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ANTIDEPRESSANT EFFICACY OF VENLAFAXINE

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Venlafaxine is a unique antidepressant medication with well documented efficacy and safety in the acute treatment of major depressive disorder. Reports suggest that it may also be effective in the treatment of dysthymic disorder and bipolar II depression, but the available data for these conditions are more limited compared to major depressive disorder. Several studies suggest that there may be a more rapid onset of action for venlafaxine in the treatment of major depression compared to other antidepressant pharmacotherapies, but this has not been fully established. Venlafaxine is also effective in the important long term continuation and maintenance phases of the treatment of depression. Depression and Anxiety, Volume 12, Supplement 1:45–49, 2000. *© 2000 Wiley-Liss, Inc.*

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INTRODUCTION

Venlafaxine is a novel bicyclic antidepressant that inhibits the neuronal reuptake of serotonin and norepinephrine. It was released for clinical use in the United States in the spring of 1994 [Golden et al., 1995], and has now become widely recognized as an effective first-line agent in the treatment of depression. Below, we review the available data regarding the antidepressant efficacy of venlafaxine, and address several specific issues regarding the onset of the acute clinical response, venlafaxines use in the treatment of dysthymic disorder and bipolar II depression, and its utility in long-term continuation and maintenance therapy. The efficacy of venlafaxine in several other specific patient populations (e.g., geriatric patients, children and adolescents) and clinical situations (e.g., refractory depression, severe depression, mixed depression-anxiety states) is covered elsewhere in this volume.

EFFICACY OF VENLAFAXINE IN THE ACUTE TREATMENT OF MAJOR DEPRESSIVE DISORDER

Several double-blind, placebo controlled studies have documented the clinical efficacy of venlafaxine in the treatment of outpatients with major depression. Two early studies, with a combined enrollment of 153 patients, found each of three doses of venlafaxine (25 mg t.i.d., 75 mg t.i.d., and 125 mg t.i.d.) to be superior to placebo during a 6-week study period [Schweizer et al., 1991; Khan et al., 1991]. Other double-blind placebo controlled studies have described a dose-response relationship, as well as superiority to placebo, in both b.i.d. and t.i.d. administration schedules [Mendels et al., 1993; Kelsey, 1996; Rudolph et al., 1998; Khan et al., 1998]. In total, premarketing studies of more than 2,000 patients demonstrated significantly greater efficacy for venlafaxine than placebo at doses between 75 mg/day and 375 mg/day in inpatient, as well as outpatient settings [Feighner, 1994]. In a meta-analysis of six comparable, double-blind placebo controlled trials involving a total of more than 1,400 patients, venlafaxine was found to have significant antidepressant efficacy across a broad range of depressed patients, regardless of patient gender, duration of illness, severity, presence of melancholia, or age (although the number of patients who were older than 65 was limited) [Entsuah et al., 1995]. More recently, these findings of efficacy have been expanded to include the newer, extended-release formulation of venlafaxine (Effexor XR), that has been shown to be significantly more effective than placebo at doses ranging from 75–225 mg/day [Thase, 1997]. In a double-blind placebo controlled trial, once-daily doses of venlafaxine extended release (75 mg/day) and venlafaxine immediate release (37.5 mg b.i.d.) were both superior to placebo in the treatment of outpatients with major depression, and at the end of that 12-week study, the extended release formulation showed superiority in all efficacy variables relative to the immediate release formulation [Cunningham, 1997].

Several double-blind studies have compared venlafaxine in the treatment of major depression to other established agents, both with and without placebo con-

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trols. A double-blind comparison of venlafaxine (up to 150 mg/day) and amitriptyline (also up to 150 mg/day) in outpatients with major depression, with or without melancholia, found similar efficacy for each treatment regardless of the presence or absence of melancholia. There were significantly more patients in the amitriptyline group who experienced an adverse event [Benedictis, 2000]. Another double-blind, randomized trial compared flexible dosing of venlafaxine (up to 150 mg/day) to sertraline (up to 100 mg/day) in depressed outpatients [Mehtonen et al., 2000]. Both treatments led to a significant reduction in HAM-D and MADRS scores by the end of the 8-week trial, and there were no differences between the treatments in these measures at any time point in the study. At the 6-week time point and at the end of the 8-week trial, the HAM-D response rate (defined as a reduction of 50% or more from baseline) was significantly greater for venlafaxine vs. sertraline, but there were no significant differences in response rates at these time points using the MADRS. At the end of the trial, the "remission" rate, defined as a HAM-D score less than 10, was significantly higher for venlafaxine (68%) compared to sertraline (45%) treatment. Costa e Silva [1998] found similar efficacy for venlafaxine and fluoxetine in outpatients with major depression. Among the subgroup of patients whose medication dose was increased at 3 weeks (from 75 mg/day to 150 mg/day of venlafaxine or from 20 mg/day to 40 mg/day of fluoxetine), significantly more patients taking venlafaxine vs. fluoxetine were "very much improved" at the final, Week 8 evaluation. Dierick et al. [1996] also compared venlafaxine to fluoxetine in a randomized, double-blind, 8-week study of 314 outpatients with major depression. Patients began treatment with either fluoxetine 20 mg/day or venlafaxine 75 mg/day, and at Week 2, the dosage of the venlafaxine could be increased to 150 mg/day if the response was inadequate. "Clinical response" was defined as a 50% decrease from baseline in HAM-D scores. At Week 6, 72% of patients receiving venlafaxine had achieved clinical response, compared to 60% of patients treated with fluoxetine, although the dosing schedules for each of the agents should be taken into account in interpreting these results.

