

EFFICACY AND TOLERABILITY OF VENLAFAXINE EXTENDED RELEASE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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SUMMARY

Background: In this study we wanted to determine the efficacy and tolerability of venlafaxine extended release in patients with major depressive disorder.

Subjects and methods: 161 patients with major depressive disorder were included in an open-label, multicentre clinical study. All patients were treated with venlafaxine extended release in flexible doses ranging from 75 to 325 mg daily over an 8-week period. Efficacy measurements included the 17-item Hamilton Depression Scale, the Clinical Global Impression-Improvement scale (CGI-I), the Severity of Illness scale (CGI-S), and the Depression and Somatic Symptom Scale (DSSS). All scales were administered at baseline and at weeks 2, 4 and 8.

Results: A total of 148 (91.2%) patients completed the study. After 8 weeks of treatment with venlafaxine extended release, response and remission rates were 93% and 45% respectively. At the end of the study, 52.7% of patients were rated on CGI-S with 2 or 1 (not ill/mildly ill) and on CGI-I 81.1% of patients were rated by the physician as much/very much improved. The severity of somatic symptoms such as headache, back pain, chest pain, tenderness of more than a half of body muscles, and fatigue or loss of energy decreased towards the end of the study ($p < .0001$). Adverse events caused discontinuation in 4.7% of patients. No significant changes of body mass ($p = .237$), Body Mass Index ($p = .281$), and heart rate ($p = .840$) were present, but systolic and diastolic blood pressure significantly decreased ($p < .0001$) towards the end of the study.

Conclusion: The data from this study indicate that venlafaxine XR is an efficient and safe therapeutic option for patients with major depressive disorder, with the additional effect of reducing associated painful physical symptoms.

Key words: major depressive disorder - somatic symptoms - venlafaxine extended release

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INTRODUCTION

Depression is the most frequent mental health problem and it is perceived as a chronic disease that substantially affects the quality of life, daily functioning and productivity of the people suffering from it (Vanoli et al. 2008).

The treatment of depressive disorders is very complex and may prove to be quite difficult. Rapid remission is an important predictor that patients will achieve long-term remission of their depressive symptoms (Szádóczy et al. 2004). Patients with depression report high rates of inadequate treatment. In a US national representative study only 21.7% of respondents with major depression stated that they were receiving adequate therapy (Lopez-Ibor et al. 2008). Almost one half of the patients receiving adequate doses of antidepressants who are respondent to the treatment do not achieve full remission (Judd et al. 2000). Almost 15% of all treated patients with depression do not show any response to treatment with the first antidepressant, and approximately 25% respond incompletely or exhibit some residual symptoms (Vanoli et al. 2008, Thompson & Thompson 1989). Patients treated to full remission are less likely to relapse and have more normal psychosocial and vocational functioning when compared with incompletely remitted patients (Thase et

al. 2001). Also, the presence of residual symptoms after remission is a predictor of early relapse and had a stronger association with relapse than the number of prior episodes (Judd et al. 1998). In clinical practice, the most common reasons for therapeutic inefficiency are poor compliance, inappropriate antidepressant dosage, and inadequate duration of treatment, somatic comorbidity, interaction with other drugs, psychoactive substance abuse, unfavourable and unstable home and work environment, and biological heterogeneity of depression.

According to the US National Comorbidity Survey data, 58% of patients with major depression also have a co-morbid anxiety disorder, and 67% of patients with generalised anxiety disorder have a life-long history of co-morbid unipolar depression (Kessler et al. 1996). The occurrence of depression and anxiety symptoms together is associated with greater severity of symptoms, greater impairment, more chronic course of illness, poorer outcome and higher incidence of suicide (Silverstone & Salinas 2001).

Patients with depressed mood often report somatic complaints or have medically unexplained symptoms, especially pain (Begré et al. 2008). The prevalence of co-morbid pain and depression is between 50 – 100% (Bair et al. 2003, Ruoff 1996, Kroenke et al. 2006). On the other hand, the risk of endorsing depressed mood in patients with chronic pain shows a 2 – 3 fold increase

(Bair et al. 2003). Chronic painful syndromes, such as headache, backache, joint pain and others, often accompany major depression and anxiety disorders (Gureje 2007).

