

PERCENT OF REMISSION IN GREEK MAJOR DEPRESSIVE DISORDER PATIENTS TREATED WITH VENLAFAXINE.

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Most clinical trials in major depression report efficacy based on patient response, defined as 50% reduction from a baseline score on a depression rating scale. However, patients with no full remission are prone to relapses.

The objective of this analysis report was to evaluate the percent of remission in Greek major depressive patients treated with venlafaxine. A score of equal or less than 7 in Hamilton Depression Rating Scale (HAM-D) was defined as remission.

Two studies with treatment duration of 6-weeks, the first an open label and the second a double blind, randomized, comparative with fluoxetine, were included in the analysis. In both studies, hospitalized and ambulatory patients with major depression and melancholia were enrolled. Diagnosis was based on the DSM IV criteria and only patients with MADRS baseline score $\geq 20-25$ were enrolled.

In the open label study of venlafaxine, initial daily dose ranged from 75 mg to 150 mg and then it was further titrated according to the needs of each patient. In the double-blind comparative study, 75 mg venlafaxine were given to patients at days 1 - 4, 150 mg at days 5 - 10 and 225 mg at days 11 - 42.

The final analysis was based on 145 patients from both studies. At final evaluation, 80 (55%) patients were remitted, i.e. final HAM-D score ≤ 7 . The mean initial and final HAM-D total scores for the 80 remitted patients were 28.8 ± 6.13 (Median = 29) and 3.3 ± 2.3 (Median = 3). Eight patients were remitted from the second week of the trial (venlafaxine dose ranged from 75 - 225 mg). In all 145 patients, the HAM-D score dropped from 27.7 ± 6.22 to 7.5 ± 6.45 (after six weeks).

These results prove the efficacy of venlafaxine in achieving remission in major depression and melancholia.

Key words : venlafaxine , major depressive disorder , remission

BACKGROUND

Major depressive disorder (MDD) is one of the most common conditions seen in clinical practice today. It is a chronic and recurrent disorder with a higher propensity of suffering in women over men at a ratio of 2:1¹. The lifetime prevalence of MDD is 17% in the United States population, which reaches 19% in urban settings in general practice².

The "response" to pharmacological therapy in MDD patients, is most often defined as a 50% reduction from a baseline score on a depression rating scale like the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS)³. However, this treatment goal appears to be rather insufficient. Subthreshold depressive symptoms that remain after therapy are still associated with dysfunction and increase the risk of relapse^{4,5}. Furthermore partial remission in MDD is associated with the potential for the development of treatment resistance or chronic depression.

A major goal in the MDD treatment should be therefore to achieve remission, potentially reducing the likelihood of relapse or recurrence and restoring normal psychosocial and occupational functioning. Compared with the definition of response, more stringent criteria should be used to determine full remission of the disorder, defined as a clinical state characterized by minimal residual symptoms. Presently a HAM-D score of 7 has been chosen as a more appropriate criterion for complete remission^{3,4} and will be used

throughout this study as a measure of the efficacy of venlafaxine in MDD patients.

Venlafaxine, an SNRI type antidepressant that inhibits the re-uptake of serotonin, noradrenaline, and to a lesser extent, dopamine, produces a rapid onset of noradrenergic subsensitivity (b-adrenergic receptor desensitization) and does not bind to muscarinic cholinergic, histaminergic, or alpha-1 adrenergic receptors and thus, it does not cause the side effects commonly associated with tricyclic antidepressants⁷.

Venlafaxine has been studied in a broad range of patients including the elderly, those with refractory depression or melancholia and those with comorbid depression and anxiety. The results showed an 82% response to therapy based on a 50% reduction of baseline scores in HAM-D and MADRS with a rapid onset of action even in severely depressed patients⁸⁻¹³. However, full remission remains the ultimate goal in antidepressant therapy. Venlafaxine has a good record of achieving full remission¹⁴.

Objective of this study was to evaluate remission rates in Greek MDD patients treated with venlafaxine.