Venlafaxine has been compared to tricyclic and other antidepressant pharmacotherapies in a few double-blind studies that included a placebo control group. In one such study of 224 outpatients with major depression,, both venlafaxine (mean maximum dose of 182 mg/day) and imipramine (mean maximum dose of 176 mg/day) were superior to placebo [Schweizer et al., 1994]. Cunningham et al. [1994] randomized 225 patients and attained 149 study completers in a double-blind, placebo controlled study of venlafaxine vs. trazodone. Venlafaxine and trazodone were both superior in efficacy compared to placebo. Venlafaxine yielded more improvement in the cognitive disturbance and retardation factors on the HAM-D compared to trazodone, whereas trazodone was more effective in the sleep disturbance factor, findings that are not surprising in light of trazodone's propensity to cause sedation. In a recent report of a randomized, double-blind, placebo controlled study, the efficacy of once daily extended release venlafaxine vs. fluoxetine was compared in 359 outpatients with major depression and concurrent anxiety. Venlafaxine XR and fluoxetine were both significantly superior to placebo as measured by changes in HAM-D scores beginning in Week 2 and continuing to the end of the study. The HAM-D remission rate was significantly higher compared to placebo at Weeks 3, 4, 6, 8, 12, and final evaluation for venlafaxine XR, and at Weeks 8, 12, and final evaluation for fluoxetine [Silverstone and Ravindran, 1999]. In another multicenter, randomized, double-blind, placebo controlled study of depressed outpatients, flexible dosing was applied in comparing venlafaxine XR (75–225 mg/day) to fluoxetine (20–60 mg/day). Venlafaxine XR appeared to outperform fluoxetine in comparison with placebo in certain efficacy ratings. The percentages of patients who achieved full remission of their depression (defined by a score of 7 or less on the 21 item version of the HAM-D), were 37%, 22%, and 18% for venlafaxine XR, fluoxetine, and placebo, that yielded statistically significant differences between venlafaxine XR and the other groups [Rudolph and Feiger, 1999].

Recently, Einarson et al. [1999] completed a meta-analysis comparing the clinical success rates of extended release venlafaxine, the serotonin selective reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), and tricyclic antidepressants (amitriptyline, imipramine, desipramine, and nortriptyline). Two independent evaluators extracted data from published randomized controlled trials meeting certain criteria, and "therapeutic success" was defined as a 50% decrease in the HAM-D or MADRS score. The resulting analysis from 44 trials with 63 study arms and 4033 patients with depression demonstrated success rates of 73.7% for venlafaxine-XR, that was statistically significantly greater than that of the SSRIs (61.1%) and tricyclic antidepressants (57.9%). Recognizing both the power and the limitations of such post hoc meta-analyses, this report does suggest that venlafaxine may have greater efficacy in the treatment of depression than other classes of antidepressants [Einarson et al., 1999].

EFFICACY OF VENLAFAXINE IN THE TREATMENT OF DYSTHYMIC DISORDER AND BIPOLAR DEPRESSION

Much of the published data regarding venlafaxines efficacy in depression, including all of the studies sum-

