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EFFICACY OF DULOXETINE COMPARED WITH IMIPRAMINE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER IN INDIAN PATIENTS

ASHOK K DUBEY[1*], OM P RAICHANDANI[2] AND SHEETAL P PANDEY[3]

[1.] Department of Pharmacology, School of Medical Sciences and Research, Sharda University, Gr. Noida (U.P.), India
[2.] Department of Psychiatry, N.S.C.B. Govt. Medical College, Jabalpur (MP), India
[3.] Department of Pharmacology, N.S.C.B. Govt. Medical College, Jabalpur (MP), India

ABSTRACT

Background: Major Depressive Disorder (MDD) is a chronic illness with large contribution to disease burden worldwide. Duloxetine, a dual reuptake inhibitor of 5-HT and NE, is a second generation antidepressant, on which, to the best of our knowledge, there is no study in the Indian adult patients of MDD. There have been studies on duloxetine in MDD patients in other parts of the world, but there has not yet been a study comparing it with the old standard imipramine, a tricyclic acid antidepressant, still commonly used in the primary health care set up. Aims: In this study the efficacy of duloxetine in MDD was compared with that of imipramine. Settings and Design: Prospective observer blinded parallel group comparative study. Materials and Methods: Consenting adult patients (N=60) meeting DSM-IV criteria for MDD who completed six weeks of treatment with, either duloxetine (40 mg) or imipramine (150 mg), were compared for improvement with their base line disease severity, measured by scores on the Hamilton Depression (HAM-D) Rating Scale with 21 items and Clinical Global Impression (CGI) scale. The primary efficacy measure was mean change from baseline to endpoint on the HAM-D scale. Results: The total change in HAM-D score in imipramine group was -25.53 (±7.82) exhibiting an improvement of 67.54% and the total change in HAM-D score in duloxetine group was -20.27(±7.04) showing an improvement of 60.45%. Imipramine showed a slightly greater reduction of HAM-D scores as compared to duloxetine, which was statistically significant, but there was no statistically significant difference between the response rates (80% vs 73.3%) and remission rates (30% vs 26.7%) for imipramine and duloxetine, respectively, at six weeks. Conclusion: The efficacy of duloxetine and imipramine is comparable in MDD with no significant difference in response and remission rates at six weeks.

KEY WORDS: **Duloxetine, Imipramine, Major Depressive Disorder**

DR ASHOK KUMAR DUBEY
Assistant Professor, Department of Pharmacology, School of Medical Sciences and Research, Sharda University, Gr. Noida (U.P.), India

INTRODUCTION

Major depressive disorder (MDD) is a chronic and recurrent psychiatric illness responsible for high morbidity and mortality. The Global Burden of Disease Study 2000 by WHO found MDD to be the fourth leading cause of disease burden. It is responsible for nearly 12% of years lived with disability worldwide.[1] By the year 2030, it is expected to become the largest contributor to the disease burden in high income countries.[2] Pharmacotherapy along with psychotherapeutic approaches are effectively used to treat MDD patients. Antidepressant drugs are the first line option for the management of MDD. Among the drugs for treating MDD, second generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) dominate the current prescriptions. These new classes of antidepressants are equivalent in efficacy to the older classical tricyclic antidepressants (TCAs) and have better tolerability due to less action on other receptors which are responsible for the adverse effects of TCAs such as anticholinergic problems, orthostatic hypotension, sedation, and overdose toxicity. As per recommendations of the American College of Physicians, the selection of a second-generation antidepressant as pharmacotherapy to treat patients of MDD should be on the basis of adverse effect profiles, cost, and patient preferences.[3] A Meta analysis of 203 studies has shown that second-generation antidepressants do not substantially differ in efficacy or effectiveness for the treatment of major depressive disorder.[4]

Duloxetine, a relatively newer SNRI antidepressant, is one of the second-generation antidepressants, which has shown better adherence and persistence in the patients of MDD.[5] It is a very potent and balanced reuptake inhibitor of both serotonin and noradrenaline and also a weak inhibitor of dopamine reuptake.[6],[7] Comparative studies have found duloxetine to be superior to placebo and comparable to SSRIs in the treatment of MDD.[8]