METHODS

A -analysis of two six-week studies⁸⁻¹⁵ has been performed in order to evaluate the percent of remitted patients with MDD and melancholia in Greek patients. The first study¹⁵ was a randomized, double-blind, comparative to fluoxetine and 55 patients (41 females) were assigned to the venlafaxine arm (total number enrolled in the study, 110 patients). Some sites of this study were developed in Italy and the patients from

these sites were not included in the analysis (n = 36). The second study⁸, was an open-label, efficacy/safety study that enrolled 126 patients (26 hospitalized, 95 females). In total 145 patients (111 females) were included in the analysis. In both studies, the study protocol was approved by the ethics committees of each participating hospital. A written informed consent was signed by all patients before enrollment.

In both studies, patients were included with respect to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria for major depressive disorder and their MADRS baseline scores ranged between 20–24 (mild/moderate disease) to 25 and over (severe depression). Hospitalized patients (n=45), patients refractory to other treatments, or day care patients were enrolled. Overall, the dosing scheme ranged from 75 mg to 225 mg. In the open label study, initial daily dose ranged from 75 mg to 150 mg and then it was further titrated according to the needs of the patient. In the double-blind comparative study, 75 mg venlafaxine were given to patients at days 1–4, 150 mg at days 5–10 and 225 mg at days 11–42.

Patients were excluded from both of these studies if they had a history of hypersensitivity to venlafaxine or did not respond to a previous treatment with this drug. Also, patients were not included if they had used any investigational drug or fluoxetine within 30 days, any monoaminoxidase inhibitor within 15 days, or any other antidepressant drugs within 7 days before baseline. Ineligible were the patients with increased suicidal ideation. Finally, patients with a history of any psychotic disorder not associated with depression, an antisocial personality or any other serious personality disorder, bipolar depression, a history of drug or alcohol abuse within 2 years of baseline were also excluded. In both studies, MADRS, HAM-D (21-item and 24-item

HAM-D scales were used in the double-blind and open label study, respectively) and Clinical Global Impression (CGI) scales were used as the primary efficacy variables. Efficacy measurements were done at baseline and after 1, 2, 4 and 6 weeks of therapy. An intention-to-treat analysis was performed.

RESULTS

The total mean baseline MADRS and HAM-D scores were 31.5 ± 7.3 (median 31) and 27.7 ± 6.22 (median 29), respectively. These scores dropped to mean 8.3 ± 7.0 and mean 7.5 ± 6.45 total scores for MADRS and HAM-D, accordingly, after 6 weeks of therapy (Table 1).

From the 145 patients included in this analysis, 80 patients reached remission (55%). Their initial mean HAM-D total score was 28.8 ± 6.1 (median 29) and their final mean HAM-D total score 3.3 ± 2.3 (median 3) (Table 2). The dosing scheme for those patients who reached remission was the same as the rest of the patients; flexible and ranged from 75 mg to 375 mg.

Eight patients attained full remission by day 14. These patients were receiving 75–100 mg initial daily dose and only one of them was taking 225 mg daily. Twenty-two of those 80 remitted patients (20.67% of the 145 patients), reached $HAMD \leq 7$ by week 4 (Figure 1).

The percent reduction in HAM-D and MADRS scores by week of trial compared to baseline is presented in Table 1. It is evident that even from the first week of treatment there is significant change (days 1 to 7, 9.7% reduction in HAM-D and 10.8% in MADRS) which increases from week to week, reaching 72.9% and 73.6% for HAM-D and MADRS scales correspondingly.

Table 1. Mean Scores of HAM-D and MADRS Scales (N = 145)

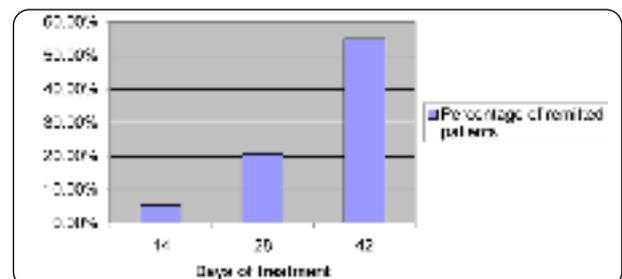
Time	HAM-D Score			MADRS Score		
	Mean Value (±SD)	Median	% change from baseline	Mean Value (±SD)	Median	% change from baseline
Baseline	27.7 ± 6.22	29	-	31.5 ± 7.3	31	-
Week 1	25.0 ± 7.48	25	9.7	28.1 ± 7.8	26	10.8
Week 2	18.8 ± 7.4	19	32.1	20.9 ± 8.4	20	33.6
Week 4	11.9 ± 6.48	12	57	13.9 ± 7.5	14	55.8
Week 6	7.5 ± 6.45	6	72.9	8.3 ± 7.0	7	73.6

