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Efficacy and Safety of Milnacipran Versus Venlafaxinein Major Depression in Indian Patients

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ABSTRACT

The objective of the study was to compare the efficacy and safety ofmilnacipran and Venlafaxine in major depressive disorder. The study was conducted in 120 patients suffering from major depressive disorder as per DSM-IV criteria. Patients were randomized to two groups and were given milnacipran (25, 50mg BD) and venlafaxine(75, 150mg OD) for 8 weeks. The primary efficacy parameter was the Hamilton Depression Rating Scale (HDRS-17) and Montgomery and Asberg depression rating scale (MADRS). Secondary efficacy parameters included proportion of patient responds to the treatment, proportion of patient remission to the treatment andchanges in the score of clinical global impression (CGI) scale. Safety evaluation was based on treatment emergent adverse effects. There was significant decrease in HDRS, MADRS, CGI scores from baseline to end of treatment($p<0.05$) in both the groups. However the difference in scores between two groups was not statistically significant. Total mean HDRS score decreased from 30.54 (SD=5.93) to 11.96 (SD=5.18) in milnacipran group and from 32.54 (SD=8.19) to 11.58 (SD=5.99) in venlafaxine group at the end of treatment. Total mean MADRS score decreased from 37.56 (SD=6.66) to 15.41 (SD=5.78) in milnacipran group and from 38.98(SD=9.42) to 14.77 (SD=6.57) in venlafaxine group at the end of treatment. Responder and remission rate was 72.22% and 31.48% in milnacipran group as compared to 75.00% and 30.77% in venlafaxine group respectively. There was no significant difference in adverse effectsbetween two groups. The findings of this study indicate that milnacipran 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: Milnacipran, Venlafaxine, Depression

INTRODUCTION

Depression is considered as an affective disorder characterized by change in mood, lack of interest in the surroundings, psychomotor retardation and melancholia. [1] Depression is the most common illness affecting many different aspects of mankind. [2] 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 [3].

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 usedin 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 [4]. To date, the efficacy of the drugs for depression is very limited so the need for newer, better-tolerated and more efficacious treatments is remaining high. [1]It has been suggested that dual inhibition of monoamine reuptake process may offer advantage over other antidepressants currently in use. These are serotonin and norepinephrine reuptake inhibitors (SNRIs). Milnacipran is a combined NA/5-HT reuptake inhibitor that has no direct action on alpha-1, alpha- 2, beta-adrenergic, muscarinergic or histaminergic postsynaptic receptors [5]Venlafaxine inhibits reuptake of both 5-HT and NE and towards lower extent dopamine.[6]

No adequate information about efficacy and safety of milnacipran in Indian population is available as well as comparison with venlafaxine is also not available. Hence, the present study was designed to compare efficacy and safety of milnacipranand venlafaxine in the treatment of major depression in Indian patients.

MATERIALS AND METHODS

This prospective, open, comparative, randomized studywas conducted at four centersinAhmedabad. The study was approved by Independent EthicsCommittee. A total of 120 patients suffering from MDDas per DSM-IV criteria were enrolled in the study afterthey signed an informed written consent [7].Newly diagnosed patients of both sexes between the ages of ≥18 yearswith Hamilton depression rating scale (HDRS-17 items)score ≥ 17and Montgomery &Asberg Depression Rating Scale (MADRS) ≥ 25 were included in the study [8,9]. Patients with significant suicide risk,having history of psychotic disorder, history of allergy to milnacipran and/or venlafaxine, currently receiving any other anti depression medication, pregnant women, lactating motherswere excluded. Patients who qualified inclusion and exclusion criteria were enrolled in the study.

Patients were divided into two groups using randomization for 8 week study. Patients randomized to each group were started on either milnacipran25 mg to 50 mg twice daily or venlafaxine75 mg to 150 mg once daily. At the end of 8 weeks if the patient did not respond (50% reduction in HDRS-17 score) from baseline then the patient was labeled as non-responder. The follow up visits were at week 2, 4, 6 and 8. At each visit efficacy and safety was evaluated. Primary outcome measure in the evaluation of efficacy was change in the total score of HDRSand MADRS 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 proportion of patient responds to the treatment, proportion of patient remission to the treatment andchanges in the score of clinical global impression (CGI)scale [10]. Safety evaluation was based on spontaneously reported adverse effects during study period.

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 to weekby-week comparison. CGI scores were subjected to Chi-Square test.The significance between the numbers of responders andnon-responders, remission and non-remission cases wassubjected to Chi-Square test. All the Statisticaltests performed were two tailed and p-value < 0.05 wasconsidered to be statistically significant.

RESULTS

A total of 120 patients (Milnacipran group: 60; Venlafaxine group: 60) were randomized to receive either milnacipran or venlafaxine in the study. Among them 106 patients (Milnacipran group: 54; Venlafaxine group: 52) completed study. The patients in both the groups had comparable demographic profile as shown in table 1. The mean age in milnacipran group and in venlafaxine group was 39 and 40 years respectively.

