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EFFICACY OF VENLAFAXINE IN MIXED DEPRESSION-ANXIETY STATES

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Patients with depression almost always suffer from comorbid anxiety or anxiety disorder. It is commonly stated that comorbid depression and anxiety has a worse prognosis, even with adequate therapy, than depression alone. An accumulation of data now make clear that the antidepressants venlafaxine and venlafaxine XR are effective in reducing anxiety in patients with depression. Several of the studies supporting this are reviewed here. Venlafaxine and venlafaxine XR have also been shown to be effective in treating anxiety disorders and venlafaxine XR is presently the only antidepressant approved by the FDA for the specific treatment of generalized anxiety disorder. The effectiveness of venlafaxine in treating anxiety associated with depression and anxiety disorders supports theories implicating abnormal noradrenergic activity as a component of pathological anxiety. Depression and Anxiety, Volume 12, Supplement 1:77–80, 2000. *© 2000 Wiley-Liss, Inc.*

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Numerous studies have made it quite clear that most patients with depression suffer from some degree of co-morbid anxiety, sometimes rising to the level of full syndromal anxiety disorder [Fawcett and Kravitz, 1983; Stein et al., 1995]. It is often stated as well that co-morbid depression and anxiety imparts to the patient a diminished prognosis, including higher risk of chronicity and suicide [Fawcett et al., 1991], compared to patients with depression alone. Hence, finding interventions that are effective for the co-morbid or mixed state is crucial.

Because of data, which suggest that venlafaxine is a potent antidepressant that may have advantages over other antidepressants in the treatment of severe depression [Schweizer et al., 1991], it was originally feared that the agent would be activating and may exacerbate anxiety. Furthermore, venlafaxine is distinguished by its dual mode of action on both the serotonin (5-HT) and norepinephrine (NE) neurotransmission systems and it was mistakenly believed that enhancing NE activity is anxiogenic.

An accumulation of data, including those derived from several large, multicenter trials, now makes clear that venlafaxine, far from exacerbating anxiety, is effective in rapidly reducing anxiety levels in depressed patients. These findings are synchronous with both preclinical and clinical findings, reviewed elsewhere, which demonstrate that enhancing NE neurotransmission is, in fact, not anxiogenic [Sullivan et al., 1999]. We will review several salient studies documenting the ability of both venlafaxine immediate release (IR) and the preferred venlafaxine extended release (XR) to reduce anxiety levels in co-morbid patients.

In a fixed-dose study, Khan et al. [1998] examined responses to venlafaxine of patients with major depression on two measures of anxiety: the Anxiety-Psychic Item of the Hamilton Depression Rating scale (HAM-D) and the Anxiety-Somatization Factor of the HAM-D. The latter is comprised of items 10 (Anxiety, Psychic), 11 (Anxiety, Somatic), 12 (Somatic Symptoms, Gastrointestinal), 13 (Somatic General), 15 (Hypochondriasis), and 17 (Insight). Four hundred three patients were randomized to receive placebo or one of three doses of venlafaxine IR, 75, 150, or 200 mg per day. Following a single-blind placebo washout, the study lasted 12 weeks. Three hundred fifty-three patients were available for the intention to treat (ITT) analysis of overall depression efficacy. Anxiety measures were analyzed for the subgroup of patients with baseline Anxiety-Psychic Item scores of at least two. Interestingly, this subgroup included 302 of the 353 ITT patients, an indication once again of the very high proportion of patients with major depression who also have substantial levels of co-morbid anxiety. Statistically significant differences from placebo on the Anxiety-Psychic Item were seen at all dosages of venlafaxine IR at weeks 6, 8, and 12. In addition, significant differences from placebo were observed at

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week 3 for the 75 mg dose group and at week 2 for the 150 and 200 mg groups. This indicates that venlafaxine begins to resolve anxiety in depressed patients fairly early in the course of treatment. In the 200 mg group, for example, venlafaxine reduced the score on the Anxiety-Psychic Item from 2.4 at baseline to approximately 1.4 by the second week of treatment, a clinically meaningful change.

On the Anxiety-Somatization Factor, there were significant differences from placebo at week 12 for all three venlafaxine IR doses as well as at weeks 6 and 8 for the 75 mg and 200 mg groups and at weeks 3 and 4 for the 200 mg group. These analyses clearly show that venlafaxine is potent in relieving concomitant anxiety in patients with mixed depression-anxiety.