Imipramine, a TCA and mainly a norepinephrine reuptake inhibitor, was introduced in 1958, and is still commonly prescribed to patients because of low cost and established efficacy, especially in the primary health care.[9] Despite the well established adverse effects of imipramine, its therapeutic potency has been found to be similar to, and sometimes even higher than, the newer antidepressants.[10],[11] Its indisputable efficacy as an antidepressant has also made it a commonly employed comparator drug in the trials of second generation antidepressants.[12]

To the best of our knowledge, there has, as yet, been no head-to-head comparative study between imipramine, the old standard, and duloxetine. Amount of data comparing duloxetine directly with other antidepressants is limited. Though meta regression analysis can predict the superiority of a particular drug over the other, the level of evidence provided by a direct comparison is higher than the level provided by indirect comparisons.[13] We also wanted to evaluate the efficacy of duloxetine in the Indian population because most of the studies related to its efficacy and tolerability have been conducted in western population and not much is known directly about its usage in Asian countries in the MDD patients. This study aimed to assess the efficacy of duloxetine in comparison with imipramine in the MDD patients.

MATERIAL AND METHODS

This was a prospective observer blinded parallel group comparative study conducted at the outpatient department of psychiatry at N.S.C.B. Govt. Medical College, Jabalpur (MP), India, over a period of one year. The study was carried on a total of 60 patients

diagnosed with MDD using the Diagnostic and Statistical Manual for Mental Disorders, fourth edition (DSM-IV) criteria and completing the six weeks of drug therapy. It was approved by the institutional ethics committee. During screening visit, each patient underwent detailed psychiatric, neurological and medical examination. After the initial screening the patients were required to give informed consent to be included in the study.

Medically stable patients of either sex above 18 years of age and willing to give informed consent were included in the study. Patients had to meet the diagnostic criteria for MDD as defined in DSM-IV. The base line disease severity was assessed by patients' scores on the Hamilton Depression Rating Scale with 21 items (HAM-D) and Clinical Global Impression (CGI) scale.

Patients were excluded for the following reasons: Any psychiatric condition other than MDD prior to entering the study; organic mental disorders; current diagnosis of substance abuse syndrome (except nicotine/caffeine); use of pharmacological agents within the last 2 weeks known to affect mood or produce somatic symptoms; diagnosis of schizophrenia and/or dementia; presence or history of hepatic disease, renal Insufficiency, narrow angle glaucoma, mania, seizures; hypertensive patients, pregnant/nursing females, and those unable to provide the informed consent.

The enrolled patients were randomly assigned to duloxetine 20 mg/day or imipramine 75 mg/day for the initial one week and then were continued with an increased dosage of duloxetine 40 mg and imipramine 150 mg daily for the rest of the study duration. Concomitant medications with primarily CNS activity were not allowed. Assessment was done after every two weeks for a total period of six weeks. The improvement in symptoms, if any, as well as the presence of any adverse effects was noted during the visits. The primary outcome measure in the evaluation of efficacy of the drugs was the change in the total score on HAM-D scale. Response to the drugs was defined by a decrease of more than 50% in the HAM-D score at the end of the study. Remission was defined as decrease of HAM-D score a total of seven or less than seven at the end of the study. Secondary outcome measure included the change in the score of Clinical Global Impression (CGI) improvement scale. Safety evaluation was based on the rates of discontinuation and the adverse events reported and observed during the study.

Statistical analysis was performed using SPSS software (version 11.5, SPSS Inc, Chicago, IL).The univariate relation between each independent factor and its related outcome in terms of response and remission were tested using the Student *t* test for the continuous variables and two-tailed Fisher exact test or chi-square (χ^2) test for categorical variables. All means were expressed as mean ± standard deviation and p-value < 0.05 was considered to be statistically significant.

RESULTS

Patient baseline characteristics

There was no significant difference between the two cohorts in the baseline demographic characteristics. The age of patients ranged from 22 to 62 years, with a mean of 37 years and 36 years in imipramine and duloxetine group respectively. The maximum number of patients was found in the age group 30-39 years (30%). Females predominated as the study participants in each group, with a female to male ratio of 2:1. The majority (86.7%) of the patients were married. The duration of symptoms varied from 2 to 12 months, with a mean of 5.52(±2.89) months. The study considered the duration of the present episode of MDD rather than the total duration of depression. The baseline value of Imipramine group on HAM-D scale was 37.80 (±4.30) and that of Group II (Duloxetine) was 33.53 (±4.99). The baseline value of imipramine group as assessed on CGI Scale was 5.40 (±0.81) and that of duloxetine group was 5.07 (±0.78).

