Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety

Andre De Nayer1, Stefaan Geerts2, Leo Ruelens3, Michel Schittecatte4, Eugeen De Bleeker5, Ignace Van Eechhoutte6, Jean-Luc Evrard7, Paul Linkowski8, Pierre Fossion9, Sophie Leyman10 and Annick Mignon10

"Hôpital Ste-Thérèse, Montignies sur Sambre, Belgium
2 Sint Lucas Hospital, Assebroek, Belgium
3 St Andries Hospital, Tielt, Belgium
4 Centre Hospitalier Universitaire de Charleroi, Marchienne au Pont, Belgium
5 St Lucia Hospital, Sint Niklaas, Belgium
6 Psychiatrisch centrum Heilig Hart, Leop, Belgium
7 CHR Val de Sambre, Chtelet, Belgium
8 Cliniques Universitaires de Bruxelles, Hôpital Erasme, Brussels, Belgium
9 Cliniques Universitaires de Bruxelles, Hôpital Brugmann, Brussels, Belgium
10 Wyeth Lederle Belgium, Louvain-la-Neuve, Belgium

Abstract
The aim of this double-blind study was to compare the efficacy and safety of venlafaxine vs. fluoxetine in the treatment of patients with depression and anxiety. A total of 146 moderately depressed patients with associated anxiety were randomized to receive 75 mg/d venlafaxine or 20 mg/d fluoxetine for 12 wk. Dose increases were permitted after 2 wk of treatment, to 150 mg/d venlafaxine and 40 mg/d fluoxetine, to optimize response. At the final visit, a statistically significantly greater efficacy of venlafaxine over fluoxetine was observed on depressive symptoms and concomitant anxiety, and 75–0 and 50–7% of patients administered venlafaxine and fluoxetine, respectively, showed an overall response. A sustained response (for at least 2 wk), present at the end of the study was achieved in 57–8 and 43–3% of patients in the venlafaxine and fluoxetine groups, respectively, and at the final visit, 59–4 and 40–3% of patients, respectively, were in remission (virtually asymptomatic). Dose increases were required by a greater percentage of patients in the fluoxetine group (52–9%), than in the venlafaxine group (37–1%), and in those patients whose dose was increased, a higher efficacy was again observed with venlafaxine. Venlafaxine and fluoxetine were well tolerated, with the most frequently experienced adverse events being nausea and headache. Fewer patients in the venlafaxine group than in the fluoxetine group reported at least one adverse event (55–7 and 67–1% patients, respectively). Venlafaxine therefore proved to be significantly more effective than fluoxetine in improving depressive symptoms and concomitant anxiety.

Received 22 July 2001; Reviewed 12 September 2001; Revised 4 December 2001; Accepted 7 December 2001

Key words: Concomitant anxiety, depression, fluoxetine, venlafaxine.

Introduction
The antidepressant venlafaxine is structurally distinct to the tricyclic, tetracyclic and other currently available antidepressant agents, and is thought to function by inhibiting the neuronal uptake of serotonin and norepinephrine, and to a lesser degree, dopamine re-uptake. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity, and has virtually no affinity for cholinergic, histaminergic, or adrenergic receptors (Muth et al., 1986). In addition, it produces a rapid onset of noradrenergic sub-sensitivity, indicating that venlafaxine has the potential to be a safe, effective antidepressant, with the capacity to invoke a relatively early onset of clinical activity (Muth et al., 1991). Clinical studies with venlafaxine, suggest that the drug

Address for correspondence: A. Mignon, Medical Department, Wyeth Lederle Belgium, rue du Bosquet 15, B-1348 Louvain-la-Neuve, Belgium.
Tel.: +32 (0) 10 494 854 Fax: +32 (0) 10 494 650 E-mail: mignon@labs.wyeth.com
This article was presented in part at the XI World Congress of Psychiatry, Hamburg, Germany, 6–11 August 1999, and at the 12th European College of Neuropsychopharmacology Congress, London, 21–25 September 1999.
is an effective and well-tolerated antidepressant. When compared with the antidepressants imipramine (Benkert et al., 1994, 1996; Ferguson et al., 1994; Schweizer et al., 1994) and trazodone (Cunningham et al., 1994), or with placebo (Guelfi et al., 1995; Khan et al., 1991; Schweizer et al., 1991), venlafaxine proved more effective than placebo in alleviating depressive symptoms, and functioned in an equivalent, and often improved manner to the established therapies. Nausea, somnolence, dry mouth and dizziness were the most frequently reported adverse events associated with venlafaxine administration, and these events were often resolved with continued drug usage.