marized above, have focused on major depressive disorder. As with antidepressant studies in general, there are relatively fewer investigations of the efficacy of venlafaxine in the treatment of dysthymic disorder and bipolar depression. In an open-label pilot study, 11 out of 15 patients with primary dysthymia without comorbid major depression responded to venlafaxine, with a dose range of 75 mg/day to 225 mg/day, during a 12-week trial [Ravindran et al., 1998]. Joffe et al. [1998] recently reported the results of a large, community-based open-label study of venlafaxine in depressed outpatients, that included 30 patients with dysthymia (among a total of 880 patients). Overall, 62% of patients were rated as either "much improved" or "very much improved," but unfortunately, the results for the dysthymia subgroup are not reported separately. In another open-label study, Dunner et al. [1997] enrolled 17 patients with dysthymic disorder in a 9-week open label trial of venlafaxine, with a maximum dose of 225 mg/day. Among the 14 completers, half responded quickly to the lower, starting dose (75 mg/day) of venlafaxine, and 3 of the remaining 7 responded to the maximum dose [Dunner et al., 1997]. The most recent report of venlafaxine in the treatment of dysthymic disorder enrolled 22 patients, of whom 5 dropped out before their second visit. In the remaining 17, open label treatment with venlafaxine (mean final dose of 179 mg/day) resulted in 13 (76.5%) treatment responders [Hellerstein et al., 1999].

To date, Amsterdam [1998] has published the only report examining the efficacy and safety of venlafaxine monotherapy in the treatment of bipolar II major depression. After a 1-week placebo lead-in period, 17 bipolar II depressed patients and 31 unipolar depressed patients were randomly assigned to once daily vs. twice daily venlafaxine treatment, under double-blind conditions, with a maximum dose of 225 mg/day. Bipolar II and unipolar patients demonstrated similar efficacy, with a more rapid reduction in depression rating scale scores by Week 2 of treatment in the bipolar patients who completed the trial. From a safety perspective, no episodes of venlafaxine-induced "switch" into mania were observed during this 6-week trial.

IS THERE AN EARLY ANTIDEPRESSANT RESPONSE TO VENLAFAXINE?

The history of second generation antidepressant pharmacotherapies is littered with initial claims for early onset of antidepressant action that failed to withstand the test of replication. The lag period between initiation of treatment and antidepressant response is very problematic and even dangerous, especially in the context of recent changes in the financing of mental health care delivery, that have effectively limited the availability of the safety afforded by inpatient care during the initial phase of treatment. Thus, the search for the "holy grail" of early therapeutic response continues with increased vigor. Yet methodological and practical aspects of study design contribute to the repetitive saga of dashed initial hopes. Most clinical trials include weekly assessment schedules, rather than daily symptom ratings that would facilitate prospective study of the percent of subjects in a group who respond within a given number of days. Instead, post hoc analyses search for statistically significant differences across groups in terms of the average time to response, that is reported in terms of days even though the assessments occurred at weekly intervals.

With the above caveats in mind, a review of putative early onset of action for venlafaxine is interesting. Several controlled clinical trials yielded post hoc analyses exploring for potential differences among active treatments at each of the first several weekly assessments. In a review of several premarketing studies, Feighner [1994] points out that in some instances, venlafaxine showed clinical superiority over placebo by Week 1, and in an inpatient study of melancholic patients (that included more frequent assessments in the study design), venlafaxine demonstrated clinical efficacy as early as Day 4, as defined by a 50% improvement in MADRS scores, and by Week 1, when HAM-D scores were examined [Guelfi et al., 1995]. In his review, Feighner [1994] found that early responses to venlafaxine are seen at higher doses, in general. Of course, higher doses can be associated with more frequent and prominent side effects, some of which may lower scores on specific depression rating scale items (e.g., activation and agitation could lower scores on psychomotor retardation and fatigue symptom items; sedation could lower scores related to sleep disturbance). In the dose-response study by Khan et al. [1998] referenced above, significant improvements in some primary response parameters were seen in Weeks 1 and 2 in patients receiving higher doses (i.e., 150 and 200 mg/day) but not the lower dose (75 mg/day) of venlafaxine. Benkert et al. [1996] looked for an earlier response in a double-blind randomized comparison of rapidly escalating dose of venlafaxine (increased to 375 mg/day over a 5-day period, maintained at that dose for 10 days, then reduced to 150 mg/day) vs. imipramine (increased to 200 mg/day over 5 days, then maintained at that level) in inpatients with major depression and melancholia. No differences in response rates, as measured by changes in the HAM-D and MADRS, were observed between the two treatments, but among those patients who responded based on the HAM-D, there was a significantly earlier onset of response and sustained response in the venlafaxine group. The median time to response on the HAM-D was 14 days for the venlafaxine group, and 21 days in the imipramine group. It should be noted, however, that there were no differences between the treatments when the MADRS was analyzed as the efficacy variable [Benkert et al., 1996].