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor used to treat depression and various anxiety disorders, and also post-stroke depression (Schmitt et al. 2009, Kucukalić et al. 2007). It has also shown efficacy in the treatment of patients with resistant depression (Bauer et al. 2009). There is some evidence that venlafaxine is effective in the treatment of various chronic pain syndromes (i.e. neuropathic pain, fibromyalgia, chronic back pain, in the prophylaxis of migraine, in tension-type headache) (Sindrup et al. 2005, Songer & Schulte 1996, Sayar et al. 2003, Ozyalcin et al. 2005, Zissis et al. 2007). The somatic presentations may lead to under-diagnosis and inappropriate treatment of patients with mood disorders. Treating pain is therefore an important part of treating depression.

The aim of this study was to examine the efficacy and safety of venlafaxine extended release (venlafaxine XR) in patients with major depressive disorder.

SUBJECTS AND METHODS

Participants

The main objective of this naturalistic, multicentre, open-label 8-week clinical study was to assess the efficacy and safety of venlafaxine XR in the treatment of patients with major depressive disorder according to the DSM IV criteria. The study was conducted in 11 psychiatric centres by psychiatrists familiar with HAMD use. It had been approved by the Slovenian Ethics Committee. Written informed consent was obtained from all patients prior to entry into the study.

Out-patients and in-patients of both genders who were over 18 with the minimum score of 14 on the Hamilton Depression Rating Scale (HAM-D₁₇ scale) were included in the study. Patients that were allergic to venlafaxine XR or excipients, those who were receiving MAOI within 14 days prior to baseline and women of childbearing potential without contraceptive protection were not included in the study. All particularities included in the SPC of venlafaxine XR were taken into account.

Table 1. Sociodemographic and clinical data

| Variables | Study population, N=161 |
|--------------------------------------------|-------------------------|
| Gender, men, N (%) | 43 (27) |
| Mean age – years (SD) | 49.7±25 |
| Concomitant disease, N (%) | 112 (69.5) |
| Concomitant medication, N (%) | 102 (63.4) |
| First episode of depression, N (%) | 67 (41.6) |
| Previous treatment of actual episode N (%) | 94 (58.4) |

Methods

The starting dose of venlafaxine XR at baseline (first visit) was 75 mg daily; on subsequent visits the patients were prescribed flexible doses up to a maximum of 375 mg daily, depending on the investigator's clinical judgment. Follow-up visits were scheduled at weeks 2, 4 and 8.

Efficacy assessments included the HAM-D₁₇ scale (Hamilton 1967), the Clinical Global Impression - Improvement scale (CGI-I) and the Severity of Illness scale (CGI-S) (Guy 1976). Response was defined as a decrease in the HAM-D₁₇ total score of at least 50% from baseline, or a score 1 (very much improved) or 2 (much improved) on the CGI-Improvement (CGI-I) scale. Remission was determined by the percentage of patients with a score ≤ 7 on HAM-D₁₇ scale (Frank et al. 1991).

Painful physical symptoms were assessed with the Depression and Somatic Symptom Scale (DSSS) (Hung et al. 2006).

Tolerability and safety measures included the recording and evaluation of reported adverse events, withdrawal and drop-outs, and the effect of treatment on physical variables such as weight, systolic and diastolic blood pressure, and heart rate.

Statistical analysis

To compare the distribution with regard to mean value and confidence intervals for mean value, the Student's t-test and t-distributions for parametric variables were used. Wilcoxon's signed-rank test was used to compare the distribution of non-parametric variables. Spearman's rank correlation test was used to test the strength of statistical dependence of the variables.

RESULTS

The study sample consisted of 161 patients, but only 148 were eligible for statistical analysis. The mean age of the patients was 49.7±25 years. Men represented 27% of the study population. In sixty-seven patients (41.6%) the depressive episode studied was their first episode of depressive disorder. Some sociodemographic and clinical data are presented in Table 1.