The comparator drug, fluoxetine, was selected at the time of study design as it was the most commonly prescribed selective serotonin re-uptake inhibitor (SSRI) and the only SSRI that had depression, with and without anxiety, as an indication for treatment in Belgium. Fluoxetine is usually prescribed at a dose of 20 mg/d for the treatment of major depressive disorders. In a 6-wk comparative study of 200 mg/d venlafaxine with 40 mg/d fluoxetine, a statistically significant clinical advantage was shown for venlafaxine over fluoxetine, with patients receiving venlafaxine showing greater improvements in Hamilton Depression Rating Scale (HAMD) scores and Montgomery and Asberg Depression Rating Scale (MADRS) scores (Clerc et al., 1994). A 12-wk study comparing the once-daily extended release formulation of venlafaxine with fluoxetine in outpatients with depression and anxiety, showed a superior efficacy over fluoxetine (Silverstone and Ravindran, 1999).

This randomized, double-blind, controlled Phase IV study was designed to compare the efficacy and safety of venlafaxine and fluoxetine in the treatment of patients with depression and concomitant anxiety. This paper aims to provide evidence of the more rapid onset of action of venlafaxine when compared with fluoxetine.

**Method**

Written approval was obtained from an Institutional Ethics Committee prior to implementation of the study, and all study procedures were conducted in accordance with the ethical standards detailed in the Declaration of Helsinki (Hong Kong, 1989). Approximately 120 outpatients were recruited into this multi-centre study. Male and female patients between the ages of 18 and 70 yr inclusive, who had provided written informed consent, were enrolled. Patients were required to have a baseline score between 18 and 25, inclusive, on the 21-item HAMD Scale, as well as a minimum baseline score of 8 on the Covi Anxiety Scale, and to be considered by the investigator to be moderately depressed. Females of childbearing potential were required to have a negative pregnancy test at baseline, and to use a medically acceptable form of contraception throughout the study.

Pregnant or breast-feeding patients were not enrolled into the study; neither were patients with concomitant psychiatric disease or personality disorder, or known clinically significant laboratory abnormalities. Patients were also excluded if they had used any other investigational or antipsychotic drug or electroconvulsive therapy (ECT) within 30 d of baseline. Prohibited medications included fluoxetine within 21 d of baseline, MAO inhibitors within 14 d of baseline, antidepressants, other psychotropic drugs, or non-psychotropic drugs with psychotropic effects in the 7 d before baseline (unless the dose had been stable for at least 1 month). Anxiolytic drugs (including lorazepam), antidepressants other than the study medication, ECT, investigational drugs, and other psychopharmacological drugs were prohibited during the study. Patients were, however, permitted to take 2 mg lormetazepam at bedtime, if required for sleep, as well as other medication to treat inter-current medical conditions, at the discretion of the investigator. Patients who had previously failed to respond to venlafaxine or fluoxetine treatment, or who were acutely suicidal were not enrolled into the study.

All study medication was taken orally, with meals. Eligible patients were randomized to receive double-blind treatment with 75 mg/d venlafaxine (37.5 mg, twice-daily) or 20 mg/d fluoxetine (20 mg in the morning, placebo in the evening) for 12 wk. If the decrease in HAMD at the week 2 visit was less than 40%, or the patient’s HAMD score was greater than 11, dose increases were required up to 150 mg/d venlafaxine (75 mg, twice-daily) and 40 mg/d fluoxetine (20 mg, twice-daily) in order to optimize the response. Dose increases were permitted in both treatment groups for equivalence, however for fluoxetine treatment it is noted that an increased dose is not associated with an increased efficacy response. The highest dose of study drug administered was maintained until the end of the study, or until the start of a 1-wk dose-tapering period. The decision to reduce the dose in patients experiencing adverse effects was based on tolerance and the clinical judgement of the investigator.

At baseline (week 0), patients were assessed for eligibility and a complete medical and psychiatric history was taken. From baseline to week 12, disease status was assessed using the HAMD Scale, the MADRS, the Clinical Global Impression (CGI) Scale and the Covi Anxiety Scale. Adverse events, vital signs and the use of concomitant medications were also recorded at these visits. Patients were withdrawn from the study if they experienced a marked increase in depression, which could not be controlled by study procedures, especially the...
emergence of suicidal thoughts requiring precautionary action.