Withdrawals from the study

In the imipramine group there were 14 dropouts. Of these, four patients wished to discontinue the treatment citing adverse reactions as the reason. These patients were excluded from the trial and were started on a different treatment. Ten patients did not report. The total dropout rate was 31.8%, and the dropout rate reported due to adverse effects was 9.1%. The common adverse events reported as a reason for discontinuation and considered to be drug related were postural hypotension, nausea and somnolence.

In the duloxetine group six patients did not complete the trial, out of which, one patient wished to discontinue the treatment because of nausea, dizziness and somnolence as the reason. The patient was excluded from the study and was started on a different treatment. Five patients did not report back. The total dropout rate was 16.7%, and the dropout rate specifically reported due to adverse effects was 2.8%.

Efficacy

The assessment on HAM-D and CGI scale on subsequent visits is depicted in table 1.

Table 1
Comparative Efficacy of Imipramine and Duloxetine in MDD

	Mean HAM-D Score		Mean CGI Score	
Weeks	**Imipramine**	**Duloxetine**	**Imipramine**	**Duloxetine**
0	37.8	33.5	5.4	5.1
2	26.4	23.9	3.8	3.3
4	17.2	18.4	3	2.7
6	12.3	13.3	2.4	2.3

On the HAM-D scale, at the end of two weeks there was an improvement of 30.16% in imipramine group and of 28.81% in duloxetine group. There was an additional improvement of 24.34% in imipramine group and 25.98% in the scores of duloxetine group at the end of four weeks. At the end of six weeks the imipramine and duloxetine groups exhibited an additional improvement of 24.34% and 5.66% respectively.

The total change in HAM-D score in imipramine group was -25.53 (±7.82) exhibiting an improvement of 67.54% and the total change in HAM-D score in duloxetine group was -20.27(±7.04) showing an improvement of 60.45%. The total improvement in the mean HAM-D scores at the end of six weeks as compared to the base line scores was beyond 60% in both the drugs and the difference between the values was statistically significant ($z=2.74$; $p<0.01$) (Figure 1)

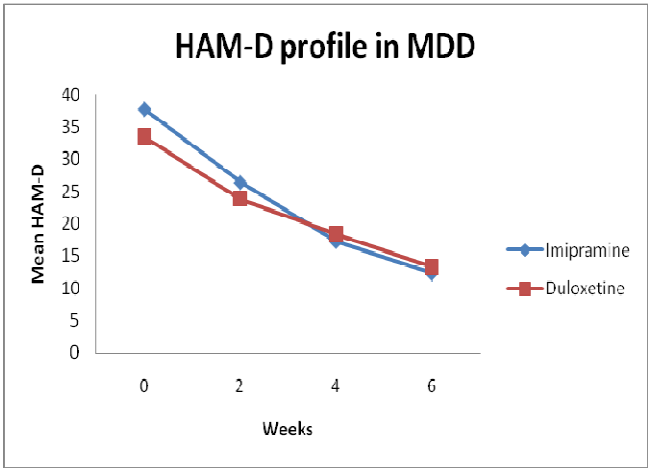

Figure 1
Mean HAM-D scores of Duloxetine and Imipramine in MDD

The total difference between the baseline and last scores at the end of the study in CGI Score in imipramine group was -3.00(±0.91) and that in the duloxetine group was -2.8 (±1.24). Since the CGI scale is very subjective, the HAMD scale was used to assess the response and remission in the patients.

