ORIGINAL ARTICLE

Safety and Efficacy of Duloxetine Versus Venlafaxine in Major Depression in Indian Patients

Dinesh K. Badyal, Prem P. Khosla, Rajinder S. Deswal,* Prithpal S. Matreja

Abstract

The objective of the study was to compare the efficacy and safety of duloxetine and venlafaxine in major depressive disorder. The study was conducted in 26 patients suffering from major depressive disorder as per DSM-IV criteria. Patients were randomized to two groups and were given duloxetine (20,40,60mg BD) and venlafaxine (75,150,225mg OD) for 6 weeks. The primary efficacy parameter was the Hamilton Depression Rating Scale (HDRS-17). Secondary efficacy parameters included the Montgomery and Asberg depression rating scale (MADRS) and clinical global impression (CGI) scale. Safety evaluation was based on treatment emergent adverse effects and laboratory investigations. There was significant decrease in HDRS, MADRS, CGI scores from baseline to endpoint ($p<0.05$) in both the groups. However the difference in scores between two groups was not statistically significant. Total mean HDRS score decreased from 27(SD=2.5) to 4 (SD=1.2) in duloxetine group and from 29(SD=2.3) to 4 (SD=1.0) in venlafaxine group at the end of therapy. Response and remission rate was 96% and 69% in duloxetine group as compared to 92% and 62% in venlafaxine group respectively. There was no significant difference in adverse effects and laboratory investigation in two groups. The findings of this study indicate that duloxetine may be an effective and safe antidepressant in Indian patients of major depressive disorder. It is equally effective to venlafaxine in patients of depression.

Key Words

Duloxetine, Venlafaxine, Depression

Introduction

Major depressive disorder (MDD) continues to be a considerable problem, both for clinician and the public health level. It is currently the fourth leading cause of disease and disability worldwide and is projected to rise to second in 2020. Unfortunately many current therapies for depression provide remission in only approximately one third of patients (1).

The current modalities of treatment of depression include tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRI). TCA acts by inhibition of neuronal transport (reuptake) of norepinephrine (NE) and variable blockade of serotonin (5-HT) transport. TCAs are not preferred these days because of their adverse effect profile i.e. anticholinergic effects, cardiac arrhythmias and seizure precipitation. MAOIs are used in refractory cases because of their interactions with foods. SSRIs are presently the most widely used antidepressants because of their better safety profile and tolerability. SSRIs selectively block neuronal transport of serotonin and increase synaptic availability of serotonin (2).

It has been suggested that dual inhibition of monoamine reuptake process may offer advantage over other

From the Department of Pharmacology and *Psychiatry, Christian Medical College and Hospital, Ludhiana 141008 India.
Correspondence to : Dr Dinesh K. Badyal, M.D., Reader, Department of Pharmacology, Christian Medical College, Ludhiana-141008 INDIA

antidepressants currently in use. Duloxetine has joined venlafaxine on the antidepressant market as a second serotonin-norepinephrine reuptake inhibitor. Duloxetine is a balanced selective serotonin and norepinephrine-reuptake inhibitor approved for the treatment of MDD and diabetic peripheral neuropathic pain (3). Duloxetine binds selectively with high affinity to both NE and 5-HT transporter and lacks affinity for monoamine receptors within the central nervous system (4). Duloxetine is more potent serotonin reuptake inhibitors as compared to fluoxetine. In behavioral experiments, duloxetine attenuates immobility in forced swim tests in animal models of depression to a greater extent than several other commonly used antidepressants (5).

Thus, duloxetine is expected to have the potential superior efficacy of dual reuptake inhibitor without compromising safety and tolerability and would represent a valuable additional treatment option for clinicians (6). Hence, the present study was designed to compare short term efficacy and safety of duloxetine and venlafaxine in the treatment of major depression in Indian patients.

Material and Methods

This prospective, open, comparative, randomized study was conducted in patients visiting the Department of Psychiatry, Christian Medical College and Hospital, Ludhiana. The study was approved by Institutional Ethics Committee. A total of 26 patients suffering from MDD as per DSM-IV criteria were enrolled in the study after they signed an informed written consent (7).