Patients were considered to be MADRS responders if their total MADRS score had decreased by at least 50% from baseline. HAMD responders were similarly defined. Patients were considered an overall responder if they were either a MADRS or HAMD responder, and in addition if they had a CGI improvement score of 1 (very much improved) or 2 (much improved). Sustained response was defined as a response present at the final visit, which had lasted for at least 2 wk. Patients were considered to be in remission, if they achieved a HAMD 21-item score of 8 or less.

Statistical analysis

Statistical analysis was performed using the SAS software package version 6.08 (SAS Institute Inc., 1989), and was based on pooled data from the individual study sites. The analysis population consisted of all patients who had received at least one dose of randomized study medication, and who had at least one evaluation during the treatment period, either whilst on therapy or within 3 d of the last dose. All analyses of efficacy and of vital signs for safety were performed using this population. Efficacy assessments for the final study visit were based on the last observation carried forward for all patients in the analysis population; for other visits efficacy assessments were based on observed cases at each visit only.

The primary efficacy variables were the final on-therapy total MADRS and HAMD scores, and the final on-therapy CGI severity score. These were analysed using summary statistics, an analysis of covariance model (with baseline values as the covariate) and on a last-observed value basis with 95% confidence intervals (CIs) calculated. Vital signs data were analysed by summary statistics and by the calculation of the incidence of patients with vital signs outside of pre-defined levels of concern. All analyses of treatment effects were two-sided and performed at the 5% level of significance. No analysis was to be performed based on observed cases at each visit only.

Adverse events occurring during the study (either whilst on therapy, or within 7 d of the last dose) were included in the analysis. Adverse events were classified with respect to treatment emergence, discontinuation and relationship to study drug.

Results

A total of 146 patients were enrolled into 14 psychiatric practices across Belgium. Seventy-three patients were randomized into each of the venlafaxine and fluoxetine treatment groups, with 64 and 67 patients, respectively, being included in the analysis population. For 9 patients in the venlafaxine group and 6 patients in the fluoxetine group, no efficacy data whilst on study medication or within 3 d of stopping study medication were obtained. There was a predominance of women in both groups (71.2% venlafaxine, 65.8% fluoxetine). In the venlafaxine group, the mean age was 41.6 yr, the mean weight was 68.8 kg and the mean height was 167.1 cm. This was comparable to the fluoxetine group, where the mean age was 43.9 yr, the mean weight was 71.4 kg and the mean height was 169.1 cm.

Most patients were moderately or markedly ill according to the baseline CGI score. In the venlafaxine group, 57.5% of patients were moderately ill and 35.6% were markedly ill, as compared with 50.7 and 38.4% of patients in the fluoxetine group, respectively. A total of 72.6% of patients in the venlafaxine group and 68.5% of patients in the fluoxetine group had taken prior antidepressant medication. Mean baseline MADRS total scores were 28.0 in both treatment groups, and mean baseline HAMD scores were 23.0 in the venlafaxine group and 23.1 in the fluoxetine group. The mean baseline CGI Anxiety scores were 8.2 in the venlafaxine group and 8.3 in the fluoxetine group.

Statistically significantly greater decreases in mean total MADRS scores were observed from baseline to week 2 and at the final visit, in the venlafaxine-treated group when compared with the fluoxetine-treated group, with mean decreases from baseline at the final visit of 17.5 [standard deviation (s.d.) 9.6] and 12.6 (s.d. 10.1), respectively ($p = 0.0035$; 95% CI for the difference in changes from baseline: 1.68 to 8.34). The difference in the changes from baseline in mean total MADRS scores between the two groups were not statistically significant at the other visits. The percentage of patients with a MADRS suicidal ideation score of 0 (absent) increased from 17.2% at baseline to 70.3% at the final visit for patients receiving venlafaxine, and from 23.9 to 62.7% for patients receiving fluoxetine; the difference between treatment groups was not statistically significant ($p = 0.164$). The MADRS response rates at the final visit were 75.0 and 49.3% in the venlafaxine- and fluoxetine-treated groups, respectively ($p = 0.001$).

Similar findings were observed for the changes in mean total HAMD scores, with mean decreases from baseline at the final visit of 14.4 (s.d. 7.6) for the venlafaxine group and 10.4 (s.d. 8.6) for the fluoxetine group ($p = 0.0048$; 95% CI for the difference in changes from baseline: 1.68 to 6.26). At week 2 (observed cases) the total HAMD scores improved significantly more in the venlafaxine-treated patients compared with the fluoxetine-treated patients ($p = 0.0058$). The difference in the changes from
baseline in mean total HAMD scores between the two groups were not statistically significant at the other visits. The percentage of patients with a HAMD suicidal ideation score of 0 increased from 26.6% at baseline, to 82.8% at the final visit in the venlafaxine group, and from 34.3 to 76.1%, in the fluoxetine group ($p = 0.187$). The HAMD response rates at the final visit were 71.9 and 49.3% in the venlafaxine and fluoxetine treatment groups, respectively ($p = 0.008$), again showing at week 2 (observed cases) a statistically significant advantage for venlafaxine (28.3 vs. 12.3%; $p = 0.018$).