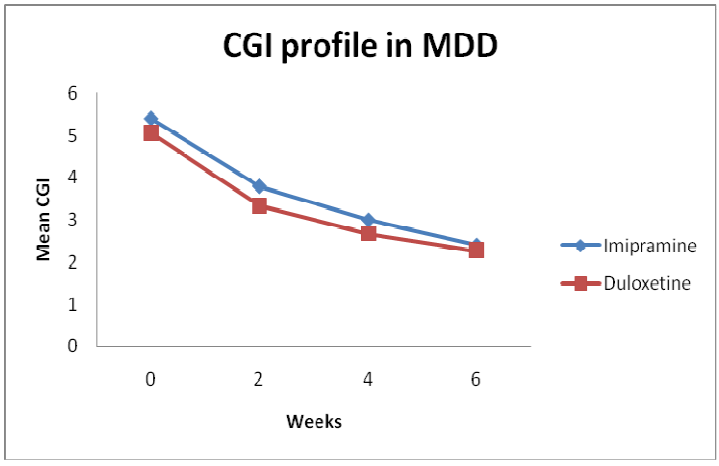

Figure 2
Mean CGI scores of Duloxetine and Imipramine in MDD

Response Rates in MDD

Response to the drugs, which was defined by a decrease of >50% in the HAM-D Scores was seen in 24 (80%) cases in imipramine group and 22 (73.3%) cases in duloxetine group (Figure 3). Both the values were comparable, with no statistically significant difference between the two groups (χ^2=0.37; p>0.05).

Remission Rates in MDD

Remission, which was defined as a HAM-D Score ≤ 7 was seen in nine (30%) patients on imipramine and eight (26.7%) on duloxetine (Figure 3). Both the values were comparable, with no statistically significant difference between the two groups (χ^2=0.08; p>0.05).

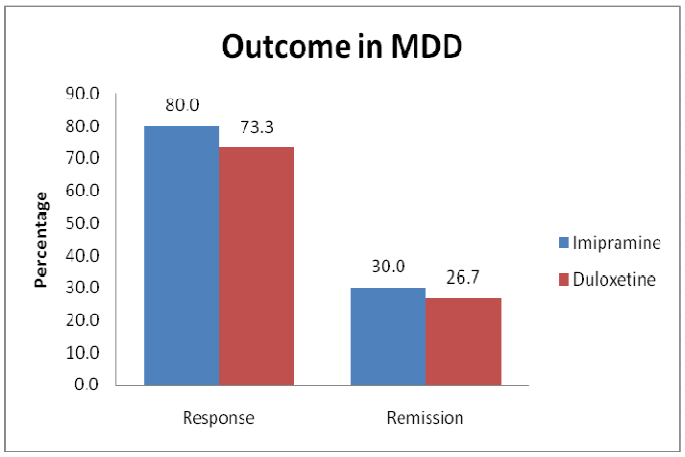

Figure 3
Response and Remission rates with Duloxetine and Imipramine in MDD

DISCUSSION

By a comparison of the improvement, response and remission rates in the two groups of patients, we found that both imipramine and duloxetine are effective in treating GAD and the efficacy of both the drugs is comparable in the treatment of Major Depressive Disorder. Imipramine shows a slightly greater reduction of HAM-D scores as compared to duloxetine, which is statistically significant, but the difference in response and remission rates between the two is not statistically significant.

Demographic profile of both the groups was as expected. As in our study, MDD is more common in females. The majority of the patients (86.7%) in the study were married, however this also is expected in a country like India where most of the marriages are arranged and the common age for depressive disorders is beyond the customary age for marriage in this country.

Treatment non-adherence and attrition during therapy is commonly seen in psychiatric patients.[14] In the present study, the total dropout rate in imipramine group (31.8%) was higher than in the duloxetine group (16.7%). More than 30 percent dropout has been reported in other studies on imipramine.[15] The common adverse events reported as a reason for discontinuation of imipramine were postural hypotension, nausea and somnolence, as in our study. The total drop outs in duloxetine group were comparable to that in other studies. The discontinuation rates in patients on duloxetine has been found to range from 13 to 17 % in a study on African Americans and Cucasians, which is similar to the total percentage of drop outs in this study.[16] Nausea and headache was the reason for our drop out case similar to those reported in the previous studies.

The dropout rate specifically reported due to adverse effects in imipramine group (9.1%) was also higher than the duloxetine group (2.8%). The rate of discontinuation due to adverse events of duloxetine has been higher in previously reported studies. An open label study on duloxetine in MDD found the discontinuation rate due to adverse effects to be 11.3%.[17] In a pooled analysis of four clinical trials on duloxetine the discontinuation rate due to adverse effects was 8.0%.[18]

