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EFFICACY, SAFETY, AND TOLERABILITY OF VENLAFAXINE XR IN GENERALIZED ANXIETY DISORDER

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Generalized anxiety disorder (GAD) is a common and chronic disorder with a low rate of spontaneous remission. A complication in treatment selection is the high rates of co-morbid major depressive disorder in this population. A number of treatments exist to treat GAD. The most recent medication to gain an indication for GAD is venlafaxine XR, a serotonin/norepinephrine reuptake inhibitor that is also approved for the treatment of major depressive disorder. More than 2,000 patients with GAD have been studied in outpatient trials of venlafaxine XR with demonstrated efficacy, tolerability and safety of this compound. This article reviews these studies, both short term and longer (6 month) continuation trials. The response to venlafaxine XR in this population, combined with good tolerability, makes this agent an appropriate first-line medication for GAD. In general, treatment with antidepressants, though associated with a longer onset of action than benzodiazepines, does not produce physiological dependency, and is useful in a patient population with a high prevalence of mood disorders. Depression and Anxiety, Volume 12, Supplement 1:81–84, 2000. *© 2000 Wiley-Liss, Inc.*

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INTRODUCTION

Generalized anxiety disorder (GAD) is an anxiety disorder that is characterized by the DSM-IV as being chronic (six months or longer), excessive and difficult to control worry about two or more life events, with consequences of at least three of the following symptoms; restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, or sleep disturbance (difficulty falling, staying asleep, or restless unsatisfying sleep). The lifetime prevalence of GAD is estimated to be about 5% [Kessler et al., 1994], making this a relatively common, but often underdiagnosed disorder. Compounding this is the chronicity of GAD for many patients with only an estimated 25% enjoying a spontaneous remission after two years [Yonkers et al., 1996].

Theories about the biology of GAD [Brawman-Mintzer and Lydiard, 1997] include well-defined systems such as the locus coeuruleus-sympathetic nervous system with norepinephrine as one of the neurotransmitters involved, and the hypothalamic-pituitary-adrenocortical (HPA) system involving corticotropin releasing factor (CRF). Other neurotransmitters are also postulated to potentially be involved such as Cholecystokinin (CCK), Serotonin (5HT), and Gamma-amino-butyric acid (GABA). Thus, one can find successful clinical trials of a diverse array of agents such as imipramine, trazodone, paroxetine, benzodiazepines, and $5HT_{1a}$ active medications such as buspirone and gepirone.

There is a significant amount of psychiatric comorbidity in patients with GAD including simple phobias, social phobia, panic disorder and major depressive disorder or dysthymia [Sanderson and Barlow, 1990; Angst, 1993; Brawman-Mintzer et al., 1993]. It is this degree of comorbidity encountered in clinical practice that often makes the choice of pharmacotherapy problematic for GAD. The traditional choices of medication for GAD, benzodiazepines or buspirone, although effective for GAD, often do not address the comorbid psychiatric conditions that are found with GAD. Venlafaxine XR, an antidepressant that inhibits both norepinephrine and serotonin reuptake, has recently received approval for the treatment of GAD from the Food and Drug Administration, making it the only antidepressant with this indication. Efficacy in GAD, coupled with effectiveness as an antidepressant, makes this agent a good

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choice for the patient with comorbid mood and anxiety disorders.

The efficacy of venlafaxine XR has been investigated in five outpatient placebo-controlled studies of which one was a flexible-dose study design (75–225 mg/day), and four were fixed-dose studies ranging from 37.5–225 mg/day. Two of the short term (8 weeks) studies were comparative against buspirone or diazepam, and two studies evaluated long-term (6 month) efficacy. Entry criteria for all the studies to be reviewed included; DSM criteria for GAD, without: Major depression within 6 months of screening, Alcohol dependence/drug abuse, Any single Raskin score >3 or a Covi anxiety score >4 for somatic complaints, previous use of antipsychotics or fluoxetine (within 30 days), previous use of any antidepressant (within 14 days), previous use of hypnotics (within 7 days), or regular use of benzodiazepines (within 7–14 days, based on half-life). The primary outcome measure for these studies was the Hamilton Anxiety Scale [Hamilton, 1959] or the psychic anxiety factors of the HAM-A. The psychic anxiety factors are often felt to better represent the distress experienced by patients with GAD, and include clinician rated measures from the HAM-A of anxious mood, tension, fears, insomnia, cognitive impairment, depression or behavior at interview.