Statistically significantly greater improvements in mean total Covi Anxiety scores were also observed from baseline to final visit in the venlafaxine-treated group when compared with the fluoxetine-treated group, with mean decreases from baseline of 5.7 (s.d. 2.6) and 3.9 (s.d. 3.1), respectively ($p = 0.0004$).

At the final visit, sub-items from the HAMD scale that had improved significantly more with venlafaxine treatment than fluoxetine treatment were depressed mood (73 vs. 59%, respectively), anxiety somatic (50 vs. 40%), agitation (63 vs. 38%) and sleep disturbance (50 vs. 28%).

The percentages of patients with a CGI global improvement score of 1 or 2 at the final visit, were 79.7 and 59.7%, for the venlafaxine and fluoxetine groups, respectively ($p = 0.016$). The venlafaxine group also showed greater improvements in mean CGI scores than the fluoxetine group at the final visit, but the difference was not statistically significant ($p = 0.073$).

At the final visit, 75.0% of patients in the venlafaxine group, and 50.7% of patients in the fluoxetine group showed an overall response, with a sustained response observed for 57.8 and 43.3% of patients, respectively. A significantly greater percentage of patients ($p = 0.028$) were in remission by the final visit following venlafaxine administration (59.4%) than following treatment with fluoxetine (40.3%). Figure 1 presents the percentage of patients with a HAMD response, from week 1 to week 12 [observed cases (OC)]. Figure 2 presents the percentages of patients with an overall response, in remission and with a sustained response at the final visit [last observation carried forward (LOCF)].

Notably fewer patients (observed cases) administered venlafaxine (37.1%) required a dose increase at week 2, when compared with those receiving fluoxetine (52.9%). In those patients who did receive a higher dose, efficacy, as assessed by overall response rates, was again greater in the venlafaxine group than in the fluoxetine group, 69.2 and 43.2%, respectively. It should be noted however that an increase in dose is not associated with an increase in efficacy with fluoxetine treatment.

**Safety assessments**

Overall, 32.9% (24/73) of patients randomized to receive venlafaxine, and 39.7% (29/73) of patients randomized to receive fluoxetine withdrew prematurely from the study. Common reasons for discontinuation were the occurrence of adverse events (11.0% of patients randomized to venlafaxine and 12.3% of patients randomized to fluoxetine), and an unsatisfactory response (6.8% of patients randomized to venlafaxine and 13.7% of patients randomized to fluoxetine). The most common adverse reported events leading to discontinuation of venlafaxine were headache, diarrhoea and nausea (3 subjects discontinued for each), and for discontinuation of fluoxetine were insomnia (3 subjects), dyspepsia, nausea, anxiety, and nervousness (2 subjects each). Venlafaxine and fluoxetine were well tolerated at all doses, and the most frequently reported treatment-emergent adverse events were nausea (28.6% of patients receiving venlafaxine and 21.4% of patients receiving fluoxetine), and headache (8.6% of patients receiving venlafaxine and 11.4% of patients receiving fluoxetine). A total of 55.7% (39/70) of patients in the venlafaxine group and 67.1% (47/70) of patients in the fluoxetine group experienced at least one adverse event, and for the majority of patients, these events were considered to be treatment-related.

No clinically significant systolic and diastolic blood
pressure, and pulse rate values were observed during the course of the study. A total of 6.8 and 9.6% of patients randomized to the venlafaxine- and fluoxetine-treated groups, respectively, experienced weight increases or decreases of more than 7.0% of their baseline measurement.

**Discussion**

Compared to the more common 8-wk studies in depression, this 12-wk study allows a more accurate assessment of the maximal and sustained effect of treatment. It was designed to examine the response of a typical outpatient population in specialized psychiatric care to venlafaxine or fluoxetine in the treatment of depression and concomitant anxiety. The participating psychiatrists selected the subjects based on the presence of clinically significant depression requiring pharmacological treatment. No formal DSM-IV interview was required by the protocol. Previous studies have shown the efficacy of venlafaxine and fluoxetine in depressed patients and as such inclusion of a placebo arm was deemed unnecessary and unethical.