Despite the total dropout rate in both the groups being comparable to other studies, the dropout rate specifically attributed to adverse effects, both in the imipramine and duloxetine groups, appears to be less in this study. The values could be apparently low because of the inability to confirm the reasons for discontinuing, in the lost to follow up cases, which apart from the lack of adequate response, distance and other problems, must

have included some percentage of dropouts due to adverse reactions also. Another reason could be that the minimum prescribed doses of imipramine (150 mg) and of duloxetine (40 mg) were used in this study whereas most of the studies have tried higher doses. Still, the tolerability should not be conclusive of the safety of the individual drug or class because the use of newer antidepressants has not been shown to be associated with a reduced risk of any of the adverse outcomes compared with TCAs.[19]

The mean changes in the total HAMD score at the end of six weeks in imipramine and duloxetine groups were -25.53 and -20.27 respectively as compared to the base values and the difference between the two was statistically significant ($p<0.01$). Reduction in the HAM-D scores was evident on the first visit which was after two weeks. Lack of a placebo arm in the study does not make it clear how much of it was a placebo effect. MDD is a highly placebo responsive state and the initial response in just two weeks may have placebo component to it.[20] That, the true antidepressant medication effect may actually begin after one to two weeks of initial therapy, has been debatable.[21] A meta analysis of forty seven studies on antidepressants measuring the response by HAM-D scoring system found that the time course of improvement on an antidepressant drug and placebo was similar and more than 60% of the improvement took place during the first 2 weeks of treatment. This analysis showed the presence of drug-placebo differences which were most pronounced during the first 2 weeks of treatment and diminished in a stepwise fashion thereafter.[22] Another meta analysis concluded that there was no significant difference in the response to placebo and drug for most patients but the initial response to placebo is poor in those patients who have more severe initial depression.[23] Patients in the present study had more severe initial depression. In this study also, the maximum improvement was seen on the first visit as 30.16% and 28.81%, in imipramine and duloxetine group, respectively. There was a decrease in the percentage of additional improvement on the subsequent visits and the decrease was more evident in case of duloxetine at the sixth week when the further improvement was 5.6% compared to 25.9% in the fourth week. The CGI score also showed a decrease in the amount of improvement on subsequent visits with the maximum difference in the score noted on the first visit.

The response rates of imipramine in MDD (80%), was comparable to previous studies in Indian population. In a prospective study in Indian population, 84% of patients on imipramine were responders at the end of six weeks.[24] High response rate has also been seen in the studies conducted elsewhere. A randomized multicentric study from Germany reported the response rate in imipramine group to be 63 % at the end of six weeks.[25] In another study in Spain the response rate to Imipramine was lower as compared to that found in the Indian population (53.7 %) but the remission rate was comparable to this study (38%).[26]

The response rate in this study for duloxetine (73.3%) was consistent with the response rate of duloxetine in other studies. A study on elderly patients of MDD showed that response rate with duloxetine at the end of six weeks was 62.9% whereas the remission rate was 41.4%.[27] In another study on duloxetine in MDD with melancholic features the response rate was 74.7% and the remission rate was 44.4%. An open-label study conducted at 29 sites in the United States, France, Italy and Spain found the response rate of 60 mg daily duloxetine to be 67.9% at the end of twelve weeks.[17] The response rate in the present study is slightly higher compared to the response rates of 65% found in a placebo controlled trial of 60 mg duloxetine in MDD whereas the remission was slightly on the lower side compared to the remission rate (43%) in the same study.[28] The slightly lower remission rate despite higher response rates in the present study could be due to the higher initial severity of the patients in this study. We

could not compare the results with any similar study in Indian population as there is no study, to the best of our knowledge, of duloxetine in adult Indian MDD patients, though there are studies of duloxetine for its other indications as diabetic neuropathy, neuropathic pain and stress urinary incontinence.

There were a few limitations with this study. Since there was no placebo arm, the placebo response in addition to the drug effect, could not be accounted for, as would have been in a double blind placebo controlled study; so the interpretation of the results should be cautious. Exclusion of the non compliers from the study could have been a potential source of selection bias in this study. The six week study period may be relatively short as it has been suggested that a longer duration could be necessary to properly evaluate the response and remission.[29]

CONCLUSION

Both duloxetine and imipramine are effective in the treatment of MDD and the efficacy of both the drugs is comparable. The response to both the drugs was slightly more and the remission rates slightly less than the earlier studies in other parts of world. Imipramine shows a slightly greater reduction of HAM-D scores as compared to duloxetine, which is statistically significant, but the difference between the two drugs, in response and remission rates at six weeks, is not statistically significant.

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