Table 2. Summary of initial and final HAM-D scores for remitted and non-remitted patients

	HAM-Di	HAM-Df
Total Patients (N = 145) ¹	27.7 ± 6.22	7.5 ± 6.45
Remitted Patients (N = 80)	28.8 ± 6.13	3.3 ± 2.3

¹Includes the remitted patients

Figure 1. Percentage of remitted patients vs. Days of treatment



Average reduction of HAM-D and MADRS total scores over 50% (response) occurred. It is important to note that the percent change of HAM-D scores matches the percent change of MADRS scores, which indicate the validity of our results.

DISCUSSION

The total baseline scores for both scales HAM-D and MADRS were high in both analyzed studies (*Table 1*) indicating that overall, patients with more severe MDD psychological and somatic symptoms have been included in the study. By the end of the treatment period (6 weeks) 55% of these patients attained full remission by the current standard of a HAM-D total score ≤ 7 . Our results are encouraging if we consider that severely symptomatic patients require more time and increased therapeutic dosage to exhibit significant improvement in their condition.

In a similar study comparing venlafaxine with paroxetine in mostly ambulatory patients, the remission rates were 42% and 20%, respectively¹⁸. Dierick et al¹⁹ also reported a 52% sustained response, in outpatients with major depression treated with venlafaxine, compared with 42% achieved with fluoxetine treated patients.

From the above it is suggested that the rate of complete remission is high in the venlafaxine treated patients and very close to the 50% of the population treated. The remission rate in our combined analysis was 55% and in the same range as in the other similar analyses.

In some other studies the cut-off point for remission is set to a total score of 10. In our study, as is most often used, the HAM-D scale total score of ≤ 7 was applied. This more stringent criterion perhaps carries higher credibility in the remission evaluation.

Regarding full remission rates with other antidepressants, in general, a percentage of 25% to 35% is reported²⁰. This is lower than that seen with venlafaxine. As an explanation to that its dual mechanism of neurotransmitter interaction and its good tolerance that allows rapid titration, could be hypothesized.

In a meta-analysis of 8 comparable double-blind, active-controlled, randomized clinical trials the remission rates with venlafaxine, after 8 weeks therapy, ranged from 40%-55%¹⁴. In this study, the comparator active therapy group with SSRIs, achieved 31%-37% remission rates, a difference which was statistically significant at the $p < 0.05$ level. No differences in remission rates regarding age or gender were detected in this study. Similarly in our study the remission rates were absolutely similar between female and male patients (exactly 55% remission rate) and the remission rates were similar in all age groups between 30 to 70 years old (55%-62.9%). For younger or older patients, the number of patients was small to reach a valid conclusion.

In another comparative with fluoxetine and placebo, multicenter, randomized, double-blind study, in depressed outpatients, the percentage of patients with total score of ≤ 7 , on HAM-D21, after 8 weeks therapy was 37% for the venlafaxine XR group (dose range 75-225 mg/day) compared

with 22% for the fluoxetine (dose range 20-60 mg/day) and 18% for the placebo groups¹⁶. The lower remission rates, compared with our study, could be due to methodological differences with a slower dose titration, lower initial dose in some cases and an ambulatory patient population. In the Greek patients dose titration started as early as the 5th day and in severely depressed patients the initial dose was 150 mg/day. Perhaps this may be an explanation for our higher remission rates. In a study by Costa e Silva¹⁷ major depressive patients on venlafaxine who increased rapidly their dose achieved a remission rate of 54%, identical to our results. In conclusion, it was observed that in moderate-to-severe depressed patients, venlafaxine is effective in achieving remission even though patients with more severe, chronic, or complicated depressions are at highest risks for doing poorly. Its fast onset of action, the potency to relieve psychological symptoms of depression and most importantly, its ability to achieve remission, underlines the effectiveness of venlafaxine in treating major depression and melancholia.

COMPETING INTERESTS

The authors are employees of Wyeth.

AUTHORS' CONTRIBUTIONS

G.S: Conducted the analysis and helped with the manuscript

N.Z.: Designed the study and prepared the manuscript

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