A total of 102 patients (63.4%) received different concomitant medications at baseline. The most common psychiatric co-medication included alprazolam (16.1%), bromazepam (8.1%), and zolpidem (6.2%). Non-psychiatric concomitant therapy consisted of omeprazole (3.1%), enalapril (1.9%), and diclophenac (1.9%). At the end of the study, only 9.7% of patients were receiving different concomitant therapy.

After 8 weeks of treatment, the venlafaxine XR starting dose of 75 mg daily was increased to a statistically significantly higher mean daily dose of 172±71 mg ($p<.0001$).

The mean HAM-D₁₇ score at baseline was 23.7±6, and the mean CGI-S score was 4.8±0.8 (moderately ill). The venlafaxine XR treatment was followed by a statistically significant decrease of HAM-D₁₇ scores to 8.5±5.3 at week 8 ($p<.0001$). According to the patients' CGI-S and CGI-I scores ($p<.0001$), their condition was statistically significantly improving through the study.

After 8 weeks of treatment with venlafaxine XR, the response rate (defined as a reduction of the HAM-D₁₇ mean score by at least 50% from baseline) was 93% and the remission rate (defined as the percentage of patients with a HAM-D₁₇ score ≤7) was 45%.

At baseline, physicians rated 93 patients (62.85%) on CGI-S as seriously/severely ill. At the end-point, 78 patients (52.7%) were rated 2 or 1 on CGI-S (not

ill/mildly ill), and only 1.4% as seriously/severely ill; 81.1% of patients were rated by the physician as much/very much improved on CGI.

After 8 weeks of treatment with venlafaxine XR, there was an overall statistically significant improvement measured on the Depression and Somatic Symptom Scale (33.6±9.3 vs. 12.4±8.0) ($p<.0001$). The improvement was statistically significant also regarding individual items such as headache (1.1±0.9 vs. 0.45±0.6; $p<.0001$), back pain (1.25±0.9 vs. 0.5±0.7; $p<.0001$), chest pain (1.5±0.8 vs. 0.44±0.63; $p<.0001$), tenderness of more than a half of body muscles (1.13±0.8 vs. 0.35±0.6; $p<.0001$), and fatigue or loss of energy (2.24±0.76 vs. 0.93±0.76; $p<.0001$).

A total of 148 patients (91.2%) completed the study. The reasons for withdrawal were adverse events in 7 patients (4.7%), lack of efficacy in 3 patients (2%), non-compliance in 2 patients (1.4%), unsatisfactory efficacy in 1 patient (0.7%). The most frequent mild to moderate adverse effects included nausea (10%), dizziness (5.4%), anxiety (2.7%), and perspiration (1.4%).

After 8 weeks of treatment there were no significant changes in body mass ($p=.237$) or Body Mass Index ($p=.281$). During the study period there was a statistically significant decrease in systolic ($p<.0001$) and diastolic blood pressure ($p<.0001$); however, there was no decrease in heart rate ($p=.840$) (Table 3).

Table 2. Primary and secondary outcome measures (N=148)

| Measure (mean scores) | Baseline | Week 2 | Week 4 | Week 8 |
|-----------------------|----------|----------|--------|----------|
| HAM-D ₁₇ | 23.8±6 | 18.3±6.7 | 13.1±6 | 8.5±5.3 |
| CGI-S | 4.8±0.8 | 4.3±0.9 | 3.4±1 | 2.5±1.1 |
| CGI-I | | 2.6±0.9 | 2.2±1 | 1.6±1 |
| DSSS | 33.6±9 | 26.5±9.9 | 19±9.3 | 12.4±8.0 |

Follow-up visits: Student pair test; $p<.0001$ at weeks 2, 4 and 8 on all measures.