Feighner et al. [1998] performed an interesting analysis of anxiety response to venlafaxine among depressed patients enrolled in two separate multicenter studies. In the first of these studies, patients with major depression were randomized to receive venlafaxine IR, venlafaxine XR, or placebo. After a placebo-controlled washout, venlafaxine IR was started at 37.5 mg twice daily and venlafaxine XR at 75 mg once daily. Doses of drug were maintained throughout the 12 week study in the range of 75 to 150 mg daily. Patients with mixed depression-anxiety were defined as those with a baseline HAM-D Anxiety-Psychic Item Score of at least two. A further subgroup of severely anxious-depressed patients was defined as having a score of at least three. Of the 293 patients randomized, 252 met criteria for co-morbid anxiety, of which 96 met criteria for severe anxiety at baseline. Within the former group with a score of two or more, there was a significant reduction in the Anxiety-Psychic Item relative to placebo for both venlafaxine IR and venlafaxine XR from weeks 4 through 12. In the subgroup defined at baseline as severely anxious, both forms of venlafaxine were superior to placebo on the Anxiety-Psychic item from weeks 6 through 12. Although not statistically significant, venlafaxine XR was numerically more potent than venlafaxine IR in reducing anxiety in the depressed patients. Overall, a reduction in anxiety scores was observed in 74% of the patients treated with venlafaxine XR, 67% treated with venlafaxine IR, and only 39% treated with placebo, a significant difference. When looking only at the subgroup of patients with severe anxiety at baseline, 88% had a reduction of anxiety on venlafaxine XR, 78% on venlafaxine IR, and 69% on placebo. Thus, for the group of anxious depressed patients as a whole, venlafaxine XR produced a reduction in anxiety in nearly twice as many patients as did placebo.

The second study analyzed by Feigner et al. [1998] for anxiety response was a straight comparison of venlafaxine XR to placebo in patients with major depression. After a single-blind placebo washout, patients were randomized to begin on venlafaxine XR 75 mg per day or placebo, with dose increases permitted up to 225 mg per day through the 8 week study, depending on response and tolerability. Of 197 patients randomized, 161 met the criterion for co-morbid moderate or greater anxiety at baseline (a score of at least two on the HAM-D Anxiety-Psychic Item) and a subgroup of 60 met the criterion for severe baseline anxiety (score of three or greater). Analyzing the data from the anxious-depressed group as a whole, venlafaxine XR was superior to placebo in reducing the score of the HAM-D Anxiety Psychic Item beginning at week 1 and continuing through week 8. A significant difference from placebo was seen within the subgroup of severely anxious patients at weeks 1, 2, and 8. Overall, 68% of the patients on venlafaxine XR had a reduction in anxiety compared to only 36% of the patients on placebo. For severely anxious patients, these rates were 80% for venlafaxine XR and 51% for placebo. In these trials, venlafaxine XR was well-tolerated, with the most common adverse side effects being nausea, dizziness, insomnia, somnolence, and dry mouth.

The secondary analysis of anxiety reduction from these two clinical trials leads to three conclusions: 1) clinically significant anxiety is present in approximately two thirds of patients with major depression; 2) venlafaxine IR and venlafaxine XR are both significantly more potent than placebo in reducing anxiety in depressed patients, with active drug inducing a reduction in anxiety in nearly twice as many patients as placebo; and 3) anti-anxiety effects of venlafaxine are seen in depressed patients as early as the first week of treatment.

Another important study addressing the effects of venlafaxine XR on anxiety in depressed patients was reported by Silverstone et al. [1999]. This study was a multicenter, double-blind, randomized, placebo-controlled comparison of venlafaxine XR and fluoxetine in patients with major depression and co-morbid anxiety. After a placebo wash-out period, patients meeting DSM-IV criteria for major depression and a minimum baseline score of 20 on the first 17 items of the HAM-D were randomized to receive venlafaxine XR 75 mg per day, fluoxetine 20 mg per day, or placebo. After the first 13 days, at clinician discretion, doses could be raised to 150 mg and 40 mg of the two active drugs and again on day 28 to a maximum of 225 mg and 60 mg, respectively. Unlike the previous studies reviewed here, the Hamilton Anxiety Rating Scale (HAM-A) was employed, with response in terms of anxiety defined as at least a 50% reduction from baseline score.

Three hundred sixty-eight patients were randomized and 359 patients included in the intention-to-treat (ITT) analysis. Chloral hydrate or zopiclone were taken for insomnia by 39%, 52%, and 40% of the patients in the placebo, venlafaxine XR, and fluoxetine groups, respectively. On the HAM-A, there were significant advantages of venlafaxine over placebo at weeks 8, 12, and the final on-therapy evaluation. There was a significant advantage of fluoxetine over placebo at the final on therapy evaluation only. Using the HAM-A response criteria, the proportion of responders to venlafaxine XR was significantly greater

than to placebo at weeks 3, 8, and 12 and the final evaluation. The proportion of responders was greater to fluoxetine than placebo at week 8 only. At week 12, there were significantly more responders to venlafaxine XR than to fluoxetine. Both drugs were well-tolerated by these mixed depression-anxiety patients. The authors concluded that venlafaxine XR is superior to fluoxetine in suppressing anxiety symptoms in depressed patients and of equal tolerability. However, it should be noted that this conclusion was challenged by Judge and Wagner [1999].