Across numerous studies, venlafaxine XR has been demonstrated to be both effective and well tolerated. Figure 1. shows the results of an eight week trial comparing venlafaxine XR at doses of 75, 150 or 225 mg/day to placebo [Rickels et al., 2000]. In this study, 349 patients were randomized to one of the four treatment conditions. In each group, 52–58% were female, with an average age of 39.6–42.4 years, and the mean HAM-A at baseline ranged from 23.8–24.7 across the groups. The subjects receiving the two higher doses, 150 and 225 mg/day, achieved consistently greater improvement than those receiving placebo at the week 8 endpoint with a change in the HAM-A psychic anxiety measure of –7.44, –6.89 and –5.62 for the groups receiving venlafaxine XR 150 mg, 225 mg or placebo respectively. The group receiving 75 mg/day was not as consistent in showing a better response than those receiving placebo. The premature discontinuation rate due to adverse reactions was 19% for patients receiving venlafaxine XR compared to 7% of the placebo treated group ($P < 0.05$). In contrast, discontinuations due to lack of efficacy was 2% in the venlafaxine XR treated group and 5% in the placebo treated group.

A comparison study of venlafaxine XR at doses of 75 or 150 mg/day with either buspirone (30 mg/day) or placebo, suggested that the two doses of venlafaxine XR were more effective than placebo treatment using the HAM-A psychic anxiety factor score as an endpoint measurement [Davidson et al., 1999]. The demographics of the 365 outpatients in this study were similar to the previous study with 61% females, an average age of 37–39 years, and a baseline HAM-A of 23–23.8. The adjusted mean scores for HAM-A total, though decreased in the subjects receiving active medication, failed to separate statistically from placebo. Subjects taking either dose of venlafaxine XR, 75 or 150 mg/day, showed statistically significant improvement compared to those getting placebo when the HAM-A psychic anxiety factor was used for comparison. Treatment with buspirone did not produce a better response than did treatment with placebo. The authors suggest that dosing, or the inclusion of patients with DSM-IV GAD may account for this.

Generalized anxiety disorder is for many a chronic disorder, so efficacy in trials longer than 6–8 weeks are needed to convince us as clinicians that an agent has relevant efficacy. The results of a 6-month study are shown in Figure 2 [Gelenberg et al., in press]. In this study of 238 outpatients with GAD, treatment re-

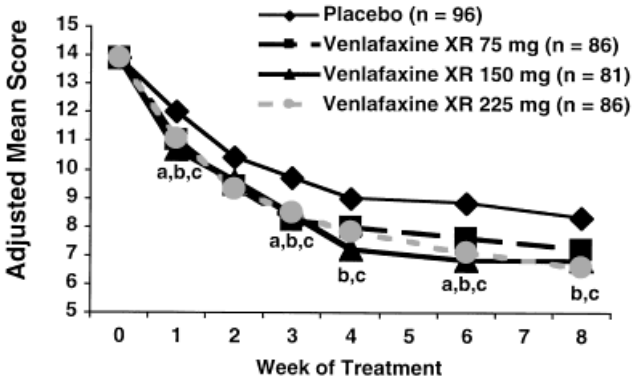

Figure 1. Adjusted mean scores for HAM-A psychic anxiety factor change from baseline in outpatients with GAD. Data represents intent-to-treat and last observation carried forward (LOCF). Change in scores is significant at $P < 0.05$ (two-way analysis of variance) for venlafaxine XR doses of 75 mg/day (a), 150 mg/day (b) or 225 mg/day (c). (Adapted from Rickels et al., 2000.)

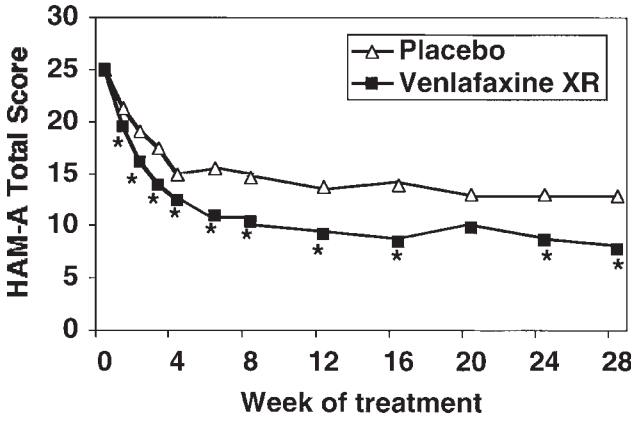

Figure 2. HAM-A total score after treatment with placebo or venlafaxine XR over 28 weeks. Data represents observed cases. Change in scores is significant at $*P < 0.01$. (Adapted from Gelenberg, et al., 2000.)