Patients of both sexes between the ages of 18-75 years with Hamilton depression rating scale (HDRS-17 items) score >18 were included in the study (8). Newly diagnosed patients, non-responders or partial responders to the earlier prescribed antidepressants and patients not tolerating earlier prescribed antidepressants were included in the study. Patients were screened at the beginning of the study. A detailed medical and psychiatry history was obtained. Mental status and physical examination was carried out. Patients with suicidal tendencies, schizoaffective disorder or bipolar disorder, seizure disorder, alcohol or substance abuse, concurrent major illness or systemic dysfunction involving hepatic and renal system were excluded. Patients currently receiving cimetidine, warfarin, tryptophan or MAO inhibitors, history of allergy to duloxetine and venlafaxine, pregnant women, lactating mothers and patients not using contraceptives or desiring to have children were excluded. Patients who qualified inclusion and exclusion criteria were enrolled in the study.

Patients were divided into two groups using randomization as per random number table. Patients randomized to each group were started on either duloxetine 20mg BD or venlafaxine 75mg OD. If the patient did not achieve response (50% reduction in HDRS score) after the completion of 2 weeks, dose was increased to 40mg BD for duloxetine or 150mg OD for venlafaxine. On completion of 4 weeks if the patient did not achieve the response (50% reduction in HDRS score), the dose was further increased to 60mg BD for duloxetine or 225mg OD for venlafaxine. At the end of 6 weeks if the patient did not respond (50% reduction in HDRS-17 score) then the patient was labeled as non-responder. The follow up visits were at week 1, 2, 3, 4, 5 and 6. At each visit efficacy and safety was evaluated and drug was supplied. Compliance was checked by pill count method at each follow up visit. Drug was given after a placebo washout period of one week to non-responders or partial responders and patients not tolerating earlier prescribed antidepressants.

Primary outcome measure in the evaluation of efficacy was change in the total score of HDRS during the study period. Response to drugs was defined as decrease in HDRS score >50% from as compared to baseline. Remission was defined as HDRS score (7). Secondary outcome measures included changes in the score of Montgomery and Asberg depression rating scale (MADRS) and clinical global impression-improvement (CGI-I) and severity (CGI-S) scale (9,10). Safety evaluation was based on spontaneously reported adverse effects, laboratory investigations and ECG examination at baseline and at the end of study i.e. 6 weeks.

Data collected was represented as mean±S.D. The primary statistical analysis was intention to treat (ITT) analysis for all safety or efficacy variables with last observation being carried forward (LOCF) for those patients who had atleast two weeks of data. The sum of ranks for all questions in HDRS and MADRS at respective visits was subjected to Wilcoxon Sign Rank test. The data was subjected to Repeated Measures Analysis of Variance (RMANOVA) with baseline as

covariate followed by Bonferroni post hoc test for week-by-week comparison between treatment groups. CGI-I and CGI-S scores were subjected to Chi-Square test. The significance between the numbers of responders and non-responders, remission and non-remission cases was subjected to Chi-Square test. Laboratory Investigations data was first checked for its Normality. The data was then subjected to parametric test (paired *t*-test) if data was found to be normal else it was subjected to non-parametric (Wilcoxon Sign Rank) test. All the Statistical tests performed were two tailed and p-value < 0.05 was considered to be statistically significant.

Results

A total of 26 patients were randomized to receive either duloxetine or venlafaxine in the study. The patients in both the groups had comparable demographic profile as shown in table 1. The mean age in duloxetine group and in venlafaxine group was 41 and 43 years respectively. The male/female ratio in duloxetine and venlafaxine group was 9/4 and 8/5 respectively.