Table 3. Cardiovascular parameters and weight. (SBP – systolic blood pressure; DBP – diastolic blood pressure; HRT – heart rate)

| Visit | SBP (mmHg) | p-value | DBP (mmHg) | p-value | HRT (b.p.m) | p-value | Weight (kg) | p-value |
|----------|------------|-----------|------------|-----------|-------------|----------|-------------|----------|
| Baseline | 130.2±14.7 | | 81.9±9.2 | | 75.4±9.2 | | 73.7±14.8 | |
| Week 8 | 126±11 | $p<.0001$ | 79±8.2 | $p<.0001$ | 75.7±8.8 | $p=.840$ | 73.6±13.5 | $p=.237$ |

DISCUSSION

This was the first study in Slovenia to examine the efficacy and safety of venlafaxine XR in patients with major depressive disorder. After 8 weeks of treatment, the response rate on HAM-D₁₇ for venlafaxine XR was 93%, and remission rate was 45%. Mehtonen and co-authors defined remission as a score of <10 on the HAM-D₂₁. They reported remission rates of 68% for venlafaxine and 45% for sertraline, and response rates of 83% and 68%, respectively (Mehtonen et al. 2000). The venlafaxine daily dose in their study was 75-150 mg; this is comparable to the average daily dose of venlafaxine in our study (172±71 mg). In another double blind comparison of venlafaxine XR and

sertraline in major depressive disorder, the response rate for venlafaxine was 65% and for sertraline 55%, and the remission rates were 49% and 38%, respectively (Shelton et al, 2006). Einarson et al. reported a response rate of 74% for venlafaxine XR and 61% for SSRIs (Einarson et al. 1999). In a pooled meta-analysis of 8 clinical trials by Thase et al. comparing venlafaxine XR to SSRIs (fluoxetine, fluvoxamine, paroxetine), the remission rate was significantly higher for venlafaxine XR (45% vs. 35%) (Thase 2003). The rate of remission is a more clinically relevant end-point than the rate of response, because responders may still have residual symptoms (Smith et al. 2001). After 8 weeks of treatment, 52.7% of patients in our study were physician-rated as “not ill/mildly ill” on CGI-S and

81.1% of patients as “much/very much improved” on CGI-I. In another study the response rates on both scales were comparable (Lopez Ibor et al. 2008).

A significant improvement of painful physical symptoms assessed by the Depression and Somatic Symptom Scale was also observed at the end-point. This is important, because pain appears to be a barrier to achieving the goals of remission and recovery for patients with depression (Geerlings et al. 2002). Antidepressants that inhibit both serotonin and norepinephrine reuptake (like venlafaxine and duloxetine) effectively remit mood disorders, and provide relief from painful physical symptoms often associated with these disorders (Wise et al. 2007, Jann & Slade 2007). Venlafaxine XR reduced pain also in elderly patients with depression (Lopez Ibor et al. 2008). Regional origin may also contribute to the magnitude of pain reduction in patients with depressive symptoms under treatment with venlafaxine; Central European patients were found to profit more from treatment with venlafaxine in terms of severity of depression and pain intensity than patients from Eastern and Southern Europe (Begré et al. 2009).

Venlafaxine XR appeared to be a safe antidepressant. In the meta-analysis of 34 randomised, double-blind studies the overall discontinuation rates for any reason were 28% for the pooled venlafaxine and 27% for the pooled SSRI therapy groups, compared with 8.1% overall discontinuation rate in our study (Nemeroff et al. 2008). Discontinuation rate due to adverse events was 4.7% and is comparable with other studies (Bielski et al. 2004, Rudolph et al. 1999, Nemeroff et al. 2008). Management of side effects of antidepressants is a part of routine clinical practice (Uzun et al. 2009). Nausea, vertigo and headache were the most common adverse events in our study. Their frequency is concordant with the basic information about the drug and other clinical trials (Nemeroff et al. 2008, Mehtonen et al. 2000, Smith et al. 2002). Over the entire duration of the study, all reported side effects were of mild to moderate severity. In our study, systolic and diastolic blood pressure significantly decreased at the end of the study, while other studies reported no effect of venlafaxine XR on these cardiovascular parameters, including an increase in blood pressure (Mehtonen et al. 2000, Sheehan et al. 2009).

This study has some limitations, the most obvious being an open-label design of the study and a mixture of in- and out-patients.

CONCLUSION

In conclusion, the data from this study indicate that venlafaxine XR is an efficient and safe therapeutic option for patients with major depressive disorder, with the additional effect of reducing associated painful physical symptoms.

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