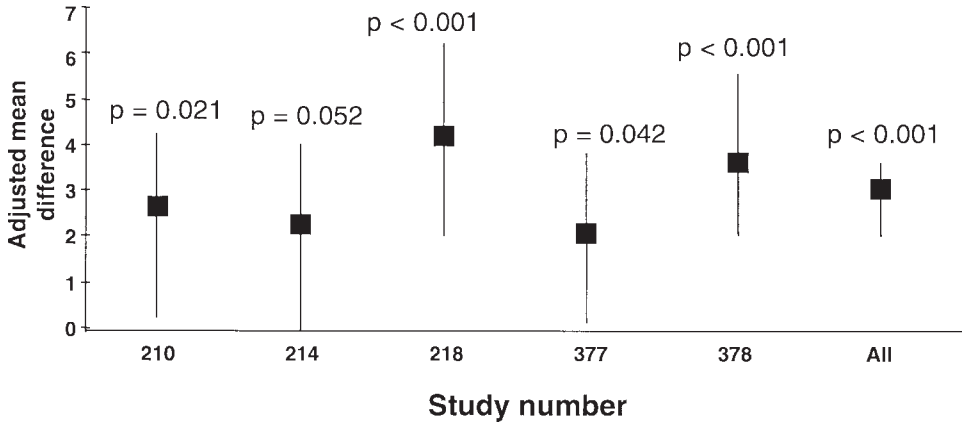

Figure 3. Adjusted mean difference between venlafaxine XR and placebo at Week 8 of treatment on the HAM-A psychic anxiety factor. Numbers represent different studies. (Data on file, Wyeth-Ayert.)

sponse with venlafaxine XR, defined by a decrease in HAM-A total or HAM-A psychic anxiety scores were sustained for the entire 28 weeks of the study beginning by week one. Attention should be drawn to the mean dose of 176 mg/day of venlafaxine XR in this trial as many studies have suggested that this moderate range of dosing is desirable for patients with GAD.

Compiling the 5 outpatient studies together shows a consistent pattern of improvement associated with the treatment of GAD using venlafaxine XR. Four out of five studies demonstrated an improvement observed after treatment with venlafaxine XR that was statistically superior to that obtained with placebo. An analysis of the pooled data also shows treatment with venlafaxine XR to be superior to treatment with placebo ($P < 0.001$) as shown in Figure 3.

Effectiveness of treatment is clearly a desirable quality; however, the treatment must be tolerated as well, not only for the long term, but also as the dose is being titrated. The data from the five outpatient trials, with a patient database of over 2,000 study participants, looking at discontinuation rates, is shown in Figure 4. Overall, the tolerability of venlafaxine XR, as indicated by the relatively small number of subjects discontinuing treatment due to adverse events is quite favorable. The most commonly observed side-effects associated with treatment were nausea, somnolence, dry moth and dizziness as shown in Table 1.

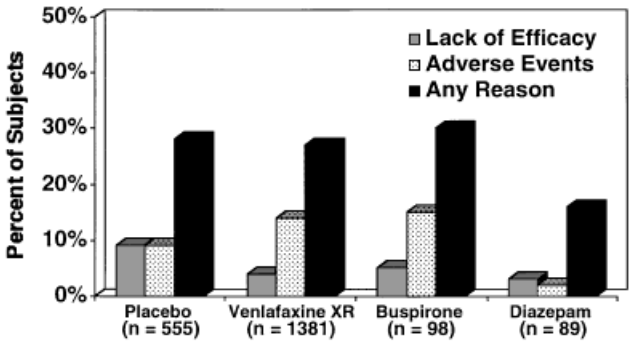

Figure 4. Pooled data from the 5 outpatient GAD trials representing the percentage of subjects discontinuing for lack of efficacy, adverse events or any reason (data on file Wyeth-Ayerst).