The mean HDRS score at baseline was 26.73 and 28.7 in duloxetine and venlafaxine group respectively. The HDRS scores decreased significantly in both the groups at 2,3,4,5 and 6 weeks as compared to baseline ($p<0.05$), but there was no statistically significant difference between the groups at any visit (Fig. 1). There was more improvement in anxiety and somatic symptoms in duloxetine group as compared to venlafaxine in HDRS subset scores. The MADRS total scores also significantly decreased following treatment in both the groups at 2,3,4,5 and 6 weeks as compared to baseline ($p<0.05$) (Fig. 1). The reduction in score from baseline to last three visits (week 4,5,6) was more in venlafaxine group as compared to duloxetine group, but this was not statistically significant. CGI-I and CGI-S showed a statistically significant improvement ($p<0.05$) in both the treatment groups (Fig. 2). However, there was no statistically significant difference between treatment groups. The percentage of responders and remitters at the 2nd, 4th and 6th week has been depicted in figure 3. Response rate after 6 weeks of treatment was 96% in duloxetine group as compared to 89% in venlafaxine group. In duloxetine group the remission rate was 69% as compared to 62% in venlafaxine group. Number of responders was more in duloxetine group as compared to venlafaxine at 2, 4 and 6 weeks, but this was not statistically significant. Number of remitters was also more

Table 1 : Demographic profile of patients

	Duloxetine	Venlafaxine
Total number of patients	13	13
Male	9	8
Female	4	5
Age(years) (Mean±SD)	41±10	43±10
Duration of illness (Median Months)	19	14
Newly Diagnosed	12	12
Not tolerated Prescribed Antidepressants	0	0
Partial or non Responder for Prescribed Antidepressants	1	1
Severity of Depression (HDRS Score) (Mean ±SD)	26.73±2.5	28.7±2.25

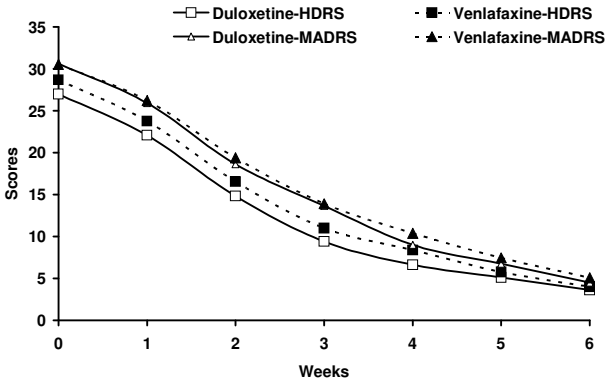

Fig. 1. HDRS and MADRS scores in duloxetine and venlafaxine group.

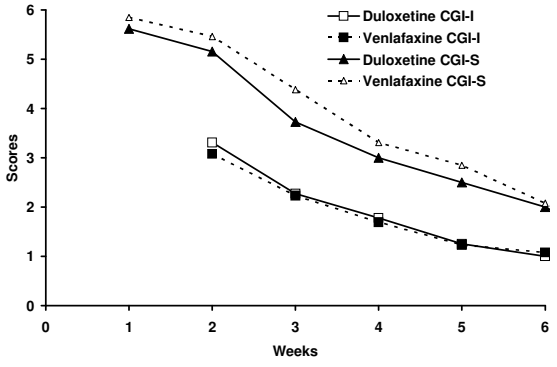

Fig. 2. CGI-S and CGI-I scores in duloxetine and venlafaxine group.

at the end of treatment in duloxetine group as compared to venlafaxine, but this was not statistically significant (Fig. 3).

The number of adverse drug events reported by the patients is tabulated in table 2. No serious adverse reaction was reported by any patient from both groups. The incidence of adverse effects was slightly more in duloxetine group. Mild nausea was reported in 4 (31%) patients in duloxetine group and 2 (15%) patients in venlafaxine group. Dyspepsia was reported in 3 patients in duloxetine group only. The laboratory investigation like hematology, biochemistry and ECG did not show significant change at the end of treatment as compared to baseline in both the groups as shown in table 3.

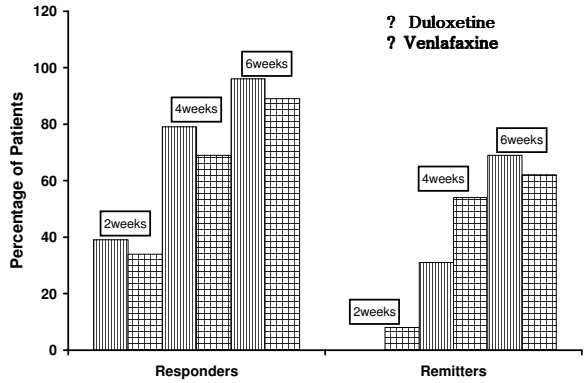

Fig. 3. Percentage of responders and remitters in duloxetine and venlafaxine group.

