooled analysis[23] of the 2 long-term studies indicated that responders separated from remitters by month 2; the overall increase in the number of responders through month 6 was largely due to an increase in the number of patients who qualified as remitters rather than simply responders.

The results of these studies also highlight the importance of adequate dosing and treatment duration. The advantages of long-term treatment are especially apparent among patients with severe GAD. In view of the fact that the majority of patients with GAD have comorbid illnesses,[1,4–6] which compounds illness severity,[30] a prolonged treatment duration is key to the attainment and maintenance of remission. Altogether, the findings from these short-term and long-term studies demonstrate the strong potential of venlafaxine XR in facilitating remission among patients with GAD.

Drug names: fluoxetine (Prozac), venlafaxine (Effexor).

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