Rudolph et al. [1998] conducted a meta-analysis of six venlafaxine studies in order to examine the antidepressant's efficacy on anxiety associated with depression. The six studies had similar designs and patient samples. Each had a single-blind, placebo wash-out prior to randomization. Three were placebo-controlled trials of three fixed doses of venlafaxine and the other three were placebo- and active-drug-controlled trials. The active comparators were imipramine in two studies and trazodone in the third. The dose of venlafaxine IR in these six studies ranged from 50 to 375 mg daily, given in divided doses. One study lasted 12 weeks and the other five were 6 week trials. All six were outpatient studies involving patients with major depression defined by DSM-III criteria. The subgroup of anxious-depressed patients was defined by a baseline score of two or greater on the HAM-D Anxiety-Psychic Item. This and the HAM-D Anxiety-Somatization Factor were the outcomes used in the meta-analysis.

The total number of patients in the 6 trials was 1,430, with 1,398 or 86% of the ITT sample meeting the anxious-depressed criterion. In the meta-analysis, venlafaxine was statistically superior to placebo on the Anxiety-Somatization Factor beginning at week 3 and on the Anxiety-Psychic Item beginning at week 1. Higher doses of venlafaxine were associated with more rapid separation from placebo on the Anxiety-Psychic Item. In one of the two studies in which imipramine was included as an active comparator, venlafaxine was superior to imipramine on the HAM-D Anxiety-Somatization Factor beginning at week 3 and throughout the study.

These studies, including the meta-analysis, show the benefits of venlafaxine in treating anxiety associated with major depression. Another way of assessing an antidepressant's anxiolytic potential is to test it in the treatment of anxiety disorders. Venlafaxine is, of course, now the only antidepressant indicated by the FDA for the specific treatment of generalized anxiety disorder, and data on this topic are reviewed elsewhere in this volume. Although less extensive, there are also data that indicate the efficacy of venlafaxine in the treatment of obsessive compulsive disorder [Anath et al., 1995; Rauch et al., 1996], as well as social phobia and panic disorder.

In the case of social phobia, Altamura et al. [1999] treated 12 patients in an open design. All of these patients were either non-responders or poor responders to previous therapy with selective serotonin reuptake inhibitors (SSRIs). Over the course of 15 weeks, doses were increased from 37.5 mg twice daily to a range of 150 to 187.5 mg per day. All 12 patients completed the study, with the most significant adverse side effects being nausea, headache, and anxiety. These adverse side effects, however, were noted to be mild to moderate and generally resolved.

Venlafaxine significantly reduced scores on the Liebowitz Social Anxiety Scale (LSAS). For example, the score on the fear subscale dropped from 56.8 at baseline to 22.5 at week 15 and the score on the avoidant behavior subscale from 57.25 at baseline to 22.7 at week 15. The authors noted that improvement in these SSRI poor responders began at about the second week of treatment. These data are compatible with a retrospective analysis of venlafaxine treatment of social phobia reported by Kelsey [1995].

Geracioti [1995] was probably the first to publish experience with venlafaxine in panic disorder, reporting on an excellent response in several patients in a case series. Papp et al. [1997] conducted an open trial of venlafaxine IR in panic disorder. Thirteen patients were entered and ten completed the trial. All ten completers were free of panic attacks by the end of the 10 week trial and had significant reduction in the HAM-A and significant improvement on the Clinical Global Impression (CGI) scale. Pollack et al. [1996] reported on the results of one of five sites in a multicenter, randomized, placebo-controlled study of venlafaxine in panic disorder. Twenty-five outpatients (twenty men and five women) participated. After a single-blind placebo wash-out, patients were randomized to 12.5 mg daily of venlafaxine IR or placebo. Over a period of 4 weeks, the dose was titrated to a maximum of 225 mg daily and over the next 4 weeks, doses were maintained in the range of 100 to 225 mg depending on response and tolerability. The mean dose was 166 mg per day. Significant differences between venlafaxine and placebo were observed for the CGI-improvement scale but not in reduction of number of panic attacks. The latter, a not uncommon outcome in panic disorder trials, appears to be due to a large placebo effect: frequency of panic attacks per week was reduced from a mean of 3.73 at baseline to 1.73 at endpoint by placebo and from 3.08 at baseline to 1.00 at endpoint by venlafaxine. Our own opinion is that venlafaxine XR is effective and well-tolerated by patients with panic disorder, but this has not been studied in large samples to date. It may work for panic disorder at lower than usual antidepressant doses [Kelsey, 1996].

The effectiveness of venlafaxine in reducing anxiety in the mixed depression-anxiety state and its efficacy in treating several different anxiety disorders should put to rest any suggestion that NE reuptake inhibition is anxiogenic. Venlafaxine clearly poses important anxiolytic properties that are undoubtedly derived at least in part from its effects on both the serotonin and NE systems.

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