The advantages and disadvantages of treating GAD with venlafaxine XR are summarized in Table 2. Briefly, treatment of GAD with an agent that also possesses antidepressant activity is useful for a number of patients with comorbid anxiety and affective disorders. Additionally, the lack of physical dependence or tolerance raises the comfort level of the physician when prescribing to a patient with a history of substance abuse. On the negative side, there is a lag time before response is observed. Treatment with venlafaxine XR, in contrast to the benzodiazepines, typically does not produce an observed decrease in anxiety after only the first few doses. For patients with a duration of illness of months to years, however, there is often not the need for immediate improvement when the use of benzodiazepines is required to achieve it.

How then should venlafaxine XR be used in the treatment of GAD? One should consider it to be a first line choice given the combination of efficacy, tolerability, and

TABLE 1. Most common treatment emergent adverse events expressed as percentages among study participants from five pooled out patient trials

	Venlafaxine XR (n = 571)	Buspirone (n = 98)	Placebo (n = 304)
Nausea	46	30	17
Dry mouth	24	5	5
Somnolence	21	47	14
Anorexia	13	3	3
Constipation	12	5	5
Sweating	12	4	2

TABLE 2. Advantages and drawbacks to venlafaxine XR in treatment of GAD

Advantages	Drawbacks
No physiological dependency	Delayed onset
One daily dosing	Expense
Treats comorbid depression	Requires continuous dosing
Generally well tolerated	

importantly for the patient with comorbid depression or dysthymia, the antidepressant activity it possesses. Dosing seems to be a key consideration. Most clinicians would suggest a starting dose of 37.5 mg/day given initially with meals with an escalation to 75 mg per day after one week. Some of the data points to higher doses working better, but this is certainly not definitive. A dose of 150–225 mg per day or higher will probably turn out to be the optimal dosage for many patients, but further research is needed to clarify this. The patient who is markedly anxious about increasing the dose may benefit from a dose of 112.5 mg per day (a combination of a 37.5 and 75 mg capsule) for a few to several days on the way to 150 mg/day.

To summarize, the efficacy of venlafaxine XR in GAD has been shown in outpatient studies with over 2,000 subjects. The tolerability of venlafaxine XR is favorable in the treatment of GAD, and initial long term (6 month) studies have reflected the same efficacy seen in shorter term studies. Currently, it is not clear which dose will be the optimal dose, but this may be a reflection of the variability of pathophysiology seen in GAD, and the dual reuptake inhibition profile of venlafaxine XR. At this time, an adequate trial should probably be defined as 150–225 mg per day for 4–6 weeks with continuation for at least twelve months if treatment is successful.

REFERENCES

Angst J. 1993. Comorbidity of anxiety, phobia, compulsion and depression. Int Clin Psychopharmacol 8(Suppl):21–5.

Brawman-Mintzer O, Lydiard RB, Emmanuel N, Payeur R, Johnson M, Roberts J, Jarrell MP, Ballenger JC. 1993. Psychiatric comorbidity in patients with generalized anxiety disorder Am J Psychiatry 150:1216–1218.

Brawman-Mintzer O, Lydiard RB. 1997. Biological basis of generalized anxiety disorder. J Clin Psychiatry 58(Suppl):16–25.

Davidson JRT, DuPont RL, Hedges D, Haskins JT. 1999. Efficacy, safety and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry 60:528–535.

Gelenberg AJ, Lydiard RB, Rudolph R, Aguiar L, Haskins J, Salinas E. 2000. Efficacy of venlafaxine extended-release capsules in non-depressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. JAMA. 283:3082–3088.

Hamilton M. 1959. The assessment of anxiety scales by rating. Br J Med Psychol 32:50–55.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshelman S, Wittchen H-U, Kendler KS. 1994. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 51:8–19.

Rickels K, Pollack MH, Sheehan DV, Haskins JT. 2000. Efficacy of venlafaxine extended-release (XR) capsules in non-depressed outpatients with generalized anxiety disorder. Am J Psychiatry 157:968–974.

Sanderson WC, Barlow DH. 1990. A description of patients diagnosed with DSM-III-R generalized anxiety disorder. J Nerv Ment Dis 178:588–591.

Yonkers KA, Warshaw MG, Massion AO, Keller MB. 1996. Phenomenology and course of generalized anxiety disorder. Br J Psychiatry 168:308–313.