Table 2 : Adverse drug reactions

Adverse drug reactions	Duloxetine	Venlafaxine
Total number of patients	13	13
Patients having atleast one adverse reaction	6	4
Nausea	4	2
Vomiting	4	0
Dyspepsia	3	0
Restlessness	3	0
Headache	2	2
Dizziness	0	1

Table 3 : Laboratory investigations at baseline and end of treatment in both groups

Investigations	Duloxetine (n=13)		Venlafaxine (n=13)	
	Baseline	End of treatment	Baseline	End of treatment
QTc interval (msec)	397.5±27.26	392.5±18.32	397.10±22.90	408.50±17.25
Hemoglobin (gm/dl)	13.83±1.62	13.48±1.59	13.41±1.75	13.35±1.76
RBC count (cells/mm^3)	4.72±0.35	4.80±0.41	4.67±0.58	4.56±0.37
WBC count (cells/mm^3)	7755±1676	7813±1670	9508±2814	9469±2389
SGOT (IU)	31.36±10.58	27.75±6.73	23.92±7.35	24.08±7.12
SGPT (IU)	34.55±19.89	30.50±17.94	27.62±19.81	27.69±18.03
Alkaline phosphatase (IU)	91.36±22.80	88.38±19.44	118.90±27.03	119.00±22.59
Total bilirubin (mg/dl)	0.53±0.26	0.63±0.24	0.82±0.16	0.90±0.13
Serum creatinine (mg/dl)	0.82±0.23	0.89±0.22	0.89±0.13	0.92±0.13
Blood urea (mg/dl)	24.82±6.60	26.88±4.16	28.23±5.42	30.77±6.19
Serum cholesterol (mg/dl)	180.70±34.78	178.10±34.15	148.6±37.10	147.2±40.91

Values represent mean±SD; *p<0.05 as compared to baseline

Discussion

Although there are a number of therapeutic choices available for the treatment of major depression, it is generally acknowledged that current first line therapies provide less than satisfactory outcome in many instances. This is because nearly two-third of all patient are either partially or completely non responsive, only one-third experience full remission and many have tolerability concern that limit long term treatment (11). Thus the development of new agents that can meaningfully expand the expected therapeutic effect and tolerability of antidepressant therapy option is an important medical need.

In the present study, duloxetine was very effective in improving HDRS score in patients of major depression. Duloxetine also significantly improved MADRS and CGI scores in these patients. These results are in agreement with earlier studies which demonstrated a statistically significant improvement in the total score on the HDRS-17 and nearly all secondary efficacy measures including MADRS and CGI (9,12,13). The effect of duloxetine was equivalent to venlafaxine. The HDRS-17 subset scores indicate that the duloxetine was more effective in improving anxiety and somatic symptoms as compared to venlafaxine. These findings are in agreement with earlier studies (13).

The most common adverse effects reported were nausea, vomiting, headache, dyspepsia, restlessness and dizziness. Dyspepsia was reported in 3 patients in duloxetine group only. Dyspepsia is not a commonly reported adverse reaction with duloxetine (14). The reason for dyspepsia may be increased 5-HT levels with duloxetine. Perhaps the most important finding regarding safety was that there was no significant effect of duloxetine on QTc interval indicating no clinically significant difference on cardiovascular parameters. There was no alteration in other laboratory parameters.

Notwithstanding the limitations of the study i.e. small sample size and open design, the patients enrolled are reflective of typical patients and treatment settings adds to the generalizations of the results.

Conclusion

In summary, the findings of this study indicate that that duloxetine, a dual reuptake inhibitor may be an effective and safe antidepressant in Indian patients of major depressive disorder. It is equally effective to venlafaxine in these patients. Both drugs were well tolerated. Controlled comparative studies with good number of patients would be more beneficial in this field.

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