Derivan et al. [1995] reanalyzed the databases from

two randomized, double-blind, placebo-controlled studies of rapid dose escalation of venlafaxine [Khan et al., 1991; Schweizer et al., 1991; Shrivastava et al., 1994a] and applied three statistical methodologies for probing for early onset of action: traditional analysis of depression scale scores, pattern analysis based on timing and persistence of response, and survival analysis of sustained response [Derivan et al., 1995]. All three analyses found venlafaxine to have significant effects early in the course of therapy.

In a different approach to onset of antidepressant action, Amsterdam et al. [1998] compared once daily vs. twice daily dosing regimens of venlafaxine. Patients were randomly assigned to either schedule, beginning with a total daily dose of 37.5 mg and with specified increments up to 225 mg/day. Patients in both groups demonstrated significant reductions in HAM-D and MADRS scores at all weekly time points throughout the 6-week study. There was a non-significant trend toward a more rapid reduction in the mean HAM-D score at Week 2 ($P < 0.06$) and in the mean MADRS score at Week 1 ($P < 0.07$) and Week 2 ($P > 0.09$) in the b.i.d. dosing group.

EFFICACY OF VENLAFAXINE IN THE LONG-TERM MANAGEMENT OF DEPRESSION

Although most studies of antidepressant pharmacotherapy focus on short-term efficacy and tolerability, there is growing recognition of the importance of the continuation and maintenance phases of therapy in decreasing the risks of relapse and recurrence [Thase, 1999]. Several studies have now addressed the efficacy of venlafaxine in the long-term treatment of depression. A pooled analysis from four double-blind, placebo controlled clinical trials examined relapse rates in outpatients with major depression who had responded to short-term treatment and were continuing long-term treatment (up to 12 months) [Entsuah et al., 1996]. The database included 185 patients treated with venlafaxine and 119 treated with placebo. Cumulative relapse rates were significantly lower for venlafaxine (11%) than placebo (23%) at 6 months of long-term treatment, and the cumulative relapse curves for the venlafaxine and placebo groups over the 1-year long-term treatment also differed significantly.

In a study designed to compare the long-term safety and clinical acceptability of venlafaxine and imipramine in outpatients with major depression, 291 patients were treated with the former agent and 91 with the latter for as long as clinically necessary, up to 1 year. Venlafaxine was reported to be significantly more acceptable than imipramine by subjective ratings from the patients. Consistent with this observation, fewer venlafaxine-treated patients withdrew because of adverse events or unsatisfactory response than imipramine-treated patients. A consistent trend in the therapeutic response rates, in favor of venlafaxine, achieved statistical significance at Months 2, 6, and 12 [Shrivastava et al., 1994b]. A double-blind, placebo controlled trial that compared venlafaxine and trazodone in both the acute and long-term phases of antidepressant treatment found that patients on venlafaxine were more likely to enter the long-term phase and to remain in the trial the longest [Cunningham et al., 1994].

Several preliminary reports describe the efficacy of venlafaxine in the prevention of depression recurrence. A 12 month, double-blind, randomized, placebo-controlled study assessed the effectiveness of venlafaxine 100 to 200 mg/day, for the prevention of recurrence in patients with recurrent major depression. Patients who had responded to an 8-week, acute treatment trial of venlafaxine were continued on open-label therapy for a total of 6 months, and then randomized to double-blind treatment with either venlafaxine or placebo for up to 12 months. Discontinuation due to lack of efficacy occurred in 48% of the placebo treatment group and in 21% of the venlafaxine group. Interestingly, the incidence of common adverse events was similar in the placebo and venlafaxine groups during the double-blind phase of treatment [Hackett et al., 1998]. An ongoing study of venlafaxine extended release for the prevention of depression recurrence has recently reported the results of an interim safety analysis [Rudolph et al., 1998]. Patients responding to venlafaxine XR during an 8-week acute treatment trial were randomly assigned to either venlafaxine XR or placebo during a 6-month continuation phase. At the interim analysis of 214 patients at 6 months, the overall rates of adverse events with venlafaxine XR and with placebo were comparable. Finally, a 24-month open label study of venlafaxine in geriatric patients with recurrent major depression found no relapses among 21 acute treatment responders during the 4 month continuation phase and 4 relapses during the additional 20 months of maintenance therapy [Amore et al., 1997].

SUMMARY

The efficacy of venlafaxine in the acute treatment of major depressive disorder is very well established. Reports suggest that it may also be effective in the treatment of dysthymic disorder and bipolar II depression, but additional data from controlled clinical trials are required to confirm these observations. Venlafaxine seems to have an early onset of action in the treatment of major depression, although this observation also needs additional confirmation. Venlafaxine has been shown to be effective in the long term management of depression, including the continuation and maintenance phases of treatment.

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