Table 1: Demographic profile of patients

	Milnacipran	Venlafaxine
Total number of patients	60	60
Male	31	32
Female	29	28
Age(years) (Mean±SD)	39 ± 10	40 ± 11
Severity of Depression (HDRS Score) (Mean ±SD)	30.54 ± 5.93	32.54 ± 8.19
Severity of Depression (MADRS Score) (Mean ±SD)	37.56 ± 6.66	38.98 ± 9.42

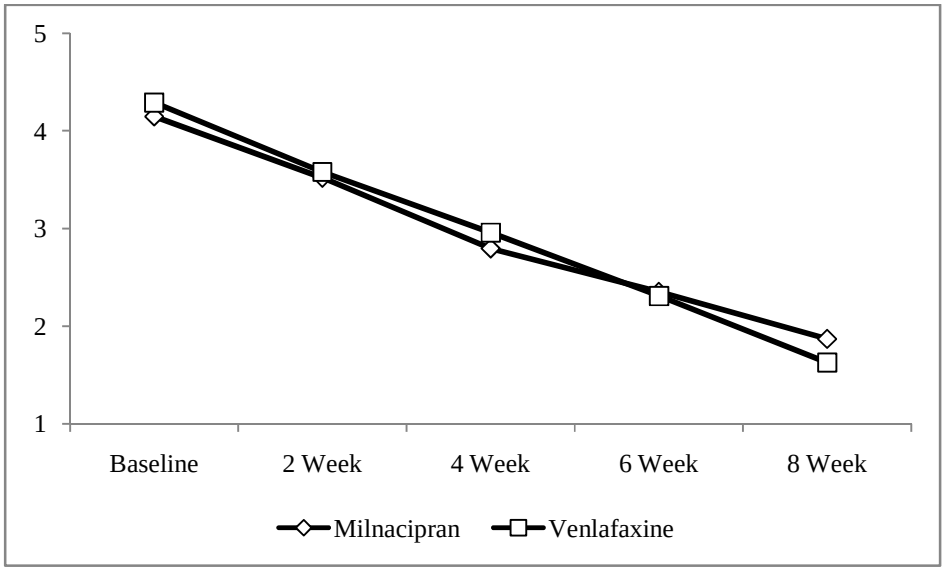
The mean HDRS score at baseline was 30.54 and 32.54 in milnacipran and venlafaxine group respectively. The HDRS scores decreased significantly in both the groups at 2,4, 6 and 8 weeks as compared to baseline ($p<0.05$), but there was no statistically significant difference between the groups (Table 2). The mean MADRS score at baseline was 37.56 and 38.98 in milnacipran and venlafaxine group respectively. The MADRS total scores also significantly decreased following treatment in both the groups at 2, 4, 6 and 8 weeks as compared to baseline ($p<0.05$), but there was no statistically significant difference between the groups (Table 2).

Table: 2 HDRS and MADRS scores in milnacipran and venlafaxinegroup

Name of Drug	Base Line (Mean ± SD)	2 Week Treatment (Mean ± SD)	4 Week Treatment (Mean ± SD)	6 Week Treatment (Mean ± SD)	8 Week Treatment (Mean ± SD)	Difference (Mean ± SD) Wk-0toWk-8
Hamilton depression rating scale (HDRS)						
Milnacipran(n=54)	30.54 ± 5.93	25.74 ± 5.23	20.15 ± 5.33	15.52 ± 5.24	11.96 ± 5.18	**-18.70±5.18***
Venlafaxine (n=52)	32.54 ± 8.19	26.98 ± 6.59	20.73 ± 6.43	15.33 ± 6.36	11.58 ± 5.99	**-20.96±9.12***
Montgomery &Asberg Depression Rating Scale (MADRS)						
Milnacipran(n=54)	37.56 ± 6.66	31.13 ± 5.97	24.91 ± 6.45	19.13 ± 6.08	15.41 ± 5.78	**-22.15±6.37***
Venlafaxine(n=52)	38.98 ± 9.42	32.50 ± 8.21	26.00 ± 7.07	19.60 ± 6.90	14.77 ± 6.57	**-24.21±10.1***

CGI showed a statistically significant improvement ($p<0.05$) in both the treatment groups (Fig. 1). However, there was no statistically significant difference between treatment groups.

Fig. 1. Clinical global impression scores in milnacipran and venlafaxine group



Response rate after 8 weeks of treatment was 72% inmilnacipran group as compared to 75% in venlafaxine group. In milnacipran group the remission rate was 31% as compared to 30.77% in venlafaxine group (Table 3).

Table 3: Percentage of responders and remitters in milnacipran and venlafaxine group

	Milnacipran	Venlafaxine
% of Responder	72.22	75.00
% of Remission	31.48	30.77

The number of adverse drug events reported by the patients is tabulated in table 4. No serious adverse reaction was reported by any patient from both groups. The incidence of adverse effects was slightly more in venlafaxine group. Constipation, dry mouth and headache were reported in milnacipran group while constipation, dry mouth and insomnia were reported in venlafaxine group. Both drugs are safe and well tolerable.

Table 4: Adverse Event

Adverse Event	Milnacipran	Venlafaxine
Constipation	4	4
Dry mouth	4	5
Headache	2	0
Insomnia	0	3

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, milnacipran was very effective in improving HDRS scorein patients of major depression. Milnacipran 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 and MADRS and nearly all secondary efficacy measures including CGI [12,13]. The effect of milnacipranwas equivalent to venlafaxine. The most common adverse effects reported were insomnia, constipation, dry mouth and headache.

CONCLUSION

In summary, the findings of this study indicate that that milnacipran, 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.

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