Comparison of the efficacy profiles of venlafaxine and fluoxetine in patients with moderate depression and anxiety, revealed a significantly greater overall response rate in those administered venlafaxine, than in those receiving fluoxetine. There were no statistically significant differences between venlafaxine and fluoxetine treatment at weeks 4, 8 and 12. Statistically significant improvements in depressive symptoms, and in concomitant anxiety, were observed in the venlafaxine-treated group as early as week 2 of the study, as well as at the final visit, when compared with the corresponding fluoxetine population. A greater proportion of patients in the venlafaxine group than in the fluoxetine group achieved remission by the final visit, a state that can be defined as virtually asymptomatic, despite having moderate depression at baseline. No analysis was performed in this study to examine the response and remission of subjects based upon the severity of their depression or anxiety at baseline.

The findings of this study further support those of earlier comparative studies, in which the benefits of venlafaxine treatment over fluoxetine treatment in depressed patients were demonstrated. In a 6-wk, double-blind study of 68 in-patients with major depression and melancholia, response rates on the MADRS and HAMD scales were significantly greater at weeks 4 and 6 for patients receiving 200 mg/d venlafaxine (76% for both scales at week 4), than for those receiving 40 mg/d fluoxetine (41% and 47%, respectively, at week 4) (Clerc et al., 1994). Similarly, a significantly greater response rate with venlafaxine, than with fluoxetine was observed in an 8-wk, double-blind study of 314 outpatients with major depression (Dierick et al., 1996). After 6 wk of treatment, 72% of patients administered venlafaxine (37.5 mg twice-daily for 2 wk, increasing to 75 mg twice-daily, as required) showed a HAMD response, compared with only 60% of patients administered fluoxetine (20 mg/d).

A randomized, double-blind, placebo-controlled study of the efficacy and safety of once-daily venlafaxine extended release and fluoxetine in outpatients with major depression and concomitant anxiety (Silverstone and Ravindran, 1999) showed that venlafaxine and fluoxetine were significantly superior ($p < 0.05$) to placebo on the HAMD total score beginning at week 2 and continuing to the end of the study. Venlafaxine, but not fluoxetine, was significantly better than placebo at week 2 on the HAMD depressed mood item.

The early clinical improvement with venlafaxine suggests a more rapid onset of action than fluoxetine, when both drugs are administered at the usual daily dose regimen. Early onset of action with venlafaxine has been reported by several groups and reviewed by Burnett and Dinan (1998). In agreement with the findings of this study, Khan et al. (1991), observed significant improvements in depressed outpatients after just 2 wk of venlafaxine treatment, as assessed on the CGI, HAMD and MADRS scales. Similarly, in placebo-controlled trials (Derivan et al., 1995), a statistically significant difference in favour of venlafaxine was observed, with patients showing a response within the first 2 wk of treatment. In two comparative, double-blind studies of venlafaxine with imipramine in 167 depressed inpatients, Benkert et al. (1994, 1996), showed that patients administered venlafaxine achieved a sustained response significantly faster than those receiving imipramine.

In these earlier studies, the more rapid onset of venlafaxine action was particularly notable when the drug dose was rapidly escalated. Indeed, in the present study, patients having their dose of venlafaxine increased after 2 wk, showed improved efficacy when compared with those receiving dose increases of fluoxetine. This observation is consistent with venlafaxine having a steeper dose–response curve than fluoxetine, and consequently dose increases, following an initial lack of response, may be a more beneficial therapeutic option with venlafaxine.

Comparable safety and tolerance profiles were observed for venlafaxine and fluoxetine. Although patients receiving fluoxetine experienced more adverse events than those receiving venlafaxine, the types of events were as expected for patients on antidepressants, with nausea and headache being reported most frequently. Fewer patients receiving venlafaxine withdrew from the study, when compared with those receiving fluoxetine, sug-
suggested that early improvement in disease status may result in enhanced compliance with study medication.

In conclusion, venlafaxine appears to be better than fluoxetine in improving depressive symptoms and concomitant anxiety, with statistically significantly greater proportions of patients achieving a response or remission on venlafaxine therapy. The assessment of remission (virtual absence of symptoms), which is a more stringent measure of efficacy, also shows that venlafaxine is significantly better than fluoxetine. In the observed case analysis a faster mode of action is observed for the venlafaxine group. This early onset of clinical action, combined with the lower occurrence of adverse events and patient withdrawals in the venlafaxine group, when compared with the fluoxetine group, indicates a potential therapeutic advantage for this antidepressant and its usefulness as a first-line treatment.

References


